

Australian Perinatal Mental Health Guideline Evidence Review

Appendix to Technical Report Part D
Harms of treatment and
prevention interventions

Prepared by



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ABBREVIATIONS

AD	antidepressant
ADHD	attention-deficit hyperactivity disorder
ADSI	Ankara Developmental Screening Inventory Subscale Scores
AED	antiepileptic drug
AOR	adjusted odds ratio
AP	antipsychotic
AR	absolute risk
ARD	absolute risk difference
ARR	adjusted risk ratio
ASD	atrial septal defect
ASD	autism spectrum disorder
BA	Bayesian analysis
BMI	Body mass index
BSID	Bayley Scales of Infant Development
BWH	Brigham and Women's Hospital
CADTH	Canadian Agency for Drugs and Technologies in Health
CAM	complementary and alternative medicine
CBCL	Child behaviour Checklist
CC	case control
CDSR	Cochrane Database of Systematic Reviews
CI	confidence interval
CNS	central nervous system
CPRD	Clinical Practice Research Datalink
DARE	Database of Abstracts of Reviews of Effect
DB	double blind
DD	developmental delay
DHA	docosahexaenoic acid
DNHR	Danish National Hospital Registry
DPCR	Danish Psychiatric Central Register
ECT	electroconvulsive therapy
ENTIS	European Network of Teratology Information
EPA	eicosapentaenoic acid
FGA	first generation antipsychotics
GMDS	Griffiths Mental Development Scales
HCAR	Hungarian Congenital Abnormality Registry
hdPS	high-dimensional propensity score
HER	electronic health record
HR	hazard ratio
HTA	Health Technology Assessment database
ICD	International Classification of Diseases
ICD	International Statistical Classification of Diseases
ICD-10	International Classification of Diseases Tenth Revision
ICD-10-CA	International Classification of Diseases Tenth Revision Canada
ICD-9	International Classification of Diseases Ninth Revision
ICD-9-CM	International Classification of Diseases Ninth Revision Clinical Modification
INFANIB	Infant Neurological International Battery
INSERM	French National Institute of Health and Medical Research
IQ	intelligence quotient
ITIS	Israeli Teratology Information Service
IUGR	intrauterine growth restriction
IV	inverse variance
K-ABC	Kaufman Assessment Battery for Children
KPNC	Kaiser Permanente Medical Care Program
LBW	low birth weight
LCPUFA	long-chain polyunsaturated fatty acids
MA	meta-analysis
MAOI	monoamine oxidase inhibitor
MD	mean difference
MDD	major depressive disorder

MGH	Massachusetts General Hospital
MRI	monoamine reuptake inhibitor
MRI	non-selective monoamine reuptake inhibitor
n-3 LCPUFA	n-3 long-chain polyunsaturated fatty acids
NA	not applicable
NaSSA	noradrenergic and specific serotonergic antidepressant
ND	no difference
NE	not estimable
NICE	National Institute of Health and Care Excellence
NICU	neonatal intensive care unit
non-comp	non-comparative study
NOS	not otherwise specified
NR	not reported
NRD	neonatal respiratory distress
NS	not statistically significant
NWH	Newton-Wellesley Hospital
OBS	observational studies
OR	odds ratio
p	prospective
PICO	Population, Intervention, Comparator, Outcome
PNAS	poor neonatal adaptation syndrome
PP	postpartum psychosis
PPD	postpartum depression
PPVT	Peabody Picture Vocabulary Test
PS	propensity score
RAMQ	Régie de l'assurance maladie du Québec
RCT	randomised controlled trial
RD	risk difference
RE	risk estimate
RR	relative risk
RR	risk ratio
rTMS	repetitive transcranial magnetic stimulation
Rx	prescription
SAMe	S-adenosyl-methionine
SD	standard deviation
SDQ	Strengths and Difficulties Questionnaire
SE	standard error
SES	socioeconomic status
SFGA	small for gestational age
SGA	second generation antipsychotic
SJW	St John's wort
SMD	standardized mean difference
SNRI	serotonin noradrenaline reuptake inhibitor
SR	systematic review
SRI	selective reuptake inhibitor
SRS	social Responsiveness Scale
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
THIN	The Health Improvement Network
TIS	Teratology Information Service
TMS	transcranial magnetic stimulation
vs	versus
VSD	ventricular septal defect
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WPPSI-II	Wechsler Preschool and Primary Scale of Intelligence-II

Appendix D1 SEARCH STRATEGY

AppD1.1 SEARCH STRINGS

AppD1.1.1 Systematic review search

Table AppD1-1 Systematic review search strings

Database/date	Search #	Search string	Results
Embase.com (MEDLINE, Embase) 01 Jun 2016	1	((pregnancy:ab,ti OR pregnant:ab,ti) OR (perinatal:ab,ti OR 'peri natal':ab,ti) OR (prenatal:ab,ti OR 'pre natal':ab,ti) OR (postnatal:ab,ti OR 'post natal':ab,ti) OR (postpartum:ab,ti OR 'post partum':ab,ti) OR (antenatal:ab,ti OR 'ante natal':ab,ti) OR puerper*:ab,ti OR maternal:ab,ti) AND ((depression:ab,ti OR depressive:ab,ti OR depressed:ab,ti) OR anxiety:ab,ti OR (psychosis:ab,ti OR psychotic:ab,ti) OR bipolar:ab,ti OR psychosocial:ab,ti) AND ('systematic review'/exp OR 'systematic review':ab,ti OR 'systematic literature review':ab,ti OR 'systematic literature search':ab,ti OR 'systematic search':ab,ti) OR ('meta analysis'/exp OR 'meta analysis':ab,ti OR metaanalysis:ab,ti) OR 'pooled analysis':ab,ti OR 'evidence synthesis':ab,ti) Limit 2009 to date	803
Cochrane Library (CDSR, DARE and HTA) 29 Jul 2016	1	(pregnancy OR pregnant) OR (perinatal OR 'peri natal') OR (prenatal OR 'pre natal') OR (postnatal OR 'post natal') OR (postpartum OR 'post partum') OR (antenatal OR 'ante natal') OR puerper* OR maternal in Title, Abstract, Keywords AND (depression OR depressive OR depressed) OR anxiety OR (psychosis OR psychotic) OR bipolar OR psychosocial OR (schizophrenia OR schizophrenic) OR "borderline personality disorder" Limit 2009 to date	153

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effect; HTA, Health Technology Assessment database.

AppD1.1.2 Updated searches

AppD1.1.2.1 Pharmacological agents (excluding z-drugs)

Database/date	Search #	Search string	Results
PubMed (MEDLINE) 11 Oct 2016	1	(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR ("pregnancy"[MH] OR pregnan*) OR ("puerperal disorders"[MH] OR puerperal) OR ("post partum period"[MH] OR puerperium)) AND (("antidepressive agents"[MH] OR antidepress* OR "serotonin uptake inhibitors"[MH] OR "serotonin uptake" OR "serotonin reuptake" OR ssri* OR "monoamine oxidase inhibitors"[MH] OR "monoamine oxidase" OR maoi* OR tricyclic* OR "serotonin and noradrenaline reuptake inhibitors"[MH] OR ssni* OR snri*) OR ("antipsychotic agents"[MH] OR antipsychotic* OR "anti psychotic" OR neuroleptic) OR (lithium[MH] OR lithium) OR (anticonvulsants[MH] OR anticonvuls* OR antiepileptic OR "anti epileptic") OR ("anxiety agents"[MH] OR anxiolytic) OR ("hypnotics and sedatives"[MH] OR sedative* OR hypnotic* OR tranquil*) OR ("benzodiazepines"[MH] OR benzodiazepine*)) AND (systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative syntheses*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data syntheses*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal: __jrid21711] OR	747

Database/date	Search #	Search string	Results
		"health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal] OR (randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw])) AND (mask*[tw] OR blind*[tw] OR dumm*[tw])) OR ("case control" OR cohort OR "cross sectional" OR "follow up" OR longitudinal OR observational OR prospective OR retrospective OR epidemiol* OR regist*) ¹ Limit 2014 to current ²	
Cochrane Library (all databases) 13 Oct 2016	1	(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR pregnan* OR puerperal OR puerperium): Title, Abstract, Keyword AND (antidepress* OR "serotonin uptake" OR "serotonin reuptake" OR ssri* OR "monoamine oxidase" OR maoi* OR tricyclic* OR ssnri* OR snri* OR antipsychotic* OR "anti psychotic" OR neuroleptic OR lithium OR anticonvuls* OR antiepileptic OR "anti epileptic" OR anxiolytic OR sedative* OR hypnotic* OR tranquil* OR benzodiazepine*): Title, Abstract, Keyword Limit 2014 to current	88
OID (Embase) 12 Oct 2016	1	(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND (('antidepressive agents'.de,sh. or antidepress*.mp. or 'serotonin uptake inhibitors'.de,sh. or 'serotonin uptake'.mp. or 'serotonin reuptake'.mp. or ssri*.mp. or 'monoamine oxidase inhibitors'.de,sh. or 'monoamine oxidase'.mp. or maoi*.mp. or tricyclic*.mp. or 'serotonin.mp.) and noradrenaline reuptake inhibitors'.de,sh.) or ssnri*.mp. or snri*.mp. or ('antipsychotic agents'.de,sh. or antipsychotic*.mp. or 'anti psychotic'.mp. or neuroleptic.mp.) or (lithium.de,sh. or lithium.mp.) or (anticonvulsants.de,sh. or anticonvuls*.mp. or antiepileptic.mp. or 'anti epileptic'.mp.) or ('anxiety agents'.de,sh. or anxiolytic.mp.) or ('hypnotics.mp. and sedatives'.de,sh.) or sedative*.mp. or hypnotic*.mp. or tranquil*.mp.) or ('benzodiazepines'.de,sh. or benzodiazepine*.mp.) [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND (systematic.ti,ab. or meta-analysis.pt. or meta-analysis as topic.de,sh. or meta-analysis.de,sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti,ab. or integrative review*.ti,ab. or integrative overview*.ti,ab. or research integration*.ti,ab. or research overview*.ti,ab. or collaborative review*.ti,ab. or collaborative overview*.ti,ab. or systematic review*.ti,ab. or technology assessment*.ti,ab. or technology overview*.ti,ab. or 'Technology Assessment, Biomedical'.de,sh. or HTA.ti,ab. or HTAs.ti,ab. or comparative efficacy.ti,ab. or comparative effectiveness.ti,ab. or outcomes research.ti,ab) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) or Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analy* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or random*.tw. or 'Placebos'.sh. or placebo.ti,ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]) ³ Limit exclude medline journals Limit 2014 to current	135
OID (PsychINFO) 12 Oct 2016	1	(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	102

¹ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].² Search to update NICE 2015. NICE 2015 search conducted to April 2014.³ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

Database/date	Search #	Search string	Results
		<p>AND</p> <p>((('antidepressive agents'.de,sh. or antidepress*.mp. or 'serotonin uptake inhibitors'.de,sh. or 'serotonin uptake'.mp. or 'serotonin reuptake'.mp. or ssri*.mp. or 'monoamine oxidase inhibitors'.de,sh. or 'monoamine oxidase'.mp. or maoi*.mp. or tricyclic*.mp. or 'serotonin.mp.) and noradrenaline reuptake inhibitors'.de,sh.) or ssni*.mp. or snri*.mp. or ('antipsychotic agents'.de,sh. or antipsychotic*.mp. or 'anti psychotic'.mp. or neuroleptic.mp.) or (lithium.de,sh. or lithium.mp.) or (anticonvulsants.de,sh. or anticonvuls*.mp. or antiepileptic.mp. or 'anti epileptic'.mp.) or ('antianxiety agents'.de,sh. or anxiolytic.mp.) or (('hypnotics.mp. and sedatives'.de,sh.) or sedative*.mp. or hypnotic*.mp. or tranquil*.mp.) or ('benzodiazepines'.de,sh. or benzodiazepine*.mp.) [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]</p> <p>AND</p> <p>(systematic.ti,ab. or meta-analysis.pt. or meta-analysis as topic.de,sh. or meta-analysis.de,sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti,ab. or integrative review*.ti,ab. or integrative overview*.ti,ab. or research integration*.ti,ab. or research overview*.ti,ab. or collaborative review*.ti,ab. or collaborative overview*.ti,ab. or systematic review*.ti,ab. or technology assessment*.ti,ab. or technology overview*.ti,ab. or 'Technology Assessment, Biomedical'.de,sh. or HTA.ti,ab. or HTAs.ti,ab. or comparative efficacy.ti,ab. or comparative effectiveness.ti,ab. or outcomes research.ti,ab.) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) or Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analy* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or random*.tw. or 'Placebos'.sh. or placebo.ti,ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures])⁴</p> <p>Limit 2014 to current</p>	

AppD1.1.2.2 Z-drugs

Database/date	Search #	Search string	Results
PubMed (MEDLINE) 11 Oct 2016	1	<p>(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR ("pregnancy"[MH] OR pregnan*) OR ("puerperal disorders"[MH] OR puerperal) OR ("post partum period"[MH] OR puerperium))</p> <p>AND</p> <p>(zopiclone OR eszopiclone OR zolpidem OR zaleplon)</p> <p>AND</p> <p>(systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative syntheses*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data syntheses*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal: __jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal]) OR (randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR</p>	11

⁴ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

Database/date	Search #	Search string	Results
		blind*[tw] OR dumm*[tw])) OR ("case control" OR cohort OR "cross sectional" OR "follow up" OR longitudinal OR observational OR prospective OR retrospective OR epidemiol* OR regist*) ⁵	
Cochrane Library (all databases) 13 Oct 2016	1	(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR pregnan* OR puerperal OR puerperium): Title, Abstract, Keyword AND (zopiclone OR eszopiclone OR zolpidem OR zaleplon): Title, Abstract, Keyword	5
OVID (Embase) 12 Oct 2016	1	(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND (zopiclone or eszopiclone or zolpidem or zaleplon).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND (systematic.ti,ab. or meta-analysis.pt. or meta-analysis as topic.de,sh. or meta-analysis.de,sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti,ab. or integrative review*.ti,ab. or integrative overview*.ti,ab. or research integration*.ti,ab. or research overview*.ti,ab. or collaborative review*.ti,ab. or collaborative overview*.ti,ab. or systematic review*.ti,ab. or technology assessment*.ti,ab. or technology overview*.ti,ab. or 'Technology Assessment, Biomedical'.de,sh. or HTA.ti,ab. or HTAs.ti,ab. or comparative efficacy.ti,ab. or comparative effectiveness.ti,ab. or outcomes research.ti,ab.) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) or Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analy* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or random*.tw. or 'Placebos'.sh. or placebo.ti,ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]) ⁶ Limit exclude medline journals	13
OVID (PsychINFO) 12 Oct 2016	1	(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] AND (zopiclone or eszopiclone or zolpidem or zaleplon).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] AND (systematic.ti,ab. or meta-analysis.pt. or meta-analysis as topic.de,sh. or meta-analysis.de,sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti,ab. or integrative review*.ti,ab. or integrative overview*.ti,ab. or research integration*.ti,ab. or research overview*.ti,ab. or collaborative review*.ti,ab. or collaborative overview*.ti,ab. or systematic review*.ti,ab. or technology assessment*.ti,ab. or technology overview*.ti,ab. or 'Technology Assessment, Biomedical'.de,sh. or HTA.ti,ab. or HTAs.ti,ab. or comparative efficacy.ti,ab. or comparative effectiveness.ti,ab. or outcomes research.ti,ab.) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) or Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analy* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or	2

⁵ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].⁶ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

Database/date	Search #	Search string	Results
		random*.tw. or 'Placebos'.sh. or placebo.ti.ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)),tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]) ⁷	

AppD1.1.2.3 *St John's wort and Gingko biloba*

Database/date	Search #	Search string	Results
PubMed (MEDLINE) 11 Oct 2016	1	(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR ("pregnancy"[MH] OR pregnan*) OR ("puerperal disorders"[MH] OR puerperal) OR ("post partum period"[MH] OR puerperium)) AND ("hypericum"[MH] OR hypericum OR "st john's wort" OR "st johns wort" OR "ginkgo biloba"[MH] OR ginkgo OR ginkgo) AND (systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative syntheses*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data syntheses*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal: __jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal]) OR (randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw])) OR ("case control" OR cohort OR "cross sectional" OR "follow up" OR longitudinal OR observational OR prospective OR retrospective OR epidemiol* OR regist*) ⁸	46
Cochrane Library (all databases) 13 Oct 2016	1	(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR pregnan* OR puerperal OR puerperium): Title, Abstract, Keyword AND (hypericum OR "st john's wort" OR "st johns wort" OR ginkgo OR ginkgo): Title, Abstract, Keyword	9
OVID (Embase) 12 Oct 2016	1	(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND hypericum.de.sh. or hypericum.mp. or st john\$ wort.mp. or st johns wort.mp. or ginkgo biloba.de.sh. or ginkgo.mp. or ginkgo.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND (systematic.ti.ab. or meta-analysis.pt. or meta-analysis as topic.de.sh. or meta-analysis.de.sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti.ab. or integrative review*.ti.ab. or integrative overview*.ti.ab. or research integration*.ti.ab. or research overview*.ti.ab. or collaborative review*.ti.ab. or collaborative overview*.ti.ab. or systematic review*.ti.ab. or technology assessment*.ti.ab. or technology overview*.ti.ab. or 'Technology Assessment, Biomedical'.de.sh. or HTA.ti.ab. or HTAs.ti.ab. or comparative efficacy.ti.ab. or comparative effectiveness.ti.ab. or outcomes research.ti.ab) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) or	16

⁷ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

⁸ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

Database/date	Search #	Search string	Results
		Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analysis* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or random*.tw. or 'Placebos'.sh. or placebo.ti,ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)),tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]) ⁹ Limit exclude medline journals	
OVID (PsychINFO) 12 Oct 2016	1	(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] AND hypericum.de,sh. or hypericum.mp. or st john\$ wort.mp. or st johns wort.mp. or ginkgo biloba.de,sh. or ginkgo.mp. or ginkgo.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] AND (systematic.ti,ab. or meta-analysis.pt. or meta-analysis as topic.de,sh. or meta-analysis.de,sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti,ab. or integrative review*.ti,ab. or integrative overview*.ti,ab. or research integration*.ti,ab. or research overview*.ti,ab. or collaborative review*.ti,ab. or collaborative overview*.ti,ab. or systematic review*.ti,ab. or technology assessment*.ti,ab. or technology overview*.ti,ab. or 'Technology Assessment, Biomedical'.de,sh. or HTA.ti,ab. or HTAs.ti,ab. or comparative efficacy.ti,ab. or comparative effectiveness.ti,ab. or outcomes research.ti,ab.) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) or Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analysis* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or random*.tw. or 'Placebos'.sh. or placebo.ti,ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)),tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]) ¹⁰	10

AppD1.1.2.4 Omega-3 fatty acids

Database/date	Search #	Search string	Results
PubMed (MEDLINE) 11 Oct 2016	1	(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR ("pregnancy"[MH] OR pregnan*) OR ("puerperal disorders"[MH] OR puerperal) OR ("post partum period"[MH] OR puerperium)) AND ("fatty acids, omega-3"[MH] OR omega-3 OR (omega AND fatty)) AND (systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR	362

⁹ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

¹⁰ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

Database/date	Search #	Search string	Results
		comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative syntheses*[tiab] OR pooled analysis*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data syntheses*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal: __jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal]) OR (randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw]))) OR ("case control" OR cohort OR "cross sectional" OR "follow up" OR longitudinal OR observational OR prospective OR retrospective OR epidemiol* OR regist*) ¹¹ Limit 2012 to date	
Cochrane Library (all databases) 13 Oct 2016	1	(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR pregnan* OR puerperal OR puerperium): Title, Abstract, Keyword AND (omega-3 OR (omega AND fatty)): Title, Abstract, Keyword Limit 2012 to date	194
OVID (Embase) 12 Oct 2016	1	(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND omega 3 fatty acid.de.sh. or omega-3.mp. or (omega and fatty).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND (systematic.ti,ab. or meta-analysis.pt. or meta-analysis as topic.de,sh. or meta-analysis.de,sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti,ab. or integrative review*.ti,ab. or integrative overview*.ti,ab. or research integration*.ti,ab. or research overview*.ti,ab. or collaborative review*.ti,ab. or collaborative overview*.ti,ab. or systematic review*.ti,ab. or technology assessment*.ti,ab. or technology overview*.ti,ab. or 'Technology Assessment, Biomedical'.de,sh. or HTA.ti,ab. or HTAs.ti,ab. or comparative efficacy.ti,ab. or comparative effectiveness.ti,ab. or outcomes research.ti,ab) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) OR Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analysis* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or random*.tw. or 'Placebos'.sh. or placebo.ti,ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)),tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]) ¹² Limit 2012 to date Limit exclude medline journals	37

¹¹ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

¹² Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

Database/date	Search #	Search string	Results
OVID (PsychINFO) 12 Oct 2016	1	<p>(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]</p> <p>AND</p> <p>omega 3 fatty acid.de,sh. or omega-3.mp. or (omega and fatty).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]</p> <p>AND</p> <p>(systematic.ti,ab. or meta-analysis.pt. or meta-analysis as topic.de,sh. or meta-analysis.de,sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti,ab. or integrative review*.ti,ab. or integrative overview*.ti,ab. or research integration*.ti,ab. or research overview*.ti,ab. or collaborative review*.ti,ab. or collaborative overview*.ti,ab. or systematic review*.ti,ab. or technology assessment*.ti,ab. or technology overview*.ti,ab. or 'Technology Assessment, Biomedical'.de,sh. or HTA.ti,ab. or HTAs.ti,ab. or comparative efficacy.ti,ab. or comparative effectiveness.ti,ab. or outcomes research.ti,ab.) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) or Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analy* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or random*.tw. or 'Placebos'.sh. or placebo.ti,ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures])¹³</p> <p>Limit 2012 to date</p>	27

AppD1.1.2.5 *Electroconvulsive therapy and transcranial magnetic stimulation*

Database/date	Search #	Search string	Results
PubMed (MEDLINE) 11 Oct 2016	1	<p>(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR ("pregnancy"[MH] OR pregnan*) OR ("puerperal disorders"[MH] OR puerperal) OR ("post partum period"[MH] OR puerperium))</p> <p>AND</p> <p>("electroconvulsive therapy"[MH] OR "electroconvulsive" OR "electroshock" OR ect OR "transcranial magnetic stimulation"[MH] OR "transcranial magnetic" OR "magnetic stimulation" OR tms)</p> <p>AND</p> <p>(systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative syntheses*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data syntheses*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal: _jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal]) OR (randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh])</p>	146

¹³ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

Database/date	Search #	Search string	Results
		OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw])) OR ("case control" OR cohort OR "cross sectional" OR "follow up" OR longitudinal OR observational OR prospective OR retrospective OR epidemiol* OR regist*) ¹⁴	
Cochrane Library (all databases) 13 Oct 2016	1	(perinatal OR antenatal OR "ante natal" OR postnatal OR "post natal" OR (post AND partum) OR "post partum" OR pregnan* OR puerperal OR puerperium): Title, Abstract, Keyword AND ("electroconvulsive" OR "electroshock" OR ect OR "transcranial magnetic" OR "magnetic stimulation" OR tms): Title, Abstract, Keyword	33
OVID (Embase) 12 Oct 2016	1	(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND 'electroconvulsive therapy'.de,sh. or 'electroconvulsive'.mp. or 'electroshock'.mp. or ect.mp. or 'transcranial magnetic stimulation'.de,sh. or 'transcranial magnetic'.mp. or 'magnetic stimulation'.mp. or tms.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND (systematic.ti,ab. or meta-analysis.pt. or meta-analysis as topic.de,sh. or meta-analysis.de,sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti,ab. or integrative review*.ti,ab. or integrative overview*.ti,ab. or research integration*.ti,ab. or research overview*.ti,ab. or collaborative review*.ti,ab. or collaborative overview*.ti,ab. or systematic review*.ti,ab. or technology assessment*.ti,ab. or technology overview*.ti,ab. or 'Technology Assessment, Biomedical'.de,sh. or HTA.ti,ab. or HTAs.ti,ab. or comparative efficacy.ti,ab. or comparative effectiveness.ti,ab. or outcomes research.ti,ab) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) or Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analy* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or random*.tw. or 'Placebos'.sh. or placebo.ti,ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]) ¹⁵ Limit exclude medline journals	50
OVID (PsychINFO) 12 Oct 2016	1	(perinatal or antenatal or 'ante natal' or postnatal or 'post natal' or postpartum or 'post partum').mp. or pregnancy.sh. or pregnan*.mp. or puerperal disorders.sh. or post partum period.sh. or puerperal.mp. or puerperium.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] AND 'electroconvulsive therapy'.de,sh. or 'electroconvulsive'.mp. or 'electroshock'.mp. or ect.mp. or 'transcranial magnetic stimulation'.de,sh. or 'transcranial magnetic'.mp. or 'magnetic stimulation'.mp. or tms.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] AND (systematic.ti,ab. or meta-analysis.pt. or meta-analysis as topic.de,sh. or meta-analysis.de,sh. or meta analy*.tw. or metanaly*.tw. or metaanaly*.tw. or met analy*.tw. or integrative research.ti,ab. or integrative review*.ti,ab. or integrative overview*.ti,ab. or research integration*.ti,ab. or research overview*.ti,ab. or collaborative review*.ti,ab. or collaborative overview*.ti,ab. or systematic review*.ti,ab. or technology assessment*.ti,ab. or technology overview*.ti,ab. or 'Technology Assessment, Biomedical'.de,sh. or HTA.ti,ab. or HTAs.ti,ab. or comparative efficacy.ti,ab. or comparative effectiveness.ti,ab. or outcomes research.ti,ab.) OR (((indirect comparison* or indirect treatment or mixed-treatment) and comparison*) or Embase* or Cinahl* or systematic overview* or methodological overview* or methodologic overview* or methodological review* or methodologic review* or quantitative review* or quantitative overview* or quantitative syntheses* or pooled analy* or Cochrane or Medline or Pubmed or Medlars or handsearch* or hand search* or meta-regression* or metaregression* or data syntheses* or data extraction or data abstraction* or mantel haenszel or peto or der-simonian	59

¹⁴ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].¹⁵ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

Database/date	Search #	Search string	Results
		or dersimonian or fixed effect*).ti,ab.) OR (('Cochrane Database Syst Rev' or 'health technology assessment' or 'Evid Rep Technol Assess Rep' or 'Evid Rep Technol Assess' or 'Int J Technol Assess Health Care' or 'GMS Health Technol Assess' or 'Health Technol Assess' or 'Health Technol Assess Rep').jn. or randomized controlled trial.pt. or randomized controlled trials as topic.de,sh. or random allocation.de,sh. or double-blind method.de,sh. or single-blind method.de,sh. or random*.tw. or 'Placebos'.sh. or placebo.ti,ab.) OR (((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)),tw. or ('case control' or cohort or 'cross sectional' or 'follow up' or longitudinal or observational or prospective or retrospective or epidemiol* or regist*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]) ¹⁶	

AppD1.2 EXCLUSION OF STUDIES

AppD1.2.1 Systematic review search

	Status	No. citations excluded	No. citations included
<i>Identified via literature search</i>			805
<i>Identified manually¹⁷</i>			5
<i>Duplicate citation</i>		92	
TOTAL	Included		718
Title/abstract	Excluded	548	
TOTAL	Included		170
Full paper	Excluded – wrong population	14	
	Excluded – wrong indication	7	
	Excluded – wrong intervention	20	
	Excluded – wrong outcomes	8	
	Excluded – not in English	1	
	Excluded – duplicate data	3	
	Excluded – not a SR	30	
	Excluded – wrong study type	4	
	Excluded – superseded	1	
TOTAL	Included		82
TOTAL	Relevant to harms		28

AppD1.2.2 Updated searches

AppD1.2.2.1 Pharmacological agents (excluding z-drugs)

	Status	No. citations excluded	No. citations included
<i>Identified via literature search</i>			1090
<i>Identified manually¹⁸</i>			215
<i>Duplicate citation</i>		154	
TOTAL	Included		1305
Title/abstract	Excluded	742	
TOTAL	Included		409
Full paper	Excluded – wrong population	3	
	Excluded – wrong intervention	13	
	Excluded – wrong/no comparator	20	
	Excluded – wrong outcomes	39	
	Excluded – not in English	4	
	Excluded – Abstract only	3	
	Excluded – duplicate data	6	
	Excluded – not adjusted for potential confounding	33	
	Excluded – not limited to/adjusted for maternal psychiatric diagnosis	73	
	Excluded – not a SR	34	
	Excluded – not a clinical study	6	
	Excluded – wrong study type	41	
TOTAL	Included		134¹⁹

¹⁶ Adapted from Strings Attached: CADTH database search filters [Internet]. Ottawa: CADTH; 2016 [2017 05 24].

¹⁷ Via the reference lists of included SRs.

¹⁸ Via the SR search and reference lists of included SRs and individual studies.

¹⁹ Includes 10 treatment/prevention studies.

AppD1.2.2.2 Z-drugs

	Status	No. citations excluded	No. citations included
Identified via literature search			31
Identified manually ²⁰			2
Duplicate citation		3	
TOTAL	Included		30
Title/abstract	Excluded		22
TOTAL	Included		
Full paper	Excluded – wrong outcomes	1	
TOTAL	Included		7

AppD1.2.2.3 St John's wort and ginkgo biloba

	Status	No. citations excluded	No. citations included
Identified via literature search			81
Identified manually ²¹			0
Duplicate citation		14	
TOTAL	Included		67
Title/abstract	Excluded	51	
TOTAL	Included		16
Full paper	Excluded – wrong population	3	
	Excluded – wrong outcomes	6	
	Excluded – not a SR	2	
TOTAL	Included		5

AppD1.2.2.4 Omega-3 fatty acids

	Status	No. citations excluded	No. citations included
Identified via literature search			1194
Identified manually ²²			0
Duplicate citation		251	
TOTAL	Included		943
Title/abstract	Excluded	838	
TOTAL	Included		105
Full paper	Excluded – wrong outcomes	12	
	Excluded – duplicate data	1	
	Excluded – wrong study type	76	
TOTAL	Included		16²³

AppD1.2.2.5 Electroconvulsive therapy and transcranial magnetic stimulation

	Status	No. citations excluded	No. citations included
Identified via literature search			274
Identified manually ²⁴			62
Duplicate citation		55	
TOTAL	Included		281
Title/abstract	Excluded	257	
TOTAL	Included		24
Full paper	Excluded – wrong population	1	
	Excluded – wrong intervention	1	
	Excluded – Wrong/no comparator	8	
	Excluded – not a SR	3	
	Excluded – wrong study type	3	

²⁰ Via the SR search and reference lists of included SRs and individual studies.²¹ Via the SR search and reference lists of included SRs and individual studies.²² Via the SR search and reference lists of included SRs and individual studies.²³ Includes eight treatment/prevention studies.²⁴ Via the SR search and reference lists of included SRs and individual studies.

	Status	No. citations excluded	No. citations included
	Excluded – unable to retrieve ²⁵	1	
TOTAL	Included		7²⁶

AppD1.3 EXCLUDED STUDIES LIST

The excluded studies lists can be found in Part C Appendix **Section C1.2.4**.

²⁵ Authors contacted.

²⁶ Includes one treatment/prevention study.

Appendix D2 IDENTIFIED STUDIES

AppD2.1 PHARMACOLOGICAL

AppD2.1.1 Antidepressants

AppD2.1.1.1 Systematic reviews – antidepressants

The scoping and updated searches identified 28 SRs relating to the assessment of antidepressant harms. A summary of the characteristics of the identified SRs is presented in **Table AppD2-1**. Eighteen SRs provide a quantitative assessment of the included studies while the remaining eight provide a narrative assessment of the individual studies only; these studies have been used to identify individual studies only.

As described below, none of the published SRs were considered suitable for inclusion as a foundation review for the current Guideline; consequently, new SRs of individual studies have been undertaken. The rationale for the inclusion/exclusion of studies in these new SRs is described below.

Table AppD2-1 Characteristics of included systematic reviews of antidepressant harms

Study ID	Study characteristics	Population for outcomes assessment	Exposure (subgroups)	Comparator (subgroups)	Outcomes
SRs – Quantitative assessment					
Jiang 2016	SR including 8 observational studies (6 cohort studies and 2 case-control studies)	Pregnant/ postpartum women	Antidepressants SRI ²⁷ Non-SRI SSRI SNRI	Unexposed	Postpartum haemorrhage
Kaplan 2016	SR/MA 6 case-control studies	Children	SSRIs during pregnancy	No exposure to SSRIs	Autism spectrum disorders
Kobayashi 2016	SR/MA 8 cohort/case-control studies	Children	SSRIs during pregnancy	No exposure to SSRIs	Autism spectrum disorder
NICE 2015	SR/MA 31 cohort/case-control studies	Pregnant women, neonates or children	Antidepressants during pregnancy or lactation	No exposure to antidepressants (women with or without depression)	Teratogenic harms Course of pregnancy, obstetric and neonatal complications Neurodevelopmental outcomes
Wang 2015	SR/MA 4 cohort studies	Neonates	SSRIs during the first trimester	No exposure to SSRIs (2 studies)/ADs (2 studies)	Cardiac malformations
Saccone 2016a	SR/MA 8 cohort/case-control studies	Neonates	SSRIs during pregnancy	No exposure to SSRIs (pregnant women with depression)	Preterm birth Respiratory distress Low birth weight
Lassen 2016	SR/pooled 8 cohort studies	Neonates	Venlafaxine or duloxetine during pregnancy	No exposure to SNRIs	Major congenital malformations
Man 2015	6 cohort/case-control studies	Children	SSRIs during pregnancy	No exposure to SSRIs	Autism spectrum disorder
McDonagh 2014	SR/MA 6 RCTs and 126 cohort and case-control studies	Pregnant women and neonates	Antidepressants/SSRIs during pregnancy	No exposure to antidepressants/SSRIs	Preterm birth Major malformations Neonatal convulsions Respiratory distress
Grigoriadis 2014	SR/MA 7 cohort/case-control studies	Neonates	Antidepressants/SSRIs during pregnancy	No exposure to antidepressants	Pulmonary hypertension
Huang 2014	SR/MA 28 cohort/case-control studies	Neonates	Antidepressants during pregnancy (SSRIs/other)	No exposure to antidepressants	Birth outcomes
Huybrechts 2014b	SR/MA 41 cohort/case-control studies	Neonates	Antidepressants during pregnancy	No exposure to antidepressants	Preterm birth
Grigoriadis 2013a	SR/MA 27 cohort/case-control studies	Neonates	Antidepressants during pregnancy	No exposure to antidepressants	Congenital malformations

²⁷ Includes SSRIs and SNRIs.

Study ID	Study characteristics	Population for outcomes assessment	Exposure (subgroups)	Comparator (subgroups)	Outcomes
Grigoriadis 2013b	SR/MA 12 cohort/case-control studies	Neonates	Antidepressants during pregnancy	No exposure to antidepressants	Neonatal adaptation
Myles 2013	SR/MA 19 cohort/case-control studies	Neonates	SSRIs during pregnancy	No exposure to SSRIs	Major malformations Minor malformations Cardiac malformations
Riggin 2013	SR/MA 21 cohort/case-control studies	Neonates	Fluoxetine during the first trimester of pregnancy	No exposure to SSRIs	Major malformations Cardiac malformations
Ross 2013	SR 23 cohort/case-control studies	Pregnant women and neonates	Antidepressants during pregnancy	No exposure to antidepressants	Pregnancy and delivery outcomes
Lopez-Yarto 2012	SR/MA 2 cohort studies	Pregnant women	Antidepressants/SSRIs during pregnancy	No exposure to antidepressants/SSRIs	Maternal metabolic outcomes
Wurst 2010	SR 15 cohort/5 case control	Neonates	Paroxetine	No SSRI/untreated depression/exposed to nonteratogenic agents/exposed to other antidepressants	Congenital malformations Cardiac malformations
Additional SRs – narrative assessment					
Bruning 2015	SR including 4 observational studies (1 prospective cohort study, 2 retrospective cohort studies and 1 case-control study)	Pregnant/ postpartum women	Antidepressants	Unexposed	Post-partum haemorrhage
Smit 2016	SR 31 observational studies	Neonates	Mirtazapine during pregnancy/postpartum	None	Malformations Pregnancy and delivery outcomes Lactation Neurodevelopment
O'Connor 2016	SR 1 SR/12 cohort/case-control studies	Pregnant and postpartum women/Children	Antidepressants during pregnancy/postpartum	No exposure to antidepressants	Malformations Pregnancy and delivery outcomes
Bruning 2015	SR 4 cohort/case-control studies	Pregnant women	Antidepressants during pregnancy	No antidepressants in women with or without depression	Postpartum haemorrhage
Gentile 2015	SR 8 cohort/case-control studies	Children	SSRIs during pregnancy	No exposure to SSRIs	Autism spectrum disorders
El Marroun 2014	SR 49 cohort/case-control studies 17 case reports	Children	Antidepressants and anxiolytics during pregnancy	No exposure to antidepressants or anxiolytics	Neurodevelopmental outcomes
Previti 2014	SR 19 cohort/case-control studies	Children	Antidepressants during pregnancy	No exposure to antidepressants	Neurodevelopmental outcomes

Study ID	Study characteristics	Population for outcomes assessment	Exposure (subgroups)	Comparator (subgroups)	Outcomes
Rais 2014	SR 3 case-control studies	Children	Antidepressants during pregnancy	No exposure to antidepressants	Autism spectrum disorder
Gentile 2011a	SR 9 cohort/case-control studies	Children	Paroxetine/SSRIs/SNRIs during early pregnancy	No exposure to antidepressants	Congenital malformations
Gentile 2011b	SR 12 cohort studies	Children	Antidepressant during pregnancy	No exposure to antidepressants	Neurodevelopmental outcomes
Gentile 2009	SR 19 cohort/6 case-control studies	Neonates	Paroxetine/SSRIs	No exposure to antidepressants	Major malformations

Abbreviations: AD, antidepressant; MA, meta-analysis; SNRI, serotonin and noradrenaline reuptake inhibitor; SR, systematic review; SRI, selective reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

AppD2.1.1.1.1 Malformations – antidepressants

Twelve SRs provide evidence related to the association between antidepressant use during pregnancy and infant malformations. Of these, eight provide synthesised/pooled evidence and four provide results for individual studies only. Different SRs included a mix of different antidepressants, and outcomes assessed included congenital, major, cardiac, septal, atrial septal and ventricular septal malformations. For this Review, based on advice from the Expert Committee on Harms, only major, cardiac, and septal malformations are included as the most important outcomes for clinical decision-making.

Table AppD2-2 presents the specific outcomes, methodological characteristics and individual studies included in each of the 12 SRs that reported on antidepressant exposure and infant malformations. The individual studies included in the SRs vary substantially due to the different antidepressants and outcomes assessed.

To be considered for inclusion in the final evidence base from which the recommendations were made, a SR had to be considered of 'higher quality'. To be assessed as higher quality an analysis was required to have adjusted for potential confounders and attempted to minimise confounding by indication. No SRs were assessed by us as providing higher quality evidence and therefore no SRs provided evidence of a sufficient quality to provide the basis for making recommendations. A number of SRs did include analyses based on adjustment for potential confounders or attempts were made to minimise confounding by indication. These SRs were considered to be of moderate quality.

See **Section AppD3.1.1.1** of these Appendices for the full data extraction from the identified SRs. The data from moderate quality studies are also presented and discussed in **Section AppD4.1.1** of these Appendices, but do not provide the basis for making recommendations.

Table AppD2-2 Studies included in systematic reviews of antidepressants reporting malformations

Assessment type	Quantitative assessment								Narrative assessment only			
Included studies	Lassen 2016	NICE 2015	Wang 2015	McDonagh 2014	Grigoriadis 2013a	Myles 2013	Riggin 2013	Wurst 2010	Smit 2016	O'Connor 2016	Gentile 2011	Gentile 2009
Search date	Apr 2015	Apr 2014	Jul 2014	Jul 2013	Jun 2010	Jun 2011	Aug 2012	Sep 2008	Jun 2014	Jan 2015	Nov 2010	Sep 2008
Interventions	Venlafaxine; Duloxetine	Any ADs; SSRIs; TCAs; paroxetine; citalopram; fluoxetine; sertraline; fluvoxamine; escitalopram; venlafaxine	SSRIs; paroxetine; sertraline; fluoxetine; citalopram	SSRIs	Any ADs	SSRIs; fluoxetine; paroxetine; sertraline; citalopram	Fluoxetine	Paroxetine	Mirtazapine	Second generation antidepressants	SSRIs	Paroxetine; SSRIs
Outcomes	Congenital	Congenital; major; cardiac; ASD/VSD	Cardiac	Major; cardiac	Congenital; major; cardiac; ASD/VSD	Major; minor; cardiac	Major; cardiac	Congenital; cardiac	Major	Major; cardiac	Structural	Major
Analysed adjusted data?	x	x	✓	✓	✓	✓ ²⁸	x	✓	-	-	-	-
Compared to an untreated/with mental health disorder population	x	x	x	✓ ²⁹	x	x	x	✓	-	-	-	-
AHRQ 2014 (SR)										✓		
Furu 2015	✓											
Ban 2014										✓		
Huybrechts 2014			✓							✓		
Louik 2014										✓		
Michielsen 2014									✓			
Uguz 2014									✓			
Yazdy 2014										✓		
Haberman 2013												
Hoog 2013	✓											
Kallen 2013	✓											
Kjaersgaard 2013												
Uguz 2013									✓			
Einarson 2012	✓											
Jimenez-Solem 2012				✓			✓					
Nordeng 2012			✓	✓			✓					
Colvin 2011			✓	✓			✓					

²⁸ Included univariate analyses for different covariates.²⁹ For bupropion only.

Assessment type	Quantitative assessment								Narrative assessment only			
Cupitt 2011									✓			
Galbally 2011									✓			
Malm 2011		✓		✓		✓	✓					
Manakova 2011	✓			✓					✓			
Bakker 2010		✓			✓	✓					✓	
Einarson 2010												
Gulec 2010									✓			
Hale 2010									✓			
Kornum 2010		✓		✓	✓		✓				✓	
Malm 2010											✓	
Reis 2010		Excluded		✓	✓	✓	✓				✓	
Bouher 2009									✓			
Davidson 2009				✓								
Einarson 2009		✓			✓		✓		✓			
Galbally 2009									✓			
Merlob 2009					✓						✓	
Pedersen 2009		✓		✓	✓	✓	✓				✓	
Tonn 2009									✓			
Wichman 2009		✓		✓	✓	✓						
Boucher 2008					✓							
Diav-Citrin 2008		✓			✓	✓	✓	✓				✓
Einarson 2008		Excluded			✓	✓						✓
Kallen 2008									✓			
Maschi 2008		✓				✓		✓				✓
Oberlander 2008	✓	✓			✓		✓	✓			✓	✓
Ramos 2008					✓	✓						✓
Schwartz 2008									✓			
Sokolover 2008									✓			
Alwan 2007		✓				✓		✓			✓	✓
Bérard 2007								✓			✓	✓
Cole 2007a		Excluded					✓	✓				✓
Cole 2007b											✓	✓
Chambers 2007								✓				
Davis 2007		✓			✓	✓		✓				✓
Källén 2007		✓	✓	✓	✓			✓			✓	✓
Klier 2007									✓			
Kristensen 2007									✓			
Lennestål 2007									✓			
Louik 2007		Excluded		✓	✓	✓		✓			✓	✓
Nash 2007												
Bakker 2008								✓				
Djulus 2006a					✓				✓			
Djulus 2006b									✓			
Källén 2006							✓				✓	✓

Assessment type	Quantitative assessment								Narrative assessment only			
Levinson-Castiel 2006		✓			✓							
Louik 2006								✓				
Schloemp 2006								✓				
Vial 2006								✓				
Wen 2006		✓		✓	✓	✓		✓				
Wogelius 2006		✓				✓					✓	✓
Chun-Fai-Chan 2005					✓							
Diav-Citrin 2005												✓
Guclu 2005									✓			
Hudson 2005	✓											
Malm 2005		Excluded			✓		✓	✓				✓
Sivojelezova 2005		✓		✓	✓	✓	✓			✓	✓	
Yaris 2005												
Aichorn 2004									✓			
Yaris 2004a									✓			
Yaris 2004b									✓			
Casper 2003				✓				✓				
Einarson 2003					✓							
Hendrick 2003												✓
Kallen 2003												✓
Laine 2003				✓								
Rohde 2003									✓			
Diav-Citrin 2002												✓
Kesim 2002									✓			
Simon 2002		✓		✓	✓	✓			✓			✓
Einarson 2001	✓				✓							
Saks 2001									✓			
Unfred 2001												✓
Diav-Citrin 2000											✓	
Ericson 1999												✓
Kulin 1998		✓		✓	✓	✓		✓				✓
Goldstein 1997							✓					
Nulman 1997							✓					
Chambers 1996		✓			✓	✓	✓					
McElhatton 1996							✓					✓
Pastuszek 1993		Excluded			✓	✓	✓					

Abbreviations: AD, antidepressant; ASD, atrial septal defect; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VSD, ventricular septal defect.

AppD2.1.1.1.2 Pregnancy and birth outcomes – antidepressants

Eleven SRs provide evidence of the association between antidepressant use in the antenatal period and pregnancy, obstetric and birth outcomes in the fetus or infant. Of these, eight provide synthesised/pooled evidence and three provide results for individual studies only. Different SRs included a mix of different antidepressants and outcomes. For this Review, based on advice from the Expert Committee on Harms, only neonatal mortality, miscarriage, preterm birth, small for gestational age, poor neonatal adaptation syndrome (PNAS), persistent pulmonary hypertension, respiratory distress, tremors and convulsions are included as the most important outcomes for clinical decision-making.

Another two SRs were identified during the assessment of infant harms that included postpartum haemorrhage which presents a risk to the mother. Jiang 2016 has been chosen as the foundation review because it is the most up-to-date, includes the most studies, and provides quantitative pooled analyses.

Table AppD2-3 presents the specific outcomes, methodological characteristics and individual studies included in each of the 11 SRs that reported on antidepressant exposure and pregnancy, obstetric and birth outcomes. The individual studies included in the SRs vary substantially due to the different antidepressants and outcomes assessed. **Table AppD2-4** presents the individual studies included in the two postpartum haemorrhage SRs identified.

To be considered for inclusion in the final evidence base from which the recommendations were made, a SR had to be considered of 'higher quality'. To be assessed as higher quality an analysis was required to have adjusted for potential confounders and attempted to minimise confounding by indication. No SRs were assessed by us as providing higher quality evidence and therefore no SRs provided evidence of a sufficient quality to provide the basis making the recommendations. A number of SRs did include analyses based on adjustment for potential confounders or attempts to minimise confounding by indication. These SRs were considered to be of moderate quality.

See **Section AppD3.1.1.1.2** of these Appendices for the full data extraction from the identified SRs. The data from moderate quality studies are also presented and discussed in **Section AppD4.1.1** of these Appendices, but do not provide the basis for making recommendations.

Table AppD2-3 Studies included in systematic reviews of antidepressants reporting pregnancy and birth outcomes

Assessment type	Quantitative assessment								Qualitative assessment only		
Included studies	NICE 2015	Saccone 2016a	Grigoriadis 2014	Huang 2014	Huybrechts 2014b	McDonagh 2014	Grigoriadis 2013b	Ross 2013	Smit 2016	Bruning 2015	McDonagh 2014
<i>Search date</i>	<i>Apr 2014</i>	<i>May 2015</i>	<i>Dec 2012</i>	<i>Dec 2012</i>	<i>Sep 2012</i>	<i>Jul 2013</i>	<i>Jun 2010</i>	<i>Jun 2010</i>	<i>Jun 2014</i>	<i>May 2014</i>	<i>Jul 2013</i>
<i>Interventions</i>	<i>Any ADs; SSRIs; TCAs; paroxetine; citalopram; fluoxetine; sertraline; fluvoxamine; escitalopram; venlafaxine</i>	<i>SSRIs</i>	<i>SSRIs</i>	<i>Any ADs; SSRIs; other ADs</i>	<i>Any ADs</i>	<i>SSRIs</i>	<i>Any ADs</i>	<i>Any ADs</i>	<i>Mirtazapine</i>	<i>Any ADs</i>	<i>SSRIs</i>
<i>Outcomes</i>		<i>Preterm birth</i>	<i>Persistent pulmonary hypertension</i>	<i>Preterm birth; low birth weight</i>	<i>Preterm birth</i>	<i>Preterm birth; persistent pulmonary hypertension</i>	<i>Poor neonatal adaptation syndrome</i>	<i>Spontaneous abortion; preterm birth; gestational age; birth weight; APGAR score</i>	<i>Pregnancy outcomes; PNAS and other neonatal outcomes</i>	<i>Postpartum haemorrhage</i>	<i>Withdrawal symptoms</i>
Hanley 2016											
Kim 2016											
Grzeskowiak 2015											
Joseph 2015					✓						
Lindqvist 2014											
Lupatelli 2014										✓	
Michielsen 2014									✓		
Uguk 2014									✓		
Habermann 2013									✓		
Kjaersgaard 2013									✓		
Palmstein 2013										✓	
Uguz 2013									✓		
El Marroun 2012				✓	✓						
Hayes 2012		✓			✓						
Grzeskowiak 2012				✓							
Källen 2012		✓									
Kieler 2012	✓		✓		✓					✓	
Klieger-Grossman 2012				✓	✓						
Lim 2012			✓								
Nordeng 2012				✓	✓						
Yonkers 2012				✓	✓	✓					
Casper 2011					✓						
Colvin 2011				✓	✓						
Cupitt 2011									✓		
Einarson 2011					✓						

Assessment type	Quantitative assessment							Qualitative assessment only		
Gulec 2011								✓		
Latrendesse 2011				✓	✓					
Manakova 2011								✓		
Mulder 2011					✓		✓			
Roca 2011				✓	✓					
Rurak 2011					✓					
Schwarzer 2011								✓		
Wilson 2011			✓						✓	
Einarson 2010				✓	✓					
Hale 2010								✓		
Kornum 2010	✓									
Lewis 2010				✓	✓					
Reis 2010			✓	✓	✓				✓	
Andrade 2009			✓						✓	
Calderon-Margalit 2009	✓				✓					
Einarson 2009								✓		
Galbally 2009	✓						✓	✓		
Gavin 2009					✓					
Lund 2009		✓		✓	✓					
Rampono 2009							✓			✓
Toh 2009				✓	✓					
Wichman 2009			✓							
Wisner 2009	✓			✓	✓	✓				
Boucher 2008	✓						✓			
Diav-Citrin 2008					✓					
Jordan 2008										✓
Kallen 2008								✓		
Maschi 2008	✓			✓	✓					
Salkeld 2008									✓	
Sokolover 2008								✓		
Davis 2007	✓			✓	✓		✓			
Ferreira 2007	✓				✓					✓
Lennestall 2007				✓	✓			✓		
Pearson 2007				✓	✓					
Suri 2007	✓			✓	✓					
Chambers 2006			✓						✓	
Djulus 2006a				✓	✓			✓		
Djulus 2006b								✓		
Levinson-Castiel 2006	✓									✓
Oberlander 2006	✓	✓			✓		✓			
Wen 2006	✓			✓	✓					
Wogelius 2006					✓					
Sivojelezova 2005	✓			✓	✓					

Assessment type	Quantitative assessment								Qualitative assessment only		
Källen 2004	✓	✓		✓	✓		✓				
Oberlander 2004							✓				
Yaris 2004									✓		
Casper 2003	✓			✓	✓						
Laine 2003	✓						✓				
Costei 2002	✓	✓			✓		✓				
Kessim 2002									✓		
Simon 2002	✓	✓		✓	✓						
Saks 2011									✓		
Ericson 1999				✓	✓						
Kulin 1998	✓						✓	✓			
Chambers 1996		✓		✓	✓						✓
Pastuszak 1993				✓	✓						

Abbreviations: AD, antidepressant; ASD, atrial septal defect; SRI, selective reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VSD, ventricular septal defect.

Table AppD2-4 Studies included in systematic reviews of antidepressants reporting maternal harm

		Quantitative evidence	Qualitative evidence
	Study type	Jiang 2016	Bruning 2015
<i>Search date</i>		May 2016	May 2014
<i>Outcome</i>		Postpartum haemorrhage	Postpartum haemorrhage
Kim 2016	Cohort	✓	
Hanley 2016	Cohort	✓	
Joseph 2015	Case control	✓	
Grzeskowiak 2015	Cohort	✓	
Lupattelli 2014	Cohort	✓	✓
Lindqvist 2014	Cohort	✓	
Palmsten 2013	Cohort	✓	✓
Reis 2010	Registry		✓
Salkeld 2008	Nested case control	✓	✓

Note: Review shown in shading is the foundation review.

AppD2.1.1.1.3 Neurodevelopmental outcomes – antidepressants

Nine SRs provide evidence of the association between antidepressant use during pregnancy and neurodevelopmental outcomes. Of these, five provide synthesised/pooled evidence and four provide results for individual studies only. Different SRs included a mix of different antidepressants and outcomes. For this Review, based on advice from the Expert Committee on Harms, only autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), speech/language, scholastic and motor disorders, intelligence quotient (IQ), behavioural problems, depression and anxiety are included as the most important outcomes for clinical decision-making.

Table AppD2-5 presents the specific outcomes, methodological characteristics and individual studies included in each of the nine SRs that reported on antidepressant exposure and neurodevelopmental outcomes. The individual studies included in the SRs vary substantially due to the different antidepressants and outcomes assessed.

To be considered for inclusion in the final evidence base from which the recommendations were made, a SR had to be considered of 'higher quality'. To be assessed as higher quality an analysis was required to have adjusted for potential confounders and attempted to minimise confounding by indication. One SR was assessed by us as providing higher quality evidence, and therefore the majority of SRs provided no evidence of a sufficient quality to provide the basis making the recommendations. A number of SRs did include analyses based on adjustment for potential confounders or attempts to minimise confounding by indication. These SRs were considered to be of moderate quality.

See **Section AppD3.1.1.1.3** of these Appendices for the full data extraction from the identified SRs. The data from moderate quality studies are also presented and discussed in **Section AppD4.1.1** of these Appendices, but do not provide the basis for making recommendations.

Table AppD2-5 Studies included in systematic reviews of antidepressants reporting neurodevelopmental outcomes

Assessment type	Quantitative assessment					Qualitative assessment only			
Included studies	NICE 2015	Kaplan 2016	Kobayashi 2016	Man 2015	Gentile 2015	El Marroun 2014	Previti 2014	Rais 2014 ³⁰	Gentile 2011b
Search date	Apr 2014	Dec 2015	Mar 2016	Jun 2014	Mar 2015	Sep 2013	May 2013	May 2013	Feb 2010
Interventions	SSRIs	SSRIs, non-SSRIs	SSRIs	SSRIs	SSRIs	Any ADs (also anxiolytics)	Any ADs	Any ADs	Any AD
Outcomes	Autism spectrum disorder and autism symptoms	Autism spectrum disorder	Autism spectrum disorder	Autism spectrum disorder	Autism spectrum disorder	Neuro-developmental outcomes	Neuro-developmental outcomes	Autism Spectrum Disorder	Neuro-developmental outcomes
Boukhris 2016		✓	✓						
Clements 2015		✓	✓		✓				
Man 2015			✓						
El Marroun 2014	✓	✓	✓		✓	✓			
Gidaya 2014		✓	✓	✓	✓				
Harrington 2014		✓	✓	✓	✓	✓			
Austin 2013						✓			
Batton 2013						✓			
Brummelte 2013						✓			
De Vries 2013						✓			
Hanley 2013							✓		
Hviid 2013		✓	✓	✓	✓				
Laugesen 2013						✓			
Leibovitch 2013						✓			
Pedersen 2013						✓			
Rai 2013		✓	✓	✓	✓	✓	✓	✓	
Smith 2013						✓			
Sorensen 2013		✓	✓	✓	✓	✓			
Weikum 2013a						✓			
Weikum 2013b						✓			
Eriksson 2012		✓	✓	✓					
Kallen 2012						✓			
Nulman 2012						✓			
Reebye 2012						✓			
Weikum 2012						✓			
Bellisima 2011						✓			
Casper 2011						✓	✓		
Croen 2011		✓	✓	✓	✓	✓		✓	
Field 2011							✓		
Galbally 2011						✓	✓		
Klinger 2011						✓			
Salisbury 2011						✓	✓		
Suri 2011						✓	✓		
Figuero 2010						✓			

³⁰ Used only to identify individual studies because meta-analysis inappropriately combined different outcomes.

Assessment type	Quantitative assessment					Qualitative assessment only			
Hale 2010						✓			
Makridis 2010							✓		
Oberlander 2010						✓			
Pedersen 2010						✓		✓	
Galbally 2009						✓			
Rampono 2009							✓		
Warnock 2009						✓			
Boucher 2008						✓			
Gidai 2008a						✓			
Gidai 2008b						✓			
Oberlander 2008						✓			
Ferreira 2007							✓		
Oberlander 2007									✓
Misri 2006						✓			✓
Oberlander 2005						✓			
Field 2004							✓		
Kallen 2004						✓			
Oberlander 2004						✓	✓		✓
Zeskind 2004							✓		
Casper 2003						✓			✓
Mortenson 2003						✓	✓		✓
Nulman 2002						✓			✓
Oberlander 2002						✓			
Reebye 2002							✓		✓
Morison 2001							✓		✓
Mattson 1999							✓		✓
Nulman 1997						✓	✓		✓
Nulman 1996							✓		✓
Viggedal 1993						✓			
Laegreid 1992a						✓			
Laegreid 1992b						✓			
Stika 1990						✓			

Abbreviations: AD, antidepressant; ASD, atrial septal defect; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VSD, ventricular septal defect.

AppD2.1.1.2 Individual studies – antidepressants

Due to the lack of data from higher quality studies, for all outcomes it was necessary to use data from individual studies. Data from individual studies was only eligible for inclusion if it was adjusted for potential confounders and attempted to minimise confounding by indication.

Forty-two studies representing data from 23 cohorts provide evidence of the association between antidepressant use during pregnancy and infant harms. The studies were largely retrospective, with a number being from state- or country-wide population-based cohorts. There were six prospective cohort studies.

Table AppD2-6 presents the characteristics of the 42 identified studies, grouped together by cohort (individual studies from the same cohort are separated in the table by dashed lines).

Table AppD2-6 Characteristics of included comparative observational studies of antidepressant harms

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Almeida 2016	Retrospective, population-based cohort study Quebec, Canada 1998–2002	Women aged 15 to 45 years with at least one pregnancy (N=41,964)	SSRI monotherapy SNRI monotherapy TCA monotherapy Other monotherapy Polytherapy	Unexposed Unexposed/depression diagnosis Hypothyroid medication	Miscarriage
Bérard 2016	Retrospective, population-based cohort study Quebec, Canada 1998–2009	Full-term singleton infants whose mothers were covered by the RAMQ drug plan for at least 12 months before and during pregnancy (N=145,241)	Citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline SNRI/TCA/MAOI/other ³¹	Unexposed/adjusted for depression or anxiety and other psychiatric disorders	Autism spectrum disorder
Boukhris 2016	Retrospective, population-based cohort study Quebec, Canada 1998–2009	Full-term singleton infants whose mothers were covered by the RAMQ drug plan for at least 12 months before and during pregnancy (N=145,456)	SSRIs SNRIs MAOIs TCAs Other ADs ³¹ ≥ 2 ADs	Unexposed/adjusted for prior AD use and other psychiatric disorders	Autism spectrum disorder
Bérard 2015	Retrospective, population-based cohort study Quebec, Canada 1998–2010	Pregnancies with a diagnosis of depression and/or anxiety or exposed to antidepressants in the 12 months prior (N=18,493)	Sertraline Non-sertraline SSRIs Non-SSRIs	Unexposed/depression or anxiety	Major congenital malformations (including nervous system, eye/ear/face/neck, circulatory system, respiratory system, digestive system, genital organs, urinary system, musculoskeletal system, cardiac malformations , ventricular/atrial septal defect, omphalocele, craniosyntosis, cleft palate)
Nakhai-Pour 2010	Retrospective nested case-control study Quebec, Canada 1998–2003	Cases: clinically detected spontaneous abortion (N=5,124) Controls: matched on index date and gestational age at spontaneous abortion (N=51,240)	SSRIs Paroxetine Sertraline Fluoxetine Citalopram Fluvoxamine Venlafaxine Polytherapy (SSRIs) TCAs SNRIs Other ADs ³² Polytherapy (classes)	Unexposed/adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	Spontaneous abortion

³¹ Includes bupropion, amoxapine, maprotiline, mirtazapine, trazodone and nefazodone.³² Includes serotonin modulators, monoamine oxidase inhibitors, tetracyclic piperazino-azepines, and dopamine and norepinephrine reuptake inhibitors.

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Ramos 2008	Retrospective, case-control study Quebec, Canada 1998–2002	Pregnant women who: (i) received at least one diagnosis of a psychiatric disorder (ICD-9) during pregnancy; (ii) have used antidepressants for at least 30 days in the year prior to pregnancy; and (iii) had a pregnancy ending with a delivery (live or stillbirth)	Any ADs Paroxetine SSRIs TCAs New antidepressants Co-exposure	Unexposed/psychiatric disorder (previous treatment with ADs)	Major congenital malformations
Petersen 2016	Retrospective, primary care-based cohort study THIN ³³ , UK 1990–2011	Mother-child pairs (live, singleton births) (N=209,135)	SSRIs	Unexposed Unexposed/stopped medication Other ADs	Congenital heart anomalies
Ban 2014a	Retrospective, primary care-based cohort study THIN, UK 1990–2009	Women prescribed antidepressants during early pregnancy, diagnosed with depression without antidepressant prescriptions, no antidepressants/depression during pregnancy (N=349,127)	SSRIs TCAs SSRIs and TCAs Fluoxetine Citalopram Paroxetine Sertraline Escitalopram	Unexposed Unexposed/ depression	Major congenital malformations
Ban 2012	Retrospective, primary care-based cohort study THIN, UK 1990–2009	Singleton pregnancies that ended in live birth, stillbirth, miscarriage or termination (N=512,574)	TCAs SSRIs Benzodiazepines Other classes Multiple classes	Unexposed Unexposed/depression or anxiety	Perinatal death Miscarriage Termination
Furu 2015	Retrospective, population-based cohort study Denmark, Finland, Iceland, Norway and Sweden 1996 to 2010	Women who gave birth to a live singleton infant Data presented here limited to women with at least two children with siblings discordant for both exposure and outcome (N=2288)	SSRIs or venlafaxine	No exposure (sibling cohort)	Congenital malformations Cardiac malformations Non-cardiac malformations
Kieler 2012	Retrospective population-based cohort study Denmark, Finland, Iceland, Norway and Sweden 1996–2007	Infants born after gestational week 33 (N=1,618,255)	SSRIs	Unexposed/subgroup of women with previous psychiatric hospitalisation	Persistent pulmonary hypertension
Grzeskowiak 2015	Retrospective, population-based case-control study Denmark 1996–2002	Singleton, live births (N=80,107)	Any ADs	Unexposed Unexposed/depression	Internalising and externalising problems

³³ The Health Improvement Network.

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Gidaya 2014	Retrospective, population-based case-control study Denmark 1997–2011	Cases: Children aged 2-15 identified from the DNHR and DPCR with 1 or more ICD-10 code F840, F841, F845, F848 or F849 diagnoses (childhood autism, atypical autism, Asperger's syndrome or pervasive developmental disorder) (N=5,215) Controls: Non-ASD children identified via the DCRS, matched on birth year and month (N=52,150)	SSRIs	Unexposed/adjusted for history of maternal depression	Autism spectrum disorder
Hviid 2013	Retrospective, population-based cohort study Denmark 1996–2009	Singleton, live births (N=626,875)	SSRIs	Unexposed/adjusted for psychiatric diagnoses before delivery	Autism spectrum disorders
Kjaersgaard 2013	Retrospective, population-based cohort study Denmark 1997–2008	Clinically recognised pregnancies (N=1,005,319)	Any ADs	Unexposed Unexposed/diagnosis of depression Unexposed/adjusted for history of severe mental disorder	Spontaneous abortion
Pedersen 2013	Retrospective, population-based cohort study Denmark 1997–2008	Singleton, live births (N=948)	Any ADS	Unexposed Unexposed/depression	Behavioural problems
Sørensen 2013	Retrospective, population-based cohort study Denmark 1996–2006	Live births (N=655,615)	Any ADs SSRIs	Unexposed Unexposed/hospital-diagnosed affective disorder Unexposed/sibling study	Autism spectrum disorder Childhood autism
Malm 2015	Retrospective, population-based cohort study Finland 1996 to 2010	Singleton live births (N= 845,345)	SSRIs	Unexposed Unexposed/psychiatric diagnosis	Preterm birth Small for gestational age Breathing problems
Malm 2016	Retrospective, population-based cohort study Finland 1996–2010	Singleton live births (N=64,754)	SSRIs	Unexposed Unexposed/ psychiatric disorder Unexposed/previous SSRI	Autism spectrum disorder ADHD Depression Anxiety
Brown 2016	Prospective, population-based cohort study Finland 1996-2010	Singleton live births (N=56,340)	SSRIs	Unexposed Unexposed/psychiatric diagnosis	Speech, scholastic and motor disorders

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Huybrechts 2014a	Retrospective insurance-based cohort study Medicaid, 46 States, US 2000–2007	Pregnant women enrolled in Medicaid during the period from 3 months before the last menstrual period through 1 month after delivery of live-born infant/s (N=949,504)	Any ADs SSRI Paroxetine Sertraline Fluoxetine TCAs SNRIs Bupropion Other ADs	Unexposed/depression	Cardiac malformation
Huybrechts 2015	Retrospective insurance-based cohort study Medicaid, 46 States, US 2000 to 2010	Completed pregnancies in women aged 12 to 55 years with live births (N=3,762,559)	SSRI Non-SSRI	Unexposed Unexposed/depression	Persistent pulmonary hypertension
Rai 2013	Retrospective, population-based, nested case-control study Stockholm county, Sweden 2001–2007	Cases: Children aged 0-17 years with ASD (via ICD-9/299 or ICD-10/F84; with or without an intellectual disability) identified via the Stockholm youth cohort (N=4429) Controls: Non-ASD children identified via the Stockholm youth cohort and matched 10:1 by age (year and month) and gender (N=43,277)	Any ADs SSRIs Non-selective MRIs	Unexposed/adjusted for any maternal psychiatric disorder	Autism spectrum disorder
Brandlistuen 2015	Retrospective, population-based sibling-controlled, cohort study Norway 1999-2010	All women in Norway giving birth between late 1999 and 2010 at hospitals and maternity units with more than 100 births annually were eligible for the study. (N=14,435 siblings)	Any ADs	Unexposed/sibling-controlled	Internalising and externalising behaviours
Clements 2015	Retrospective, state-based case-control study Partners HealthCare System, Massachusetts, US 1997–2010	Cases: Children aged 2-19 identified from the Partners HealthCare EHR with 1 or more ICD-9 code 299 (pervasive developmental disorder) diagnoses and were delivered at the MGH, BWH or NWH Controls: Non-ASD children delivered at the MGH, BWH or NWH matched on birth year, hospital, sex, insurance type (as proxy for SES), race/ethnicity and preterm/full-term status	Any ADs	Unexposed/adjusted for history of maternal depression	Autism spectrum disorder ADHD
Cole 2007a	Retrospective, health plan-based cohort study United Health Group, US 1995-2004	Women whose pregnancy resulted in a live birth and who were continuously enrolled in United Health Group for 1-year before delivery	Bupropion	Other ADs	Congenital malformations Cardiovascular malformations

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Cole 2007b	Retrospective, health plan-based cohort study United Health Group, US 1995-2004	Women whose pregnancy resulted in a live birth and who were continuously enrolled in United Health Group for 1-year before delivery	Paroxetine monotherapy Paroxetine mono- or polytherapy	Other AD monotherapy Other AD mono- or polytherapy	Congenital malformations; Cardiovascular malformations
Croen 2011	Retrospective, population-based case-control study KPNC, Northern California, US 1995–2002	<u>Cases</u> Children aged 2-8 identified from the KPNC with a diagnosis of ICD-9 code 299.0 (autism), 299.8 (Asperger syndrome) or 299.8 (pervasive developmental disorder – NOS) (N=298) <u>Controls</u> Non-ASD children identified via the KPNC, matched on sex, birth year and hospital of birth (N=1,507)	SSRIs	Unexposed; unexposed/adjusted for history of depression in year before delivery; unexposed/adjusted for any mental health disorder in year before delivery	Autism spectrum disorder
Djulus 2006	Prospective cohort study Teratogen information services; Canada, US, Israel, Italy, Australia Drug Safety Research Unit, UK 2002–2005	Women contacting a teratogen information service with depression (N=104)	Mirtazapine	Other ADs	Major malformations Spontaneous abortion Preterm birth
El Marroun 2014	Prospective, population-based cohort study Rotterdam, The Netherlands 2002–2006	Children who participated in pre- and postnatal follow-up of the ongoing Generation R Study (N=5,976)	SSRIs	Unexposed unexposed/depression	Pervasive developmental problems Autistic traits Social cognition Social communication Autistic mannerism
Grzeskowiak 2012	Retrospective cohort study South Australia, Australia 2000–2008	Women who gave birth to singleton, live-born infants	SSRIs	Unexposed/psychiatric illness No psychiatric illness	Preterm delivery Low birth weight Small for gestational age Neonate hospital admission Neonate length of hospital stay > 3 d
Harrington 2014	Prospective population-based case-control study California, US 2003–2010	<u>Cases</u> Children aged 2-5 with ASD or DD (confirmed) identified via California-based service providers (N=646) <u>Controls</u> Non-ASD children identified via state birth files and matched by age, gender and regional centre (N=320)	SSRIs	Unexposed; unexposed/history of anxiety/mood disorder	Autism spectrum disorder

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Hayes 2012	Retrospective cohort study Medicaid, Tennessee, US 1995–2007	Singleton pregnancies among women aged 15–44 years enrolled in the Tennessee Medicaid programme (N=228,876)	Any ADs SSRIs Non-SSRIs	Unexposed/adjusted for psychiatric diagnoses	Birth weight Gestational age Early gestational age Early preterm labour Respiratory distress Convulsions
Figueroa 2010	Retrospective, insurance-based cohort study US 1997–2006	Live deliveries (N=38,074 families)	SSRIs Bupropion Other ADs Anticonvulsants Benzodiazepines Other psychotropics	Unexposed/adjusted for maternal and paternal mental health diagnoses, mental health visits and psychotropic drug use	ADHD
Johnson 2016	Prospective cohort study Georgia, US 2010–2012	Women taking part in a study at the Emory Women's Health Program in Atlanta, Georgia with preschool-aged children (N=178)	SSRIs	Unexposed/treated at mental health centre	PDD Expressive language and cognitive functioning
Kieviet 2015	Prospective single-centre cohort study The Netherlands 2007 to 2012	Mothers who used an SSRI, SNRI or NaSSA during at least the third trimester of pregnancy admitted to the maternity ward	SSRI	SNRI	PNAS
Margulis 2013	Retrospective, population-based cohort CPRD, UK 1996–2010	Singleton pregnancies ending in a live birth (N=149,464)	SSRIs	Unexposed/ matched for mental health conditions	Cardiac malformations
Nulman 2015	Prospective cohort study Motherisk, Toronto, Canada NR	Women with depression who contacted the Motherisk service who had two children only, one exposed and one not exposed (N=45 sibling pairs)	SRIs (SSRIs and SNRIs)	Unexposed	IQ Behavioural problems
Oberlander 2006	Retrospective cohort study British Columbia Linked Health Database, Canada 1998–2001	All live births (N=119,547)	SSRIs	Unexposed Unexposed/depression	Caesarean section Birthweight Gestational age Preterm birth Small for gestational age Hospital stay Respiratory distress Feeding problems Jaundice Convulsions
Oberlander 2008a	Retrospective, population-based cohort study British Columbia Linked Health Database, Canada 1998–2001	Women who had registered live births (N=20,188)	SSRIs Benzodiazepines SSRIs + benzodiazepines	Unexposed Adjusted/matched on psychiatric variables	Major congenital anomalies Cardiovascular congenital defects Ventricular septal defects Atrial septal defects

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Oberlander 2008b	Retrospective, population-based cohort study British Columbia Linked Health Database, Canada 1998–2001	Women who had registered live births, matched on pre-pregnancy and prenatal characteristics (N=3,500)	SSRIs/early exposure	SSRIs/late exposure	Birth weight Gestational age Preterm birth Length of hospital stay Small for gestational age Caesarean section Respiratory distress Feeding problems
Simon 2002	Matched cohort study Washington State, US 1986–1998	Women whose pregnancy resulted in a live birth and who were continuously enrolled in Group Health Cooperative (a prepaid health service plan) for 360 days before delivery	SSRIs TCAs	Unexposed/matched on psychiatric variables	Major congenital malformations Minor congenital malformations Specific congenital malformations (genitourinary, cardiac , skeletal, vascular, craniofacial)

Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; BWH, Brigham and Women's Hospital; CPRD, Clinical Practice Research Datalink; DD, developmental delay; DNHR, Danish National Hospital Registry; DPCR, Danish Psychiatric Central Register; HER, electronic health record; ICD, International Statistical Classification of Diseases; IQ, intelligence quotient; KPNC, Kaiser Permanente Medical Care Program; MAOI, monoamine oxidase inhibitor; MGH, Massachusetts General Hospital; MRI, monoamine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NOS, not otherwise specified; NR, not reported; NWH, Newton-Wellesley Hospital; PNAS, poor neonatal adaptation syndrome; RAMQ, Régie de l'assurance maladie du Québec; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; THIN, The Health Improvement Network.

AppD2.1.2 **Antipsychotics****AppD2.1.2.1** ***Systematic reviews – antipsychotics***

The scoping and updated searches identified 10 SRs relating to the assessment of infant harms associated with antipsychotic use: six for exposure during pregnancy, three during lactation, and one during pregnancy and/or lactation. A summary of the characteristics of the identified SRs is presented in **Table AppD2-7**. Four SRs provide a quantitative assessment of the included studies (Coughlin 2015; Ennis 2015; NICE 2015; Terrana 2015). The remaining six, which provide a narrative assessment only of individual studies, have been used to identify original studies.

Table AppD2-7 Characteristics of the included systematic reviews of antipsychotic harms

Study ID	Study characteristics	Population	Exposure/s (subgroups)	Comparator/s (subgroups)	Outcomes [outcomes not in PICO]
SRs – Quantitative assessment					
Coughlin 2015	SR/MA 12 cohort studies	Pregnant women	Antipsychotics during pregnancy (any, aggregated reporting)	No exposure to antipsychotics	Major congenital malformations ³⁴ Cardiac malformations Miscarriage (spontaneous abortion/pregnancy loss early in gestation) Stillbirths/late pregnancy loss Preterm birth (<37 weeks) Small for gestational age <i>[Elective termination, large for gestational age, gestational age, birth weight]³⁵</i>
Ennis 2015	SR/MA 11 cohort studies/20 case reports/1 registry	Pregnant women	SGAs during 1 st trimester (disaggregated reporting for olanzapine, quetiapine, risperidone, aripiprazole)	None	Major congenital malformations ³⁶
NICE 2015	SR/MA (guideline) 12 cohort studies for antipsychotics	Pregnant women	Antipsychotics during pregnancy	None	Major congenital malformations Preterm delivery Stillbirth Miscarriage Infant Neurological Battery Bayley scales of infant development Small for gestational age <i>[Congenital malformations, large for gestational age, gestational diabetes, low birth weight, birth weight]</i>
Terrana 2015	SR/MA 12 cohort studies	Pregnant women	SGAs – during 1 st trimester for malformations (aggregated reporting for aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) ³⁷	Healthy women (i.e. no exposure)	Major congenital malformations Miscarriage Stillbirth Preterm birth (<37 weeks) Small for gestational age <i>[Gestational age, large for gestational age, birth weight, admissions to neonatal ICU]</i>
Additional SRs – narrative assessment					
Pacchiarotti 2016	SR 2 cohort/5 case series/19 case reports	Breast-feeding women with bipolar disorder	Antipsychotics during lactation (disaggregated for olanzapine, aripiprazole, quetiapine, risperidone, amisulpride, ziprasidone, clozapine, haloperidol, chlorpromazine, trifluoperazine, perphenazine, flupenthixol, zuclopenthixol)	None	Bayley Scales of Infant and Toddler Development scores Speech development delay <i>[Increased sedation, jaundice]</i>

³⁴ Major congenital malformations, structural, or functional abnormalities present at birth resulting in severe functional impairment, serious cosmetic defect, or death.³⁵ Maternal side effects were also reported (gestational diabetes, weight gain) but not meta-analysed.³⁶ Unclear whether this review intended to restrict events to 'major' malformations. The outcome is inconsistently referred to as 'major' or, more frequently, 'congenital' malformations, and this systematic review appears to have extracted data for 'any' malformations from at least some studies (e.g. hip dysplasia for olanzapine from Kulkarni 2014).³⁷ No studies identified for asenapine or paliperidone.

Study ID	Study characteristics	Population	Exposure/s (subgroups)	Comparator/s (subgroups)	Outcomes <i>[outcomes not in PICO]</i>
Mehta 2016	SR 4 cohort studies/ 16 case studies /series/ 1 summary paper ³⁸ / 1 pharmacovigilance registry	Pregnant or breast-feeding women	Clozapine during pregnancy and/or lactation	None	<u>Exposure during pregnancy:</u> Congenital malformations Miscarriage Neonatal seizures <i>[Other malformations, foetal decreased HRV, floppy infant syndrome]³⁹</i> <u>Exposure during lactation:</u> Speech development delay <i>[Agranulocytosis, increased sedation]</i> <u>Exposure during pregnancy and/or lactation:</u> Bayley Scales of Infant and Toddler Development scores <i>[1-min Apgar scores, disturbed sleep]</i>
Uguz 2016	SR 1 cohort studies /3 pharmacovigilance database studies/3 case studies/27 case reports	Breast-feeding women	SGAs during lactation (disaggregated for olanzapine, quetiapine, risperidone/ paliperidone, clozapine, aripiprazole, ziprasidone, amisulpride)	None	Development scores (unspecified) Speech development delay Motor development delay <i>[Agranulocytosis, increased sedation, tremor/shaking, poor suckling, disturbed sleep/insomnia, cessation of breast-feeding, diarrhea & nappy rash, jaundice, irritability]</i>
CADTH 2014	Non-SR (rapid review) 1 cohort study	Pregnant women with mental disorders	Aripiprazole during pregnancy	None	Preterm birth (cutoff unspecified) ⁴⁰ <i>[Abortions – type not specified]</i>
Gentile 2014a	SR 2 cohort studies/1 pharmacovigilance database/1 national health register/11 case reports	Pregnant women with gestational diabetes	SGAs during pregnancy (disaggregated for clozapine, olanzapine, quetiapine, risperidone, ziprasidone, amisulpride, asenapine, amisulpride, aripiprazole, and any SGA)	None	Major malformations Stillbirth Preterm birth (<37 weeks) Neonatal seizures Neonatal respiratory failure/distress Neurodevelopmental delay <i>[Other malformations, neonatal hypoglycaemia, foetal arrhythmia, shoulder dystocia, floppy infant syndrome, coma, heart murmur, umbilical hernia]⁴¹</i>
Klinger 2013	SR 4 cohort studies /12 case series/28 case reports/1 pharmaceutical registry (3 studies)	Breast-feeding women	Antipsychotics during lactation	None	Development scores (unspecified) Speech development <i>[Agranulocytosis, increased drowsiness and lethargy, slow weight gain]</i>

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviation: HRV, heart rate variability; ICU, intensive care unit; MA, meta-analysis; min, minute; NICE, National Institute of Health and Care Excellence; ns, not specified; PICO, population–intervention–comparator–outcome; SGA, second generation antipsychotic; SR, systematic review.

³⁸ Referred to as a case series by Klinger 2013.

³⁹ Maternal side effects also reported: gestational diabetes; reduced haemoglobin; pregnancy-induced hypertension; excess weight gain.

⁴⁰ Cut-off not reported in rapid review, nor in abstract of original study (Manakova 2011). No electronic holdings at Sydney University for full text of original study.

⁴¹ Maternal side effects reported: gestational diabetes.

AppD2.1.2.1.1 Malformations – antipsychotics

Six SRs provide evidence of the association between antipsychotic use and infant malformations. Of these, four report synthesised/pooled evidence and two provide narrative results for individual studies only. The SRs included a mix of different antipsychotics, and malformation outcomes assessed include any congenital malformation, major malformations, and cardiac malformations (including atrial septal malformations); however, for this guideline, only major and cardiac malformations are included.

Table AppD2-8 shows methodological characteristics for each SR, the type of malformation outcomes reported, and the individual studies that report these outcomes. Included studies vary substantially across the different SRs. The Ennis 2015 SR includes the greatest number of original studies, at 32, as it is the only SR to report an absence of malformations. Across the other quantitative SRs, only three studies are common to all. Most of the study non-overlap can be attributed to either differences in the antipsychotics investigated (any versus second generation only) or outcomes investigated (e.g. cardiac versus major malformations only) or the date of the literature search.

To be considered for inclusion in the final evidence base from which the recommendations were made, a SR had to be considered of 'higher quality'. To be assessed as higher quality, an analysis was required to have adjusted for potential confounders and attempted to minimise confounding by indication. The pooled analyses in the identified SRs used data unadjusted for confounders, or a mix of adjusted and unadjusted data, and neither of the quantitative SRs used control groups restricted by indication. Therefore, no SRs were assessed by us as providing evidence for malformation outcomes of sufficient quality to provide the basis for making recommendations.

Table AppD2-8 Studies included in systematic reviews of antipsychotics reporting malformations

Assessment type		Quantitative assessment				Narrative assessment	
Included studies	Study design	Terrana 2015	Ennis 2015	NICE 2015	Coughlin 2015	Mehta 2016	Gentile 2014a
Search date		Dec 2014	May 2014	April 2014	Jun 2013	Jun 2016	April 2014
Interventions		SGAs	SGAs (disaggregated) ⁴²	Antipsychotics (any)	Antipsychotics (any)	Clozapine	SGAs (disaggregated) ⁴³
Outcomes		Congenital: major	Congenital; major ⁴⁴	Congenital; major; any	Congenital: major ⁴⁵ ; cardiac	Congenital (major/minor not specified); cardiac	Major
Analysed adjusted data?		✗	✗	✗	✗	-	-
Compared to an untreated/with mental health disorder population		✗	✗	✗		-	-
Bellet 2013	comparative cohort	✓					
Habermann 2013	comparative cohort	✓	✓	✓	✓		
Källén 2013	comparative cohort				✓		
Paulus 2013	comparative cohort	✓					
Peng 2013	comparative cohort		✗				
Sadowski 2013	comparative cohort	✓	✓	✓	✓		
Bodén 2012a ⁴⁶	comparative cohort			✓			
Vial 2009	comparative cohort	✓					
Reis 2008	comparative cohort	✓		✓			
Diav-Citrin 2005	comparative cohort			✓	✓		
McKenna 2005	comparative cohort	✓	✓	✓	✓	✓	
Paulus 2005	comparative cohort	✓					
Rumeau-Rouquette 1977	comparative cohort				✓		
Slone 1977	comparative cohort				✓		
Manakova 2011	comparative cohort		✗				
Yaris 2005	comparative cohort		✗				
Novartis registry (year NR)	cohort – non-comp.					✓	
Swedish Birth Registry 2014	cohort – non-comp.		✓				
Brunner 2013	cohort – non-comp. ⁴⁷		✓				
Goldstein 2000	cohort – non-comp. ⁴⁷		✗				
Kulkarni 2014	cohort – non-comp.		✓			✓	
Wichman 2009	cohort – non-comp.		✓				
Coppola 2007	cohort – non-comp.		✓				
Twaites 2007	cohort – non-comp.		✗				
Tenyi 2013	case report		✗				
Grover 2012	case report		✗				

⁴² Disaggregated for olanzapine, quetiapine, risperidone, aripiprazole.⁴³ Disaggregated for clozapine, olanzapine, quetiapine, risperidone, ziprasidone, asenapine, amisulpride, aripiprazole, and any SGA.⁴⁴ Unclear whether this review intended to restrict events to 'major' malformations. The outcome is inconsistently referred to as 'major' or, mostly, 'congenital' malformations, and this systematic review appears to have extracted data for 'any' malformations from at least some studies (e.g. hip dysplasia for olanzapine from Kulkarni 2014).⁴⁵ Major congenital malformations, structural, or functional abnormalities present at birth resulting in severe functional impairment, serious cosmetic defect, or death.⁴⁶ Reports major malformations but intervention not restricted to antipsychotics (extended to lithium and anticonvulsants). NICE 2015 referred to this study as Bodén 2012A, and included it in meta-analyses of any malformations (i.e. not major malformations).⁴⁷ Qualitative comparisons were made between the study cohort and historic reports of rates from the general population.

Assessment type		Quantitative assessment				Narrative assessment	
Widschwendter 2012	case report		✖				
Gentile 2011	case report		✖				
Nguyen 2011	case report		✖				
Lutz 2010	case report		✖				
Mendhekar 2008	case report		✖				
Mervak 2008	case report		✖				
Rodriguez-Salgado 2008	case report		✖				
Kim 2007	case report		✖				
Klier 2007	case report		✖				
Yeshayahu 2007	case report		✓				
Arora 2006	case report		✓				
Dabbert 2006	case report		✖				
Gentile 2006	case report		✖				
Menhhekar 2006b	case report		✖				
Spyropoulou 2006	case report		✓				
Karakula 2004	case report					✓	✓
Ratnayake 2002	case report		✖				
Tenyi 2002	case report		✖				
Vavrusova and Konikova 1998	case report					✓	
Stoner 1997	case series					✓	
Dev and Krupp 1995	review paper					✓	

Abbreviation: NICE, National Institute of Health and Care Excellence; non-comp., non-comparative study; SGA, second generation antipsychotic.

✖ indicates an absence of adverse events was reported for this study.

AppD2.1.2.1.2 Pregnancy and birth outcomes – antipsychotics

Six SRs provide evidence of the association between antipsychotic use and pregnancy or birth outcomes; three quantitative and three narrative reviews. A large array of outcomes is reported across these studies; those of relevance to the current Review are miscarriage, stillbirth, neonatal death, preterm birth (< 37 weeks), small for gestational age, neonatal seizures and neonatal respiratory failure/distress. Over 13 additional reported outcomes are not extracted for the current Review.

Table AppD2-9 shows the methodological characteristics for each SR, the pregnancy and birth outcomes reported, and the individual studies that report these outcomes; this table includes studies reporting outcomes not relevant to the current Review. Compared with the SRs reporting malformation outcomes, there is substantially more overlap of included comparative studies across the quantitative reviews reporting pregnancy and birth outcomes. The larger number of included studies in Coughlin 2015 and NICE 2015 is consistent with the broader range of included interventions.

To be considered for inclusion in the final evidence base from which the recommendations were made, a SR had to be considered of 'higher quality'. To be assessed as higher quality, an analysis was required to have adjusted for potential confounders and attempted to minimise confounding by indication. The pooled analyses in the identified SRs used data unadjusted for confounders, or a mix of adjusted and unadjusted data, and neither of the quantitative SRs used control groups restricted by indication. Therefore, no SRs were assessed by us as providing evidence for pregnancy and birth outcomes of sufficient quality to provide the basis for making recommendations.

Table AppD2-9 Studies included in systematic reviews of antipsychotics reporting pregnancy and birth outcomes

Assessment type -		Quantitative assessment			Narrative assessment only		
Included studies	Study design	Terrana 2015	NICE 2015	Coughlin 2015	Mehta 2016	CADTH 2014	Gentile 2014a
Search date		Dec 2014	April 2014	Jun 2013	Jun 2016	Oct 2014	April 2014
Interventions		SGAs	Antipsychotics (any)	Antipsychotics (any)	Clozapine	Aripiprazole	SGAs (disaggregated)
Outcomes		Miscarriage; stillbirth; preterm birth; gestational age; birth weight; small/large for gestational age; neonatal intensive care.	Preterm delivery; stillbirth; miscarriage; Infant Neurological Battery; Bayley scales of infant development; small/large for gestational age; gestational diabetes; low birth weight; birth weight	Miscarriage ⁴⁸ ; elective abortion; stillbirth; preterm birth; gestational age; birth weight; small/large for gestational age.	Miscarriage; stillbirth; neonatal death; foetal decreased HR; foetal arrhythmia; shoulder dystocia; birth weight; floppy infant syndrome; neonatal seizures; neonatal respiratory failure/distress; heart murmur; other birth outcomes.	Abortions (type not specified); preterm birth	Stillbirth; foetal arrhythmia; preterm birth; hypoglycaemia; shoulder dystocia; floppy infant syndrome; neonatal seizures; neonatal respiratory failure/distress; coma; heart murmur; umbilical hernia.
Analysed adjusted data?		✗	✗	✗	-	-	-
Compared to an untreated/with mental health disorder population		✗	✗	✗	-	-	-
Shao 2015	comparative cohort				✓		
Bellet 2013	comparative cohort	✓					
Habermann 2013	comparative cohort	✓	✓	✓			
Källén 2013	comparative cohort			✓			
Peng 2013	comparative cohort		✓ ⁴⁹				
Sadowski 2013	comparative cohort	✓	✓	✓			
Bodén 2012b	comparative cohort	✓	✓	✓	✓		
Hironaka 2011	comparative cohort	✓					
Manakova 2011	comparative cohort					✓	
Lin 2010	comparative cohort	✓	✓	✓			
Newham 2008	comparative cohort	✓	✓	✓			
Reis 2008	comparative cohort		✓	✓			
Diav-Citrin 2005	comparative cohort		✓	✓			
McKenna 2005	comparative cohort		✓	✓	✓		
Paulus 2005	comparative cohort			✓			
Auerbach 1992 ⁵⁰	comparative cohort		✓				
Slone 1977	comparative cohort			✓			
Goldstein 2000	cohort – non-comp. ⁵¹						✓
Wichman 2009	cohort – non-comp.						✓
Duran 2008	case series				no AE		
Stoner 1997	case series				✓		
Dev and Krupp 1995	case series				✓		

⁴⁸ Spontaneous abortion or pregnancy loss early in gestation.⁴⁹ Birth weight is the only pregnancy/birth outcome reported extracted by NICE 2015 from this study.⁵⁰ Only birth weight extracted from this study by NICE 2015, but this study does report developmental outcomes, which are extracted in Section Error! Reference source not found..⁵¹ Qualitative comparisons were made between the study cohort and historic reports of rates from the general population.

Assessment type		Quantitative assessment			Narrative assessment only		
Burt 2010	case report						✓
Guyon 2015	case report				✓		
Gilbert 2009	case report						✓
Klys 2007	case report				✓		
Doherty 2006	case report				✓		
Karakula 2004	case report				✓		✓
Mendhekar 2003	case report				✓		
Yogev 2002	case report				✓		
Dickson and Hogg 1998	case report				✓		✓
Vavrusova and Konikova 1998	case report				✓		
Di Michele 1996	case report				✓		
Waldman and Safferman 1993	case report				✓		✓

Abbreviation: CADTH, Canadian Agency for Drugs and Technologies in Health; NICE, National Institute of Health and Care Excellence; non-comp., non-comparative study; SGA, second generation antipsychotic.

* indicates an absence of adverse events was reported for this study.

AppD2.1.2.1.3 Neurodevelopmental outcomes – antipsychotics

One quantitative SR and four narrative SRs reported developmental outcomes – two investigated antipsychotic exposure during lactation, and three during pregnancy.⁵² Most studies were case reports with limited study overlap (**Table AppD2-10**).

For exposure during pregnancy, three studies were comparative in design; Peng 2013, Johnson 2012 and Shao 2015, with the latter being a subgroup analysis of the exposed cohort in Peng 2013. For exposure during lactation, one study was comparative, examining antipsychotic use in mothers with either breast-feeding or bottle-feeding infants (i.e. both the control and intervention groups had a mental health disorder and were on antipsychotic medication). Most women were treated with haloperidol, and this study was included in the Pacchiarotti 2016 review but not the Uguz 2016 review, which was limited to SGAs.

To be considered for inclusion in the final evidence base from which the recommendations were made, a SR had to be considered of 'higher quality'. To be assessed as higher quality, an analysis was required to have adjusted for potential confounders and attempted to minimise confounding by indication. As the comparative studies examined different outcomes, no estimates were pooled

The pooled analyses in the identified SRs used data unadjusted for confounders, or a mix of adjusted and unadjusted data, and neither of the quantitative SRs used control groups restricted by indication. Therefore, no SRs were assessed by us as providing evidence for neurodevelopmental outcomes of sufficient quality to provide the basis for making recommendations.

No data was extracted from these systematic reviews, but data from the original studies (Peng 2013, Johnson 2012, Shao 2015) was extracted. (see **Section AppD3.1.2.2.3** of these Appendices).

⁵² While Mehta 2016 included studies of exposure during pregnancy or lactation, only studies of exposure during pregnancy report developmental outcomes in this systematic review.

Table AppD2-10 Studies included in systematic reviews of antipsychotics reporting neurodevelopmental outcomes

Assessment type	-	Quantitative assessment	Narrative assessment			
Included studies	Study design	NICE 2015	Mehta 2016	Gentile 2014a	Pacchiarotti 2016	Uguz 2016
Search date		April 2014	Jun 2016	April 2014	Feb 2016	Jun 2015
Period of exposure		Pregnancy	Pregnancy ⁵³	Pregnancy	Lactation	Lactation
Interventions		Antipsychotics (any)	Clozapine	SGAs (disaggregated) ⁵⁴	Antipsychotics during lactation (disaggregated) ⁵⁵	SGAs during lactation (disaggregated) ⁵⁶
Outcomes		Infant Neurological Battery; Bayley Scales of Infant Development	Bayley Scales of Infant and Toddler Development scores; speech developmental delay 1-min Apgar scores	Neurodevelopment delay	Bayley Scales of Infant and Toddler Development scores; speech developmental delay	Development scores (unspecified); speech developmental delay; neurodevelopment delay
Analysed adjusted data?		✗	-	-	-	-
Compared to an untreated/with mental health disorder population?		✗	-	-	-	-
Shao 2015	comparative cohort		✓			
Peng 2013	comparative cohort	✓				
Johnson 2012	comparative cohort	✓ ⁵⁷				
Yoshida 1998	comparative cohort (breast fed vs bottle fed) ⁵⁸				✓	
Gilbert 2009	case report			✓		
Mendhekar 2007	case report				✓	✓
Mendhekar 2006a	case report		✓			
Misri 2006	case series				✓	✓
Gupta and Grover 2004	case report		✗			
Karakula 2004	case report		✓	✓		
Kirchheiner 2000	case report					✓
Tényi and Trixler 1998	case report		✗			

Abbreviation: NICE, National Institute of Health and Care Excellence; SGA, second generation antipsychotic.

✗ indicates an absence of adverse events was reported for this study.

⁵³ This SR was also inclusive of exposure during lactation, but exposure was during pregnancy in all studies reporting these developmental outcomes.

⁵⁴ Disaggregated for clozapine, olanzapine, quetiapine, risperidone, ziprasidone, amisulpride, asenapine, amisulpride, aripiprazole, and any SGA.

⁵⁵ Disaggregated for olanzapine, aripiprazole, quetiapine, risperidone, amisulpride, ziprasidone, clozapine, haloperidol, chlorpromazine, trifluoperazine, perphenazine, flupenthixol, zuclopenthixol.

⁵⁶ Disaggregated for olanzapine, quetiapine, risperidone/ paliperidone, clozapine, aripiprazole, ziprasidone, amisulpride.

⁵⁷ Score as a continuous outcome reported by NICE 2015, but categorical data was also reported by this study.

⁵⁸ All nine breast-feeding mothers exposed to haloperidol, three also to clozapine. Control group (n = 18) on haloperidol but bottle-feeding.

AppD2.1.2.1.4 Other outcomes – antipsychotics

Three SRs provided narrative reviews of studies reporting other outcomes – two investigated antipsychotic exposure during lactation while one (Mehta 2016) included studies of exposure during pregnancy or lactation.

Table AppD2-11 shows the methodological characteristics for each SR and the included studies. A large array of outcomes is reported across these studies – those of relevance to the current Review are tremor or shaking, agranulocytosis, and increased sedation, drowsiness or lethargy. **Table AppD2-11** shows all included studies regardless of relevance of outcomes to the current Review.

Nine of the ten total included studies are in Uguz 2016 (the tenth investigated fetal exposure so was ineligible for Uguz 2016). Pacchiarotti 2016 did not include case series, so included a single study only. Only one study, Shao 2015, was comparative – a subgroup analysis of the exposure cohort from Peng 2013. Shao 2015 compared infants of mothers with schizophrenia exposed to clozapine with those exposed to other antipsychotics during pregnancy. Only the Mehta 2016 SR includes this study, and results for the clozapine-exposed group only are extracted (disturbed sleep).

To be considered for inclusion in the final evidence base from which the recommendations were made, a SR had to be considered of 'higher quality'. To be assessed as higher quality, an analysis was required to have adjusted for potential confounders and attempted to minimise confounding by indication. None of the SRs presented pooled estimates – only one study from one SR was comparative (Shao 2015), and while the comparator group was restricted by indication, only crude results were reported. Therefore, no SRs were assessed by us as providing evidence for postnatal outcomes of sufficient quality to provide the basis for making recommendations.

No data was extracted from these systematic reviews, and data from the single comparative included study (Shao 2015) was not extracted as the postnatal outcome was out of scope (parental report of disturbed sleep and labile state during first 2 months).

Table AppD2-11 Studies included in systematic reviews of antipsychotics reporting postnatal harms (exposure during lactation)

Assessment type -		Narrative assessment		
Included studies	Study design	Mehta 2016	Pacchiarotti 2016	Uguz 2016
Search date		Jun 2016	Feb 2016	Jun 2015
Interventions		Clozapine	Antipsychotics during lactation (disaggregated) ⁵⁹	SGAs during lactation (disaggregated) ⁶⁰
Period of exposure		Pregnancy and/or lactation	Lactation	Lactation
Outcomes		Agranulocytosis; increased sedation/ drowsiness; disturbed sleep/ insomnia	Increased sedation/ drowsiness; jaundice	Agranulocytosis; increased sedation/ drowsiness; tremor/ shaking; poor suckling; disturbed sleep/ insomnia; cessation of breast-feeding; diarrhea and nappy rash; jaundice; irritability
Analysed adjusted data?		-	-	-
Compared to an untreated/with mental health disorder population		-	-	-
Shao 2015	comparative cohort	✓		
Brunner 2013	cohort – non-comp. ⁶¹			✓
Goldstein 2002	cohort – non-comp. ⁶¹			✓
Goldstein 2000	cohort – non-comp.		✓	✓
Dev and Krupp 1995	case series	✓		✓
Teoh 2011	case report			✓
Watanabe 2011	case report			✓
Ambresin 2004	case report			✓
Ilett 2004	case series			✓
Kirchheiner 2000	case report			✓

Abbreviation: non-comp., non-comparative study; SGA, second generation antipsychotic.

Note: a fifth systematic review, Klinger et al 2013, reported infant harms but, in most instances, the authors did not ascribe outcomes to particular studies. Klinger 2013 reported pharmacokinetic data in addition to infant harms (agranulocytosis; increased sedation/ drowsiness, slow weight gain) and developmental outcomes (development scores (unspecified), speech developmental delay), and included 45 studies (19 of which were unique to this Review). Insufficient information was provided to determine which studies reported health outcomes and which reported pharmacokinetics.

⁵⁹ Disaggregated for olanzapine, aripiprazole, quetiapine, risperidone, amisulpride, ziprasidone, clozapine, haloperidol, chlorpromazine, trifluoperazine, perphenazine, flupenthixol, zuclopenthixol.

⁶⁰ Disaggregated for olanzapine, quetiapine, risperidone/ paliperidone, clozapine, aripiprazole, ziprasidone, amisulpride.

⁶¹ Qualitative comparisons were made between the study cohort and historic reports of rates from the general population.

AppD2.1.2.2 Individual studies – antipsychotics

None of the pooled risk estimates reported by the systematic reviews exclusively used data adjusted for confounders, nor restricted comparator groups to unexposed women with a mental health disorder diagnosis. Therefore, it was necessary to assess the evidence from original comparative studies. **Table AppD2-12** shows the study characteristics of original studies identified from the systematic reviews and the updating literature search from 2014.

Twenty-six comparative studies from systematic reviews were identified, of which eight were excluded; three for confounded intervention (Bodén 2012a, Manakova 2011, Auerbach 1992), three for publication type (conference abstracts; Paulus 2015, Vial 2009, Paulus 2005), one for small size (N = 30; Yoshida 1998)⁶² and one for using historical rates only for comparison (Goldstein 2000). A further six studies were identified from the updating literature search (as indicated), making a total of 24 individual comparative studies of antipsychotics for infant harms included in this Review.

⁶² All nine breast-feeding mothers exposed to haloperidol, three also to clozapine. Control group (n = 18) on haloperidol but bottle-feeding.

Table AppD2-12 Characteristics of the included comparative observational studies of antipsychotics harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s Timing of exposure	Comparator/s	Outcomes [outcomes not in PICO]
Cohen 2016 <i>identified by update search</i>	Prospective hospital-based pregnancy registry for SGAs US 2008–2014	Pregnant women aged 18–45, recruited through provider referral, self-referral, and the Center’s web site. Analysis based on live births. (N = 303)	SGAs <u>Timing:</u> 1 st trimester (<13 weeks)	Majority with a psychiatric illness history, being treated with psychotropic medications other than SGAs. ⁶³	Major malformations
Huybrechts 2016 <i>identified by update search</i>	Retrospective cohort nested in the nationwide Medicaid Analytic Extract database US 2000–2010	Women aged 12–55 enrolled in Medicaid from 3 months before their last menstrual period through at least 1 month after delivery of live-born infant. Infants were required to have coverage through Medicaid for the first 3 months of life unless they died sooner. (N = 1,341,715)	SGAs FGAs <u>Timing:</u> 1 st trimester	Two comparator groups: <ul style="list-style-type: none"> • Unexposed • Unexposed, restricted to schizophrenia, bipolar disorder or psychosis⁶⁴ 	Major malformations Cardiac malformations
Petersen 2016a ⁶⁵ <i>identified by update search</i>	Retrospective cohort, linked primary care databases ⁶⁶ The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD) UK 1995–2012	Mother-infant pairs: live-birth singleton infants of mothers registered at practice for at least 6-months prior to pregnancy and throughout pregnancy (N = 211,748)	Any antipsychotic SGAs FGAs <u>Timing:</u> two cohorts: <ul style="list-style-type: none"> • early (31–105 days) • 3rd trimester both exposed between 4 and 24 months before start of pregnancy	Two comparator groups: <ul style="list-style-type: none"> • Unexposed • 4–24 months’ prior exposure, discontinued at least 4 months before start of pregnancy 	Major congenital malformation Neurodevelopment/behaviour disorders [poor birth outcomes; ⁶⁷ transient poor birth outcomes ⁶⁸]
Bellet 2015 ⁶⁹	Prospective cohort, matched controls Paris TIS, Terappel pharmacovigilance database France 2004–2011	Women pregnant at first contact (N = 258)	Aripiprazole <u>Timing:</u> embryogenesis (4–10 weeks)	Unexposed – matched for age (±2 years) and gestational age at first contact (±2 weeks).	Major congenital malformation Miscarriage⁷⁰ Preterm (<37 weeks) Small for gestational age [elective abortion]

⁶³ Only 1.1% of women in the comparator group (1/89) was taking first generation antipsychotics.⁶⁴ The exposed group was also restricted in this sensitivity analysis. Diagnoses were from inpatient and outpatient records.⁶⁵ Data was extracted from the HTA (Petersen 2016a) but not from the study publication in Schizophrenia Research (Petersen 2016b). The latter reports unadjusted absolute risk and risk differences for typical and atypical antipsychotics, and notes the findings are similar in the two groups. These outcomes were not extracted as they are unadjusted and the composite outcomes reported do not match those reported in the HTA.⁶⁶ Two studies performed, one in a pregnant women cohort reporting maternal outcomes, and another in a mother-child cohort (live births), with the latter study reporting infant harms and extracted here.⁶⁷ Composite outcome of prematurity, low Apgar score, low birthweight and small for gestational age.⁶⁸ Composite outcome of tremor, agitation, breathing and muscle tone problems.⁶⁹ Identified by inclusion or prior poster presentation of this data (Bellet 2013) included in Terrana 2016 SR.⁷⁰ Spontaneous abortion before 22 weeks’ gestation.

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s Timing of exposure	Comparator/s	Outcomes [outcomes not in PICO]
Clements 2015 <i>identified by update search</i>	Retrospective, state-based case-control study Partners HealthCare System, Massachusetts, US 1997–2010	Cases: Children aged 2-19 identified from the Partners HealthCare electronic health record with 1 or more ICD-9 code 299 (pervasive developmental disorder) or ICD-9 code 314.x (attention-deficit disorders) diagnoses and were delivered at the MGH, BWH or NWH. Controls: Non-ASD/ADHD children delivered at the MGH, BWH or NWH matched on birth year, hospital, sex, insurance type (as proxy for SES), race/ethnicity and preterm/full-term status.	Any antipsychotics	Unexposed – adjusted for history of maternal depression	Autism spectrum disorder ADHD
Shao 2015	Subgroup analysis of exposed group in Peng 2013 Second Xiangya Hospital, Central South University China 2007–2010	Live-birth singleton infants of mothers with schizophrenia taking SGAs (exposure group from Peng 2013) (N = 63)	Clozapine for schizophrenia <u>Timing</u> : pregnancy	SGAs (not clozapine) for schizophrenia <u>Timing</u> : pregnancy	Bayley Scales of Infant and Toddler Development (Bayley-III) [disturbed sleep, labile state, Apgar score, brain circumference, weight, height, gestational age, complications during delivery, neonatal complications]
Sorensen 2015 <i>identified by update search</i>	Retrospective, linked, population-based cohort Denmark 1997–2008	Clinically recognised pregnancies in nationwide health registry (N = 1,005,319)	Any antipsychotics Individual antipsychotics ⁷¹ <u>Timing</u> : 30 days before start of pregnancy to one day prior to spontaneous abortion/ stillbirth/ birth	Two comparator groups: • Unexposed • Unexposed, restricted to bipolar disorder, including mania or schizophrenia ⁷²	Stillbirth Miscarriage (spontaneous abortion) [induced abortion, live births]

⁷¹ Adjusted results reported (and extracted here) for chlorprothixene, flupenthixol, perphenazine, zuclopenthixol, levomepromazine, quetiapine, olanzapine. Unadjusted results reported (not extracted here) for lithium, risperidone, aripiprazole, ziprasidone, haloperidone, prochlorperazine, fluphenazine, chlorpromazine.

⁷² The exposed group was also restricted in this sensitivity analysis. Excludes diagnoses made by general practitioners or private psychiatrists.

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s Timing of exposure	Comparator/s	Outcomes [outcomes not in PICO]
Vigod 2015 <i>identified by update search</i>	Retrospective, linked, population-based, hdPS-matched cohort Ontario, Canada 2003–2012	Live-born or stillborn singleton infants of mothers covered under the provincial drug plan during the pregnancy ⁷³ (N = 41,523; matched cohorts 1,021 each)	Any antipsychotic <u>Timing</u> : ≥2 consecutive prescriptions during pregnancy, at least one of which was filled in the 1 st or 2 nd trimester	Unexposed – matched for high-dimensional propensity score and age (±3 years)	Preterm (<37; <32; <28 weeks) Small for gestational age (<3rd; <10th centile birth weight) Stillbirth Respiratory distress syndrome (not acute)⁷⁴ Poor neonatal adaptation syndrome Seizures Mortality <90 days [any congenital malformations, large for gestational age, sepsis, intraventricular haemorrhage, persistent fetal circulation, congenital or neonatal infection; Gestational diabetes, hypertensive disorders of pregnancy, venous thromboembolism, various other non-infant outcomes]
Habermann 2013	Prospective cohort, matched controls Teratology Information Service Berlin, Germany 1997–2009	Women exposed to at least 1 SGA during pregnancy (FGAs allowed) (N = 1967)	SGAs FGAs (excluding SGAs) <u>Timing</u> : pregnancy	Unexposed, matched to SGA group ("matched to the study cohort p.a." – not further described)	Major malformations Major malformations (1st trimester exposure) Cardiac malformations Miscarriage Stillbirth⁷⁵ Neonatal death Preterm (<37 weeks) [minor malformations, elective termination, birth weight, postnatal disorders ⁷⁶]
Källén 2013	Retrospective, linked, population-based cohort of live births. Medical Birth Register, Register of Birth Defects, Hospital Discharge Register, Register of Prescribed Drugs Sweden 1996–2011	Live-birth infants of mothers reporting use of antipsychotics (neuroleptics) during early pregnancy, or dispensed drug in later pregnancy (N = 1,575,847)	Antipsychotics or lithium ⁷⁷ Also, reported separately for haloperidol, perphenazine, flupenthixol and olanzapine. <u>Timing</u> : early pregnancy; 2 nd or 3 rd trimester	Unexposed	Relatively severe malformations (may include malformations not strictly classifiable as major⁷⁸) Cardiac defects Septal defects Preterm birth <37 weeks, Small for gestational age Respiratory diagnosis [abruption of placenta, haemorrhage around delivery, large for gestational age, induction of delivery, low birth weight any neonatal diagnosis, hypoglycaemia, jaundice, CNS diagnoses, low 5 min Apgar score.]

⁷³ To ensure that all participants were covered under the provincial drug plan during the index pregnancy, only those who had filled a provincially funded drug prescription within 180 days before pregnancy and one during pregnancy or within 180 days of delivery were included.

⁷⁴ No instances of acute respiratory distress observed in either of the matched groups.

⁷⁵ The cumulative incidence of livebirths was also reported, but this outcome is impacted by elective abortion and miscarriage.

⁷⁶ Considering liveborns exposed at least during the last gestational week, and categorised as disorders of the respiratory system, digestive system, cardiac disorder (other than malformations), nervous system or multiple systems.

⁷⁷ Data aggregated for antipsychotics and lithium, which is the most commonly used drug in this group (17% of infants exposed to lithium). Dixyrazine and prochlorperazine, used for nausea and vomiting during pregnancy, are excluded from the main treatment group results but are reported separately (results for these two drugs are not extracted in the current Review).

⁷⁸ Excludes the following common and clinically little important conditions: preauricular appendices, tongue tie, patent ductus at preterm birth, single umbilical artery, undescended testicle, unstable hip or hip (sub)luxation, and nevus. Unclear whether included malformations are classifiable as major.

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s Timing of exposure	Comparator/s	Outcomes [outcomes not in PICO]
Peng 2013	Prospective, longitudinal, cohort study Second Xiangya Hospital, Central South University China 2007–2010	Women with schizophrenia and singleton pregnancy taking antipsychotics during pregnancy (N = 154 infants)	SGAs for schizophrenia <u>Timing</u> : throughout pregnancy (not further defined)	Unexposed, healthy – matched for age (± 1 y) and education	Major malformations (<i>reported none in either group</i>) Bayley Scales of Infant and Toddler Development (Bayley-III) [Apgar score, brain circumference, weight, height, gestational age]
Sadowski 2013	Prospective cohort, matched controls Motherisk Program, Hospital for Sick Children ⁷⁹ Toronto, Canada 2005–2009	Women who contacted the service inquiring about the safety of an SGA and confirmed use for ≥ 4 weeks of pregnancy (N = 266)	SGAs <u>Timing</u> : at least 4 weeks of pregnancy	Unexposed, healthy – matched for age and gestational age at first contact	Major malformations ⁸⁰ Miscarriage (<20 weeks) Foetal death (≥ 20 weeks) Preterm birth Small for gestational age [large for gestational age, gestational age, birth weight, method of delivery, foetal distress, admission to neonatal ICU]
Bodén 2012b	Retrospective, linked, population-based cohort Swedish Medical Birth Register, Prescribed Drug Register, National Patient Register Sweden 1997–2009	Singleton infants (or stillborns) of mothers dispensed antipsychotics during pregnancy (N = 385,203)	Olanzapine and/or clozapine Other antipsychotics ⁸¹ <u>Timing</u> : pregnancy	Unexposed	Stillbirth Neonatal death Preterm birth (<37 weeks) Small for gestational age (<i>measured 3 ways</i>) [large for gestational age]
Johnson 2012	Prospective cohort, Emory Psychological Center US 1999–2008	Infants from mothers with psychiatric history (unexposed control) (N = 107)	Any antipsychotic	Unexposed ⁸² Any antidepressant	Infant Neurological International Battery (INFANIB) [habituation look time]
Gilad 2011	Prospective cohort Beilinson Teratology Information Service Israel 2005–2008	Women contacting service regarding olanzapine use. (N = 88)	Olanzapine <u>Timing</u> : lactation	Olanzapine, not breast-feeding Acetaminophen, breast-feeding	Speech delay Motor developmental delay [any adverse outcomes (%), feeding problems, failure to gain weight, small head circumference]
Hironaka 2011	Retrospective cohort, Nagoya University Hospital, Japan 2005–2009	Pregnant women with mental disorder (subgroup analysis for schizophrenia) (N = 287)	SGA and schizophrenia <u>Timing</u> : pregnancy N = 9	No mental disorder, unexposed N = 278	Preterm birth (<i>not defined</i>) [gestational age, threatened preterm labor, birth weight, umbilical cord artery pH, low birth weight, Apgar]

⁷⁹ Free counselling service offering evidence-based information regarding the reproductive safety of medications and other potentially teratogenic agents to pregnant and breastfeeding women across Canada and the USA.

⁸⁰ Inconsistently reported as congenital malformation and major malformation – may include minor malformations.

⁸¹ Prochlorperazine, levomepromazine, and melperone prescriptions because these drugs are mainly used as antiemetics or anxiolytics with low and intermittently administered doses.

⁸² The comparator group was a mix of women with and without mental health disorders (53/85 had a lifetime history of psychiatric illness, no data reported for current disease status).

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s Timing of exposure	Comparator/s	Outcomes [outcomes not in PICO]
Lin 2010	Retrospective, population-based cohort National Health Insurance Research Database Taiwan 2001–2003	Live-birth singleton infants of mothers with schizophrenia prescribed antipsychotics (N = 696) ⁸³	SGAs and schizophrenia FGAs and schizophrenia <u>Timing</u> : pregnancy	Unexposed and schizophrenia ⁸⁴	Preterm birth (<37 weeks) Small for gestational age [large for gestational age, low birth weight]
Newham 2008	Retrospective review, prospectively collected data National TIS database UK 1995–2006	Pregnant women who contacted the service and were exposed to therapeutic doses of antipsychotics or reference medication. (N = 108)	SGAs FGAs <u>Timing</u> : pregnancy	Unexposed (exposed to non-teratogens)	Premature birth (<37 weeks) Small for gestational age (for infants 37-42 weeks' gestation) [large for gestational age, birth weight, gestational age]
Reis 2008	Retrospective linked, population-based cohort Swedish Medical Birth Register, Register of Congenital Malformations, Hospital Discharge Register Sweden 1995–2005	Infants (or stillborns) of mothers reporting use of antipsychotics in early pregnancy. (N = 973,767)	Antipsychotics ⁸⁵ <u>Timing</u> : early pregnancy	Unexposed	Relatively severe malformations (may include malformations not strictly classifiable as major ⁸⁶) Stillbirth Preterm birth (<37 weeks), singletons Small for gestational age [large for gestational age, low/high birth weight]
Diav-Citrin 2005	Prospective cohorts, multicentre ENTIS Israel, Germany, The Netherlands, Italy 1989–2001	Women contacting one of four TIS to seek counseling in regard to gestational exposure to haloperidol or penfluridol (N = 846)	Haloperidol or penfluridol <u>Timing</u> : pregnancy	Unexposed (exposed to non-teratogens)	Major anomalies (structural abnormalities with a serious medical, surgical or cosmetic consequence) Stillbirth Preterm (≤37 weeks) [live births, terminations, ectopic pregnancy, gestational age at delivery, birth weight]
McKenna 2005	Prospective cohorts, multicentre, matched controls 3 databases ⁸⁷ Canada, Israel, UK Period not reported	Women who contacted one of the services regarding SGAs. (N = 302)	SGAs <u>Timing</u> : 1 st trimester	Unexposed – matched 1:1 for age (±2 years) and gestational age at first contact (±2 weeks)	Major malformations Miscarriage Stillbirth [therapeutic abortions, birth weight, gestational age at delivery, neonatal complications (3 rd trimester exposure)]
Yaris 2005	Prospective cohort Toxicology Information and Follow-up Service Turkey 1999–2004	Women who contacted service and had been exposed to psychotic drugs. (N = 301, although some still pregnant)	Subgroup: antipsychotics (92% FGAs; 8% risperidone or quetiapine) <u>Timing</u> : pregnancy	Unexposed to any drugs	Major malformations (none reported) This and other outcomes not extracted due to poor reporting (denominator unclear due to remaining pregnancies across entire psychotics group).

⁸³ A further 3480 women without a history of a mental health disorder were also included (matched 5:1 with the combined cohorts of women with schizophrenia) but this health cohort was compared only with women with schizophrenia and unexposed to antipsychotics.

⁸⁴ Both exposed and unexposed groups had at least three consensus schizophrenia diagnoses in a hospital or ambulatory care setting.

⁸⁵ Dixyrazine and prochlorperazine, used for nausea and vomiting during pregnancy, are excluded from the main treatment group results but are reported separately (not extracted in the current Review).

⁸⁶ Excludes some common and variable mild conditions: preauricular tag, tongue tie, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testicle, unstable hip, and nevus. Unclear whether included malformations are classifiable as major.

⁸⁷ Motherisk Program, Hospital for Sick Children, Toronto, Canada; Israeli Teratogen Information Service, Israel; Drug Safety Research Unit database, England.

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s Timing of exposure	Comparator/s	Outcomes [outcomes not in PICO]
Rumeau-Rouquette 1977	Prospective cohort Constructed by INSERM at 12 university hospitals Paris, France 1963–1969	French-speaking residents of Paris who visited these hospitals for examination during the first trimester and who delivered in these hospitals. (N = 12,764)	Phenothiazines <u>Timing</u> : 1 st trimester	Unexposed	Congenital malformations ⁸⁸
Slone 1977	Prospective cohort Collaborative Perinatal Project ⁸⁹ US Period NR	Mother-child pairs identified prior to birth at 12 hospitals (N = 50,282)	Phenothiazines <u>Timing</u> : first 4 months of pregnancy	Unexposed	Major malformations Cardiac malformations Stillbirth Neonatal mortality [any malformations, birth weight, IQ ⁹⁰]

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; BWH, Brigham and Women's Hospital; CNS, central nervous system; ENTIS, European Network of Teratology Information; FGAs, first generation antipsychotics; hdPS, high-dimensional propensity score; ICD-9, International Classification of Diseases, Ninth Revision; INSERM, French National Institute of Health and Medical Research; IQ, Intelligence quotient; MGH, Massachusetts General Hospital; NR, not reported; NWH, Newton-Wellesley Hospital; PICO, population–intervention–comparator–outcome; SES, socioeconomic status; SGA, second generation antipsychotic; TIS, Teratology Information Service.

⁸⁸ Unequivocal malformation, defined as an abnormality of appearance or function evident at birth, or within the first four weeks of life, minor malformation of the skin excluded. Control group included “liveborn infants without any apparent or suspected major and minor anomalies”. Therefore, this outcome is likely not restricted to major malformations. No risk estimates are reported by this study, however, so while data is extracted in **Section D3**, it is not considered in the assessment of evidence in Section D4.

⁸⁹ Methodology extracted from companion article (Shapiro 1977).

⁹⁰ Intelligence quotient scores were reported (continuous outcome) but no statistical comparison of groups was made.

AppD2.1.3 Anticonvulsants***AppD2.1.3.1 Systematic reviews – anticonvulsants***

The scoping and updated searches identified nine SRs relating to the assessment of anticonvulsant harms. All included SRs either limited the inclusion of studies to those in women with epilepsy, or included predominantly studies of women with epilepsy. A summary of the characteristics of the identified SRs is presented in **Table AppD2-13**. Five SRs provide a quantitative assessment of the included studies while the remaining four provide a narrative assessment of the individual studies only.

Table AppD2-13 Characteristics of the included systematic reviews of anticonvulsant harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Quantitative review					
Weston 2016	SR (50 prospective cohort or registry studies)	Pregnant women with epilepsy	Sodium valproate Carbamazepine Lamotrigine ⁹¹	Unexposed/no epilepsy Unexposed/epilepsy Other AED/epilepsy	Major congenital malformations Specific major congenital malformations Minor congenital malformations
NICE 2015	SR (21 prospective cohort studies, 10 retrospective cohort studies and 4 retrospective case-control studies)	Pregnant women	Sodium valproate Carbamazepine Lamotrigine	Unexposed	Teratogenic harms Pregnancy, obstetric and neonatal complications Neurodevelopmental outcomes
Tanoshima 2015	SR 59 OBS (44 prospective cohort studies and 15 retrospective cohort studies)	Pregnant women with epilepsy	Sodium valproate	Carbamazepine/epilepsy Lamotrigine/epilepsy	Major congenital malformations Congenital heart defects Clef lip and/or palate Genitourinary anomalies Musculoskeletal anomalies
Bromley 2014	SR 28 OBS (22 were prospective cohort studies)	Pregnant women with epilepsy	Sodium valproate Carbamazepine Lamotrigine ⁹²	Unexposed/no epilepsy Unexposed/epilepsy Other AED/epilepsy	Global cognitive functioning or ability/IQ ASD ADHD Dyspraxia Cognitive function
Banach 2010	SR 11 cohort studies	Pregnant women with epilepsy	Sodium valproate Carbamazepine	Unexposed/epilepsy Unexposed/any	IQ
Qualitative review					
Gentile 2014b	SR	Pregnant women	Sodium valproate	Unexposed Active-controlled Uncontrolled	Neurobehavioural teratogenicity

⁹¹ Also included phenobarbitone, phenytoin, oxcarbazepine, topiramate, gabapentin, vigabatrin, tiagabine, zonisamide, levetiracetam, ethosuximide, clobazam, clonazepam, zonisamide, pregabalin, lacosamide, retigabine, rufinamide or sulthiame.

⁹² Also included phenobarbitone, phenytoin, oxcarbazepine, topiramate, gabapentin, vigabatrin, tiagabine, zonisamide, levetiracetam, ethosuximide, clobazam, clonazepam, zonisamide, pregabalin, lacosamide, retigabine, rufinamide, and sulthiame.

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Galbally 2010	SR	Pregnant women	Sodium valproate Carbamazepine Lamotrigine Lithium	Unexposed Uncontrolled	Malformations Perinatal outcomes Neurodevelopmental outcomes
Harden 2009a	SR	Pregnant women	Sodium valproate Carbamazepine Lamotrigine ⁹³	Unexposed Active-controlled	Obstetrical complications
Harden 2009b	SR	Pregnant women	Sodium valproate Carbamazepine Lamotrigine ⁹⁴	Unexposed Active-controlled	Teratogenesis Perinatal outcomes

Abbreviations: ADHD, attention-deficit hyperactivity disorder; AED, antiepileptic drugs; ASD, autism spectrum disorder; IQ, intelligence quotient; OBS, observational studies; SR, systematic review.

⁹³ And other antiepileptic drugs.

⁹⁴ And other antiepileptic drugs.

AppD2.1.3.1.1 Malformations – anticonvulsants

Five SRs provide evidence related to the association between anticonvulsant use during pregnancy and infant malformations. Of these, three provide synthesised/pooled evidence and two provide results for individual studies only. Different SRs included a mix of different anticonvulsants, and outcomes assessed included a variety of grouped and specific congenital malformations; however, for this Review, only major, cardiac, and septal malformations are included in our review.

Table AppD2-14 presents the specific outcomes, methodological characteristics and individual studies included in each SR. Included studies vary across different SRs due to the different anticonvulsants and outcomes assessed. No SRs provide ‘higher quality’ evidence; i.e. based on analyses adjusted for potential confounders and attempted to minimise confounding by indication, although a number did include analyses based on either adjustment for potential confounders or attempted to minimise confounding by indication. See **Section AppD3.1.4** These results are also presented and discussed in **Section AppD4.1.3** of these Appendices.

Table AppD2-14 Studies included in systematic reviews of anticonvulsants reporting malformations⁹⁵

Assessment type	Quantitative assessment			Narrative assessment only	
Included studies	Weston 2016	NICE 2015	Tanoshima 2015	Galbally 2010	Harden 2009b
Search date	Sep 2015	Apr 2014	May 2014	Jun 2009	Jun 2007/ Feb 2008
Interventions of interest	Monotherapy with sodium valproate, carbamazepine, lamotrigine; other antiepileptic drugs	Sodium valproate; carbamazepine; lamotrigine	Sodium valproate	Sodium valproate; carbamazepine; lamotrigine; lithium	Sodium valproate; carbamazepine; lamotrigine; other antiepileptic drugs
Outcomes	Malformations	Malformations ; pregnancy outcomes; neurodevelopmental outcomes	Congenital malformations	Malformations ; perinatal outcomes; neurodevelopmental outcomes	Teratogenesis ; perinatal outcomes
Included study types	Prospective cohorts and registry studies	Any observational studies	Cohort studies	Any study type	Any study type
Analysed adjusted data?	x	x	x	-	-
Compared to an untreated/with mental health disorder population	✓	✓	✓	-	-
Campbell 2014	✓	Excluded			
Veiby 2014	Excluded		✓		
Abre 2013			✓		
Arkilo 2013			✓		
Artama 2013	Excluded	✓			
Cassina 2013	✓	✓	✓		
Bodén 2012a		✓			
Hernandez-Díaz 2012	✓	✓	✓		
Vajda 2012	✓				
Noonan 2012			✓		
Borthen 2011		✓			
Brosh 2011		✓			
Charlton 2011		✓			
Cunnington 2011		Excluded			
Molgaard-Nielsen 2011		✓			
Tomson 2011	✓		✓		
Vajda 2011			✓		
Werler 2011		✓			
Jentink 2010		Excluded			
Kaabi 2010			✓		
Mawer 2010	✓				
Miskov 2010			✓		
Vajda 2010			✓		
Bozhinova 2009	✓				
Martinez Ferri 2009	✓		✓		
Mawer 2009			✓		
Diav-Citrin 2008	✓	✓		✓	
Dolk 2008		✓			

⁹⁵ Only comparative studies related to the three anticonvulsants of interest (sodium valproate, carbamazepine and lamotrigine) are included here.

Assessment type	Quantitative assessment			Narrative assessment only	
Eroglu 2008	✓		✓		
Holmes 2008		✓		✓	
Morrow 2008			✓		
Thomas 2008	✓	Excluded	✓		
Titze 2008				✓	
Dean 2007			✓		
Kantola-Sorsa 2007				✓	
Kini 2007		✓	✓	✓	
Thomas 2007				✓	
Vajda 2007		✓	✓	✓	✓
Arulmozhi 2006	✓	Excluded			
Burja 2006		✓	✓		
Meador 2006	✓				✓
Morrow 2006		✓		✓	✓
Vajda 2006			✓		
Viinikainen 2006			✓	✓	
Artama 2005		✓	✓		✓
Barqawi 2005	✓				
Eriksson 2005		✓			✓
Kini 2005			✓		
Morrow 2005			✓		
Rasalam 2005				✓	
Wide 2004			✓		✓
Wyszynski 2005		Excluded	✓	✓	✓
Adab 2004		✓			✓
Endo 2004			✓		
Gaily 2004		✓			✓
Meischenguiser 2004	✓		✓		
Richmond 2004	✓				
Sabers 2004	✓				
Kaaja 2003	✓	✓	✓	✓	
Kaaja 2002		Excluded			
Laskowska 2002	✓				
Mawer 2002					✓
Wide 2002					✓
Diav-Citrin 2001		✓		✓	
Holmes 2001		✓	✓		
Arpino 2000					✓
Ebbesen 2000		Excluded			
Fairgrieve 2000	✓				
Rodriguez-Pinilla 2000		✓			
Wide 2000	✓	Excluded		✓	
Al Bunyan 1999	✓		✓		
Bag 1999	✓				
Canger 1999	✓	✓	✓	✓	✓

Assessment type	Quantitative assessment			Narrative assessment only	
Kaneko 1999	✓	✓	✓	✓	
Samren 1999		Excluded	✓		✓
Nulman 1997	✓	Excluded		✓	
Samren 1997	✓		✓		✓
Garza-Morales 1996	✓		✓		
Ornoy 1996		✓			
Torres 1995	✓				
Scolnick 1994					✓
Steeegers-Theunissen 1994	✓	✓	✓	✓	
Waters 1994	✓				
Kaneko 1993			✓		
Battino 1992			✓		
Dravet 1992	✓				
Koch 1992	✓		✓		
Lindhout 1992	✓	Excluded			
Oguni 1992	✓				
Omtzigt 1992	✓	Excluded	✓		✓
Tanganelli 1992	✓	Excluded	✓	✓	
Yerby 1992	✓			✓	
D'Souza 1991			✓		
Delmiš 1991	✓				
Froscher 1991	✓		✓		
Tanaka 1991			✓		
D'Souza 1990	✓				
Diaz-Romero 1990	✓				
Hunter 1990			✓		
Gaily 1989					
Jones 1989	✓				
Kaneko 1988			✓		
Bertollini 1987		Excluded	✓		
Lazzaroni Fossati 1986			✓		
Bertollini 1985					✓
Koch 1985				✓	
Robert 1985			✓		
Kelly 1984	✓		✓		
Markestad 1984			✓		
Koch 1983			✓		
Pardi 1982	✓				
Hiilesmaa 1981					
Nau 1981		Excluded		✓	

Abbreviations: NICE, National Institute of Health and Care Excellence.

AppD2.1.3.1.2 Pregnancy and birth outcomes – anticonvulsants

Four SRs provide evidence related to the association between anticonvulsant use during pregnancy and pregnancy and birth outcomes. Of these, one provides synthesised/pooled evidence and three provide results for individual studies only.

Table AppD2-15 presents the specific outcomes, methodological characteristics and individual studies included in each SR. Included studies vary across different SRs due to the different anticonvulsants and outcomes assessed. No SRs provide ‘higher quality’ evidence; i.e. based on analyses adjusted for potential confounders and attempted to minimise confounding by indication, although a number did include analyses based on either adjustment for potential confounders or attempted to minimise confounding by indication. See **Section AppD3.1.4**. These results are also presented and discussed in **Section AppD4.1.3** of these Appendices.

Table AppD2-15 Studies included in systematic reviews of anticonvulsants reporting pregnancy outcomes⁹⁶

Assessment type	Quantitative assessment	Narrative assessment only		
Included studies	NICE 2015	Galbally 2010	Harden 2009a	Harden 2009b
Search date	Apr 2014	Jun 2009	Jun 2007/ Feb 2008	Jun 2007/ Feb 2008
Interventions of interest	Sodium valproate; carbamazepine; lamotrigine	Sodium valproate; carbamazepine; lamotrigine; lithium	Sodium valproate; carbamazepine; lamotrigine; other antiepileptic drugs	Sodium valproate; carbamazepine; lamotrigine; other antiepileptic drugs
Outcomes	Malformations; pregnancy outcomes ; neurodevelopmental outcomes	Malformations; perinatal outcomes ; neurodevelopmental outcomes	obstetrical complications	Teratogenesis; perinatal outcomes
Included study types	Any observational studies	Any study type	Any study type	Any study type
Analysed adjusted data?	✗	-	-	-
Compared to an untreated/with mental health disorder population	✓	-	-	-
Artama 2013	✓			
Diav-Citrin 2008	✓			
Pilo 2006				✓
Viinikainen 2006			✓	✓
Richmond 2004			✓	✓
Kaaja 2002	Excluded	✓		
Diav-Citrin 2001	✓			
Laskowska 2001			✓	✓
Hvas 2000	✓		✓	✓
Wide 2000	Excluded	✓		
Olafsson 1998			✓	
Sawhney 1996			✓	
Martin 1993			✓	
Yerby 1992		✓		
Gaily 1990		✓		
Wilhelm 1990			✓	✓
Gaily 1989		✓		
Koch 1985		✓		
Hiilesmaa 1985			✓	✓
Hiilesmaa 1981		✓		
Nau 1981	Excluded	✓		

Abbreviations: NICE, National Institute of Health and Care Excellence.

⁹⁶ Only included comparative studies related to the three anticonvulsants of interest (sodium valproate, carbamazepine and lamotrigine) are included here.

AppD2.1.3.1.3 Neurodevelopmental outcomes – anticonvulsants

Five SRs provide evidence related to the association between anticonvulsant use during pregnancy and neurodevelopmental outcomes. Of these, three provides synthesised/pooled evidence and two provide results for individual studies only.

Table AppD2-16 presents the specific outcomes, methodological characteristics and individual studies included in each SR. Included studies vary across different SRs due to the different anticonvulsants and outcomes assessed. No SRs provide ‘higher quality’ evidence; i.e. based on analyses adjusted for potential confounders and attempted to minimise confounding by indication, although a number did include analyses based on either adjustment for potential confounders or attempted to minimise confounding by indication. See **Section AppD3.1.4** These results are also presented and discussed in **Section AppD4.1.3** of these Appendices.

Table AppD2-16 Studies included in systematic reviews of anticonvulsants reporting neurodevelopmental outcomes⁹⁷

Assessment type	Quantitative assessment			Narrative assessment only	
Included studies	NICE 2015	Bromley 2014	Banach 2010	Gentile 2014b	Galbally 2010
Search date	Apr 2014	May 2014	Apr 2009	Nov 2013	Jun 2009
Interventions of interest	Sodium valproate; carbamazepine; lamotrigine	Sodium valproate; carbamazepine; lamotrigine; other antiepileptic drugs	Sodium valproate; carbamazepine	Sodium valproate	Sodium valproate; carbamazepine; lithium
Outcomes	Malformations; pregnancy outcomes; neurodevelopmental outcomes	ASD; ADHD; dyspraxia; cognitive function	IQ	Neurobehavioural teratogenicity	Malformations; perinatal outcomes; neurodevelopmental outcomes
Study types included	Any observational studies	Prospective cohorts and registry studies	Any observational studies	Observational studies or RCTs	Any study type
Analysed adjusted data?	✗	✗	✗	-	-
Compared to an untreated/with mental health disorder population	✓	✓	✓	-	-
Bromley 2013	Excluded	✓		✓	
Christensen 2013	✓				
Cohen 2013				✓	
Cummings 2013		✓			
Jackson 2013		✓			
Meador 2013		✓		✓	
Rihtman 2013	✓	✓			
Vieby 2013	✓	✓		✓	
Meador 2012	Excluded			✓	
Christensen 2011				✓	
Cohen 2011				✓	
Cummings 2011		✓		✓	
Nadebaum 2011	Excluded	✓		✓	
Shallcross 2011		✓		✓	
Bromley 2010		✓		✓	
McVearry 2009	Excluded			✓	
Meador 2009				✓	
Vinten 2009					✓
Bromley 2008				✓	
Thomas 2008	Excluded	✓		✓	✓
Titze 2008					✓
Kantola-Sorsa 2007				✓	✓
Thomas 2007					✓
Arulmozhi 2006	Excluded	✓			
Viinikainen 2006				✓	✓
Eriksson 2005	✓	✓	✓	✓	✓
Rasalam 2005		Excluded			✓

⁹⁷ Only included comparative studies related to the three anticonvulsants of interest (sodium valproate, carbamazepine and lamotrigine) are included here.

Assessment type	Quantitative assessment			Narrative assessment only	
Vinten 2005	✓		✓	✓	✓
Adab 2004	✓			✓	✓
Gaily 2004	✓	✓	✓	✓	✓
Dean 2002		Excluded		✓	
Wide 2002		✓			
Adab 2001	Excluded			✓	
Koch 1999	Excluded		✓		
Gaily 1998		✓			
Ornoy 1996	✓	✓	✓		
Regesta 1996		✓			
Reinisch 1995			✓		
Rovet 1995		✓			
Scolnick 1994			✓		
Leavitt 1992		✓			
D'Souza 1991		✓			
Jones 1989		✓			

Abbreviations: NICE, National Institute of Health and Care Excellence.

AppD2.1.3.2 Individual studies – anticonvulsants

An a priori decision was made to limit the assessment of evidence for infant harms related to the use of anticonvulsants to SRs only. As such, no individual studies are included in the current Review.

AppD2.1.4 Benzodiazepines and z-drugs

The scoping and updated searches identified two SRs relating to the assessment of benzodiazepine harms. A summary of the characteristics of the identified SRs is presented in **Table AppD2-17**.

AppD2.1.4.1 Systematic reviews – benzodiazepines and z-drugs**Table AppD2-17 Characteristics of the included systematic reviews of benzodiazepines and z-drug harms**

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Quantitative					
NICE 2015	SR 18 observational studies	Pregnant women	Benzodiazepines and related drugs ⁹⁸	Unexposed	Congenital malformations Major congenital malformations Cleft lip/palate Cardiac abnormalities Septal heart defects Gestational age at delivery Birth weight Caesarean delivery Miscarriage Instrumental delivery Respiratory disorder
Enato 2011	SR 9 observational studies	Pregnant women	Benzodiazepines	Unexposed	Major malformations Cardiac malformations

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: SR, systematic review.

⁹⁸ Identified one study that examined zopiclone also (Ban 2014) but results not included in analyses.

Table AppD2-18 Studies included in systematic reviews of benzodiazepine harms

Assessment type	Quantitative assessment	
Included studies	NICE 2015	Enato 2011
<i>Search date</i>	<i>Apr 2014</i>	<i>Jun 2010</i>
<i>Interventions of interest</i>	<i>Benzodiazepines</i>	<i>Benzodiazepines</i>
<i>Outcomes</i>	<i>Malformations; pregnancy outcomes</i>	<i>Malformations</i>
<i>Study types included</i>	<i>Any observational studies</i>	<i>Any observational studies</i>
<i>Analysed adjusted data?</i>	<i>x</i>	<i>x</i>
<i>Compared to an untreated/with mental health disorder population</i>	<i>x</i>	<i>x</i>
Ban 2014	✓	
Leppee 2010	✓	
Wang 2010	Excluded	
Oberlander 2008	✓	✓
Kjaer 2007	Excluded	
Wikner 2007	✓	✓
Czeizel 2004	Excluded	
Czeizel 2003	Excluded	
Eros 2002	Excluded	
Bonnot 2001	Excluded	
Czeizel 1999	Excluded	
Diav-Citrin 1999	Excluded	
Ornoy 1998	✓	✓
Pastuszek 1996	✓	✓
Correa-Villasenor 1994	Excluded	
Laegreid 1992	✓	✓
Laegreid 1990	✓	
Czeizel 1987	✓	
Kullander 1976		✓
Hartz 1975		✓
Crombie 1975		✓
Milkovich 1974		✓

AppD2.1.4.2 Individual studies – benzodiazepines and z-drugs

Table AppD2-19 Characteristics of the included comparative observational studies of benzodiazepines and z-drugs harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Odsbu 2015	Prospective cohort study Norway 1999-2008	Pregnant women and their offspring age 3 (N=51,748 singleton pregnancies)	Benzodiazepines Z-drugs	Unexposed/adjusted for anxiety and depression	Lower language competence
Ban 2014b	Retrospective primary care-based cohort study THIN, UK 1990–2010	Singleton live births (N=20,137)	Diazepam Temazepam Zopiclone	Unexposed/no depression or anxiety Unexposed/depression or anxiety	Major congenital malformations Heart malformations Limb malformations Genital system malformations
Wikner 2011	Retrospective population-based cohort study Sweden 1995-2007	Live-born infants (N=1,127,075)	Z-drugs (zolpidem, zopiclone and zaleplon)	Unexposed	Relatively severe congenital malformations Any cardiovascular defect Hypospadias Other intestinal malformations than atresia/stenosis
Wikner 2007	Retrospective population-based cohort study Sweden 1995-2004	Infants born (N=873, 879)	Benzodiazepines and z-drugs	Unexposed	Preterm birth Low birth weight Small for gestational age Low Apgar score Respiratory problems Neonatal jaundice Hypoglycaemia Convulsions CNS problems Any malformations Major malformations Individual malformations (including cardiovascular defects)
Wang 2010	Retrospective population-based cohort study Taiwan 2005	Singleton live births (N=14,982)	Zolpidem	Unexposed	Low birth weight Preterm birth Small for gestational age Congenital abnormalities (major) Caesarean delivery
Juric 2009	Prospective cohort study US NR	Women enrolled in a study of pharmacokinetics of psychotropic medications during pregnancy (N=90)	Zolpidem	Unexposed/psychiatric disorders	Preterm delivery EGA at delivery Low birth weight Birth weight NICU admission Respiratory difficulty Lethargy Hypotonia APGAR 1 and 5 HTN/pre-eclampsia

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Oberlander 2008a	Retrospective, population-based cohort study British Columbia Linked Health Database, Canada 1998–2001	Women who had registered live births (N=20,188)	SSRIs Benzodiazepines SSRIs + benzodiazepines	Unexposed Adjusted/matched on psychiatric variables	Major congenital anomalies Cardiovascular congenital defects Ventricular septal defects Atrial septal defects
Kjær 2007	Retrospective population-based cohort study Hungary 1980-1996	<u>Cases</u> Identified within 3 months of birth via HCAR <u>Controls</u> 2:1 identified via the National Birth Registry (3:1 during 1986-1992)	Diazepam	Unexposed	Individual congenital abnormalities (including cardiovascular congenital abnormalities)
Eros 2002	Retrospective population-based case-control study Hungary 1980-1996	<u>Cases</u> Identified within 3 months of birth via HCAR <u>Controls</u> 2:1 identified via the National Birth Registry	Benzodiazepines (including nitrazepam, medazepam, tofisopam, alprazolam and clonazepam)	Unexposed/adjusted for chronic maternal disease (included psychiatric disorders)	Isolated congenital abnormalities (including cardiovascular congenital abnormalities)
Diav-Citrin 1999	Prospective cohort study Canada 1993-1997	Women contacting the Motherisk program (i) exposed to zopiclone and (ii) matched non-teratogen-exposed (N=80)	Zopiclone	Unexposed	Live birth Spontaneous abortion Therapeutic abortion Major birth defects Minor birth defects Delivery method Gestational age Preterm delivery Birth weight/ small for gestational age Meconium Fetal distress NICU admission

Abbreviations: HCAR, Hungarian Congenital Abnormality Registry; NICU, neonatal intensive care unit.

AppD2.1.5 Lithium

AppD2.1.5.1 Systematic reviews – lithium

The scoping search identified two SRs relating to the assessment of infant harms associated with lithium use, one of which provides a quantitative assessment of the included studies (NICE 2015), while the other provides a narrative assessment (Galbally 2010). A summary of the characteristics of the identified SRs is presented in Table AppD2-20.

Table AppD2-20 Characteristics of the included systematic reviews of lithium harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Quantitative					
NICE 2015	SR/MA 6 observational studies	Pregnant women	Lithium	Unexposed – any	Congenital malformations Heart defects Ebstein's anomaly Course of pregnancy, obstetric and neonatal complications ⁹⁹ Neurodevelopmental outcomes ⁹⁹
Qualitative					
Galbally 2010	SR 12 observational studies	Pregnant women	Lithium	Not specified	Cardiovascular malformations Ebstein's anomaly Prematurity Increased birth weight Neurodevelopmental outcomes

Note: Outcomes shown in bold are those included in the Summary of Findings tables.

Abbreviations: MA, meta-analysis; SR, systematic review.

Table AppD2-21 lists the individual studies included in the identified SRs. Only two of the cohort studies (Jacobson 1992; Kallen 1983) were included in both SRs.

NICE 2015 included four prospective cohort studies (three with unexposed controls) and two retrospective case-control studies. An additional four studies were excluded (van der Lugt 2012; Czeizel 1990; Zalstein 1990; Weinstein 1975) because they did not have an unexposed control group or no (or very few) cases of lithium exposure were found.

Galbally 2010 included seven cohort studies (six with unexposed controls), four case series, and one case report (of anencephaly, as it had not been examined in other studies). Two studies included in Galbally 2010 were excluded in NICE 2015 due to no/low lithium exposure (Czeizel 1990; Zalstein 1990).

The NICE 2015 SR noted that there was limited evidence for lithium due to the small number of studies that provided extractable data. Data were available for congenital malformations and heart defects only. There was insufficient evidence for outcomes relating to course of pregnancy, neonatal and obstetric complications, and neurodevelopment.

Table AppD2-21 Studies included in systematic reviews of lithium harms

Assessment type		Quantitative assessment	Narrative assessment only
Included studies		NICE 2015	Galbally 2010
Search date		Apr 2014	Jun 2009
Interventions of interest		Lithium	Lithium
Outcomes		Malformations ¹⁰⁰	Malformations; increased birth weight; neurodevelopmental outcomes
Study types included		Comparative cohort and case control studies	Observational studies
Analysed adjusted data?		✗	-
Compared to an untreated/with mental health disorder population		✓	-
Bodén 2012a	prospective cohort with controls	✓	
Reis 2008	prospective cohort with controls	✓	
Grover 2005	case report		✓
Correa-Villasenor 1994	retrospective case control	✓	

⁹⁹ NICE 2015 noted insufficient evidence relating to lithium for neurodevelopmental outcomes, and outcomes relating to course of pregnancy, obstetric and neonatal complications.

¹⁰⁰ NICE 2015 noted insufficient evidence relating to lithium for outcomes relating to course of pregnancy, obstetric and neonatal complications, and neurodevelopment.

Assessment type		Quantitative assessment	Narrative assessment only
Troyer 1993	cohort with controls		✓
Jacobson 1992	prospective cohort with controls	✓	✓
Czeizel 1990	retrospective case control	✓	
Edmonds 1990	cohort with controls		✓
Zalzstein 1990	cohort with controls		✓
Kallen 1988	cohort with controls		✓
Kallen 1983	prospective cohort	✓	✓
Schou 1976	prospective cohort with controls		✓
Weinstein 1976	case series		✓
Weinstein 1975	case series		✓
Schou 1973a	retrospective case series		✓
Schou 1973b	case series		✓

AppD2.1.5.2 Individual studies – lithium

None of the pooled risk estimates reported in NICE 2015 exclusively used data adjusted for confounders. Therefore, it was necessary to assess the evidence from original comparative studies in the current Evidence Review. Table AppD3-21 shows the study characteristics of original studies identified from the published SRs and a literature search from 2014 onwards to update the evidence base. A total of eight comparative studies were identified, six from the SRs and a further two (Diav-Citrin 2014; Källén 2013) from the updating literature search.

Two of the studies in the NICE 2015 SR are not included in the table below. Correa-Villasenor 1994 reviewed 44 cases of Ebstein's anomaly and 3,572 controls without cardiovascular malformations from the Baltimore-Washington Infant Study (BWIS). Reports of lithium use were rare in this population (no case mothers and two control mothers). As such, the evidence is not particularly informative for this intervention. NICE 2015 also included a study, Bodén 2012a, which investigated exposure to either lithium, antipsychotics, or anticonvulsants, so is excluded from this Review.

The Galbally 2010 SR also identified three comparative studies that are not included in the table below (Edmonds 1990; Zalzstein 1990; Kallen 1988). Edmonds 1990 reviewed 34 cases of Ebstein's anomaly and 34 control children and identified no history of maternal use of lithium or manic depression in pregnancy for any of the children. Zalzstein 2010 reviewed 59 cases of patients born between 1971 and 1988 who were diagnosed with Ebstein's anomaly in a single hospital in Canada. No cases had a lithium exposure recorded. Likewise, Kallen 1988 found no instances of lithium exposure in a review of 69 cases of Ebstein's anomaly or tricuspid atresia from the International Clearinghouse for Birth Defects Monitoring Systems and a review of 15 Ebstein cases from the France Rhone-Alps-Auvergne monitoring system.

The literature search also identified one retrospective cohort study (Petersen 2016) that used data from two large United Kingdom clinical databases – The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD) – to examine the risks of adverse maternal and child outcomes in women who use psychotropic medication (including lithium) in pregnancy. However, only a small number of women were prescribed lithium before and during pregnancy and for all adverse child outcomes there were very few events and therefore no analyses were carried out by those authors.

Table AppD2-22 Characteristics of the included comparative observational studies of lithium harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes [outcomes not in PICO]
Diav-Citrin 2014 [identified by update search]	Prospective cohort Israeli Teratology Information Service (ITIS) Israel 1994–2010 Also included data from two additional services: ¹⁰¹ MotherSafe (Australia) 2000-2011 Motherisk Program (Canada) 2001-2005	Women contacting the ITIS in regard to gestational exposure to lithium ¹⁰² (N = 183)	Lithium	Two comparator groups: <ul style="list-style-type: none"> Pregnant women (randomly selected from ITIS) with exposures known not to be teratogenic Pregnant women with bipolar disorder who were unexposed to lithium (untreated or treated with other medications) 	Major anomalies ¹⁰³ (major anomalies without chromosomal or genetic conditions, cardiovascular anomalies ¹⁰⁴ , cardiovascular anomalies excluding resolved cases, non-cardiovascular anomalies, Ebstein's anomaly) Miscarriage Stillbirth Preterm delivery (<37 weeks) [live births, elective terminations, ectopic pregnancy, gestational age at delivery, birthweight]
Källén 2013 [identified by update search]	Retrospective, linked, population-based cohort of live births. Medical Birth Register, Register of Birth Defects, Hospital Discharge Register, Register of Prescribed Drugs Sweden 1996–2011	Live-birth infants of mothers reporting use of antipsychotics (neuroleptics) during early pregnancy, or dispensed drug in later pregnancy (N = 1,575,847)	Antipsychotics or lithium ¹⁰⁵	Unexposed	Relatively severe malformations (may include malformations not strictly classifiable as major ¹⁰⁶) ¹⁰⁷ Cardiac malformations Preterm birth <37 weeks, Small for gestational age Respiratory diagnosis [abruption of placenta, haemorrhage around delivery, large for gestational age, induction of delivery, low birth weight any neonatal diagnosis, hypoglycaemia, jaundice, CNS diagnoses, low 5 min Apgar score]

¹⁰¹ According to the publication, the three participating centers are members of the Organization of Teratology Information Specialists, an organisation of counseling services pertaining to environmental exposures during pregnancy, and use similar methodologies. Data from Australia and Canada were included to increase the power of the study.

¹⁰² The reported indications for treatment with lithium were as follows: bipolar disorder (65.9%), depression (16.7%), schizoaffective disorder (6.8%), schizophrenia (3.8%), mania (1.5%), and psychosis (2.2%). Concurrent psychiatric medications were taken by 66.1% of women in the cohort.

¹⁰³ Defined as structural anomalies in the offspring that have serious medical, surgical or cosmetic consequences. Significant neurodevelopmental or functional problems were also considered to be major anomalies, even in the absence of a structural anomaly, when they required special education or interventions. Mild hypospadias not requiring an intervention and functional problems without any morphological changes, or complications of preterm delivery were not considered to be major anomalies. The analysis of major congenital anomalies was performed in all live-born infants, as well as in stillbirths and in elective terminations of pregnancy as a result of prenatally diagnosed anomalies.

¹⁰⁴ Such as septal defects

¹⁰⁵ For most outcomes data are aggregated for antipsychotics and lithium (17% of infants exposed to lithium).

¹⁰⁶ Excludes the following common and clinically little important conditions: preauricular appendices, tongue tie, patent ductus at preterm birth, single umbilical artery, undescended testicle, unstable hip or hip (sub)luxation, and nevus. Unclear whether included malformations are classifiable as major.

¹⁰⁷ Data specifically relating to lithium is only available for the relatively severe malformations outcome. For all other outcomes, no data were available for lithium.

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes [outcomes not in PICO]
Reis 2008	Retrospective linked, population-based cohort Swedish Medical Birth Register, Register of Congenital Malformations, Hospital Discharge Register Sweden 1995–2005	Infants (or stillborns) of mothers reporting use of antipsychotics in early pregnancy. (N=958,729 women; 973,767 infants)	Antipsychotics, including lithium ¹⁰⁸	Unexposed	Congenital malformations ¹⁰⁹ Stillbirth Preterm birth (<37 weeks), singletons Small for gestational age or large for gestational age [low/high birth weight]
Troyer 1993 ¹¹⁰	Retrospective cohort Record linkage of discharge diagnosis and a medical birth registry Sweden 1973-1979	Women who were manic-depressive inpatients and delivered a child in the same year (N=350)	Lithium (first trimester)	Unexposed (to lithium) – manic depression	Preterm delivery (<38 weeks) Large for gestational age
Jacobson 1992	Prospective cohort Four teratogen information services: Motherisk (Toronto); the California Teratogen Information Service (CTIS) (San Diego); Philadelphia Pregnancy Helpline; Foetal Risk Assessment from Maternal Exposure (FRAME) (Ontario) United States and Canada Program initiation until Feb 1991 ¹¹¹	Women who consulted one of four teratogen information centres to obtain information about the potential risks of therapeutic drugs (lithium) during pregnancy (N=148)	Lithium (first trimester) ¹¹²	Unexposed (to lithium or another teratogen) ¹¹³	Congenital malformations (major anomaly) ¹¹⁴ Cardiac malformations Ebstein's anomaly [normal live births, ectopic pregnancy, birthweight, gestational age at birth]

¹⁰⁸ Women using lithium were treated separately in the publication and presented at the end of the Results section as a Note regarding lithium exposure.

¹⁰⁹ Congenital malformations was the only outcome reported in relation to lithium exposure.

¹¹⁰ Troyer 1993 and Kallen 1983 appear to include the same cohort of women, but report different outcomes.

¹¹¹ Program initiation for each service: CTIS 1979, Philadelphia Pregnancy Healthline 1984, Motherisk 1985, FRAME 1989.

¹¹² An unknown proportion were also exposed to other drugs during the first trimester, such as carbamazepine, fluoxetine, trazodone, and L-thyroxine.

¹¹³ Controls were women who were seen at the Motherisk clinic for counselling about drugs that are not known or suspected to be teratogenic. Each study patient was matched with a woman of similar age (to within 2 years).

¹¹⁴ Defined as an anomaly that has an adverse effect on either the function or social acceptability of the individual.

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes [outcomes not in PICO]
Czeizel 1990	Retrospective case control Hungarian Case-Control Surveillance of Congenital Anomalies (HCCSCA) Hungary 1980-1987	<u>Cases</u> Notified cases of congenital anomalies ¹¹⁵ (still- and live-born) diagnosed from birth till the age of one (N=10,698) <u>Controls</u> Newborns without congenital anomalies, matched to every index patient according to sex, birth week, and district of parents' residence (N=21,546)	Lithium	Unexposed (to lithium)	Congenital anomalies (major isolated congenital anomalies and unidentified multiple congenital anomalies)
Källén 1983	Retrospective cohort Record linkage using Discharge Registry for Inpatient Psychiatric Wards (DRPW), Medical Birth Registry (MBR) and Registry of Congenital Malformations (RCM) Sweden 1973-1979	Infants born to women who had been treated as inpatients for manic-depressive disease, identified from central registries and information from hospital charts (N=121)	Lithium	Unexposed – manic depression	Congenital malformations (relatively severe) ¹¹⁶ Heart defects Neonatal deaths
Schou 1976	Retrospective case control Scandinavian Register of Lithium Babies Scandinavia 1968-1976	<u>Cases</u> Babies exposed to lithium during pregnancy who had been born without malformations and had reached the age of five years or older (N=67) <u>Controls</u> Siblings not exposed to lithium during pregnancy (N=57)	Lithium	Unexposed siblings	Developmental anomalies ¹¹⁷

Note: Outcomes shown in bold are those included in the Summary of Findings tables.

Abbreviations: CNS, central nervous system; ITIS, Israeli Teratology Information Service; PICO, Population, Intervention, Comparator, Outcome.

¹¹⁵ Excluded: mild congenital anomalies such as congenital dislocation of hip, congenital inguinal hernia, hemangiomas, etc.; minor variants; and congenital anomaly syndromes of known origin.

¹¹⁶ Subluxation of the hip, retention testis, and hydrocele testis are provided in the publication as examples of malformations that are not registered (i.e. not classified as relatively severe).

¹¹⁷ Based on response letters and questionnaires from psychiatrists or general practitioners who had originally reported the children. No validated tools were used.

AppD2.2 COMPLEMENTARY

AppD2.2.1 Omega-3 fatty acids

AppD2.2.1.1 *Systematic reviews (SRs) – omega-3 fatty acids*

Eight SRs provided evidence regarding the association between the use of omega-3 fatty acids during pregnancy and infant harms. A summary of these SRs is presented in **Table AppD2-23**. Five SRs provided a quantitative assessment of the included studies and the remaining three provided a qualitative assessment only. **Table AppD2-24** presents the specific outcomes, methodological characteristics and individual studies included in each SR. Included studies vary substantially across different SRs due to the different outcomes assessed. All the SRs identified on omega-3 included in this report investigated the safety of omega-3 fatty acids in a pregnant population and on their neonates; no SRs specifically addressed the harms of omega-3 fatty acids in a population with a mental health issue. Only SRs based on RCT evidence are included and as such, there were no issues regarding confounding by indication or confounding in general. See **Section AppD3.2.1.1** of these Appendices for the full data extraction from the identified SRs. These results are also presented and discussed in **Section AppD4.2.1.1** of these Appendices.

Table AppD2-23 Characteristics of the included systematic reviews of omega-3 fatty acids harms

Study ID	Study characteristics	Population for outcomes assessment (N)	Exposure (subgroups)	Comparator (subgroups)	Outcomes
Quantitative assessment					
Kar 2016	SR 9 RCTs	Pregnant women and neonates (N=5,980)	Omega-3 fatty acids	Placebo	Early preterm delivery, any preterm delivery, gestational age, neonatal death
Saccone 2016b	SR 34 RCTs	Pregnant women and neonates (N=16,684)	Omega-3 fatty acids	Placebo	Preterm birth, perinatal death, small for gestational age, pre-eclampsia, intrauterine growth restriction, gestational diabetes, birthweight, infant eye and brain development, postpartum depression
Imhoff-Kunsch 2012	SR 15 RCTs 14 OBS	Pregnant women and neonates (N=8,454 for RCTs and N=114,006 for Observational studies)	n-3 LCPUFA	Placebo	IUGR, preterm birth, early preterm birth, SGA, stillbirth, infant death
Salvig 2011	SR 3 RCTs	Pregnant women and neonates (N=2,108)	Marine n-3 fatty acids	Placebo or no intervention	Preterm delivery, early preterm delivery, gestational age
Gould 2013	SR 11 RCTs	Pregnant or lactating women (N=5,272)	Omega-3 LCPUFA	Placebo	Cognitive development Motor development Language development
Qualitative assessment					
Campoy 2012	SR 16 RCTs	Pregnant or lactating women or infants receiving formula	Omega-3 fatty acids	Placebo	Child growth Visual acuity Neurodevelopment
Leung 2011	SR 18 RCTs and cohort studies	Pregnant women/infants	Various including omega-3 fatty acids	Placebo	Neurodevelopment
Dziechciarz 2010	SR 13 RCTs	Pregnant or lactating women	n-3 LCPUFA	Placebo	Neurodevelopment Visual function

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; n-3 LCPUFA, n-3 long-chain polyunsaturated fatty acids; IUGR, intrauterine growth restriction; OBS, observational studies; SGA, small gestational age.

Table AppD2-24 Studies included in systematic reviews of omega-3 fatty acids reporting pregnancy and birth outcomes¹¹⁸

Assessment type	Quantitative Assessment			
Included studies	Saccone 2016b	Kar 2016	Imhoff-Kunsch 2012	Salvig 2011
Search date	Mar 2015	2014	Jan 2011	2010
Interventions	<i>Omega-3 fatty acids versus placebo</i>	<i>Omega-3 fatty acids versus placebo</i>	<i>n-3 long-chain polyunsaturated fatty acids versus placebo</i>	<i>Marine n-3 fatty acids versus placebo</i>
Outcomes	<i>Preterm birth; perinatal death; SGA</i>	<i>Gestational age, preterm delivery, early preterm delivery, neonatal death.</i>	<i>IUGR, preterm birth, early preterm birth, SGA, stillbirth, infant death</i>	<i>Preterm birth, gestational age, length of gestation, birth weight and low birth weight.</i>
Gould 2014	✓			
Mulder 2014	✓			
Carlson 2013	✓	✓		
Colombo 2013	✓			
Escalano-Margarit 2011	✓			
Harper 2010	✓		✓	
Makrides 2010	✓	✓	✓	
Ramakrishnan 2010		✓	✓	
Ranajurasgbab 2010	✓			
Bergmann 2008			✓	
Helland 2008			✓	
Judge 2007			✓	
Mardones 2007		✓		
Knudsen 2006	✓			
Tofail 2006	✓		✓	
Boris 2004	✓			
Colombo 2004	✓			
de Groot 2004	✓			
Decsi 2005	✓			
Dunstan 2004			✓	
Sanjuro 2004	✓			
Helland 2003	✓			
Malcolm 2003	✓			
Montgomery 2003	✓			
Smuts 2003	✓	✓	✓	✓
Helland 2001	✓			
Olsen 2000	✓	✓	✓	✓
Borod 1999	✓			
Herrera 1998	✓			
Salvig 1996	✓		✓	
Onwude 1995	✓	✓	✓	
Van Houwelingen 1995	✓			
Bulstra-Ramakers 1994	✓	✓	✓	
Laivuori 1993	✓			

¹¹⁸ Only studies that were noted as reporting infant harms in general, or harms of specific interest to this review, are included here.

Assessment type	Quantitative Assessment			
Sorensen 1993	✓			
D'Almeida 1992	✓		✓	
Olsen 1992	✓	✓	✓	✓
Olsen 1990	✓			

Abbreviations: DB, double blind; IUGR, intrauterine growth restriction; RCT, randomised controlled trial; SGA, small gestational age.

Table AppD2-25 Studies included in systematic reviews of omega-3 fatty acids reporting neurodevelopmental outcomes¹¹⁹

Assessment type	Quantitative Assessment	Qualitative Assessment		
Included studies	Gould 2013	Campoy 2012	Leung 2011	Dziechciarz 2010
Search date	Aug 2012	April 2011	Dec 2009	Dec 2009
Interventions	<i>Omega-3 long-chain polyunsaturated fatty acids versus placebo</i>	<i>Omega-3 fatty acids versus placebo</i>	<i>Various including omega-3 fatty acids versus placebo</i>	<i>n-3 long-chain polyunsaturated fatty acids versus placebo</i>
Outcomes	<i>Cognitive development; motor development; language development</i>	<i>Neurodevelopment</i>	<i>Neurodevelopment</i>	<i>Neurodevelopment</i>
Campoy 2011	✓			
Drover 2011		✓		
Van Goor 2011	✓			
Makrides 2010	✓			
Dunstan 2008	✓		✓	✓
Helland 2008 (2003, 2001)	✓		✓	✓
Innis 2008			✓	✓
Judge 2007		✓	✓	✓
Tofail 2006	✓		✓	✓
Jensen 2005				✓
Lauritzen 2005		✓		✓
Lauritzen 2004				✓
Helland 2003		✓		
Malcolm 2003			✓	✓

Abbreviations: DB, double blind; IUGR, intrauterine growth restriction; RCT, randomised controlled trial; SGA, small gestational age.

¹¹⁹ Only studies that were noted as reporting infant harms in general, or harms of specific interest to this review, are included here.

AppD2.2.2 St John's wort***AppD2.2.2.1 Systematic reviews – St John's wort***

Three SRs provided evidence regarding the association between the use of St John's wort during pregnancy and infant harms; a summary of these SRs is presented in **Table AppD2-26**, while **Table AppD2-24** presents the individual studies included in each SR that were relevant to the assessment of St John's wort and infant harms. No SRs provided a pooled analysis of included studies; therefore, their included studies will be considered for inclusion in a de novo assessment of individual studies.

Table AppD2-26 Characteristics of the included systematic reviews of St John's wort harms

Study ID	Study characteristics	Population	Exposure/s	Comparator/s	Outcomes
Qualitative assessment					
Dante 2014	SR Included studies relevant to St John's wort: 2 cohort studies, 2 case reports	Pregnant women	St John's wort Other CAMs included: ginger, cranberry, garlic, blue cohosh, primrose oil, Echinacea, castor oil, raspberry leaf, valerian, green tea, peppermint, aloe, chamomile, almond oil	-	Fetal outcomes (congenital abnormalities, central nervous system damage, Apgar scores, birth weight, heart failure)
Budzynska 2012	SR Included studies relevant to St John's wort: 1 cohort study and 2 case reports	Breast-feeding women	St John's wort Other CAMs included: garlic extract, cassia senna L, traditional herbal teas, various preparations of herbs; warm or cold food; wine; baths (mother wort); dietary supplements, herbal liqueur	-	Infant harms (colic, drowsiness, rashes, unusual behavior [lethargy, rashes, photosensitivity, sleep patterns])
Freeman 2009	SR Included studies relevant to St John's wort: 1 cohort study and 2 case reports	Women with perinatal depression	St John's wort Omega-3 Folate SAME Bright light therapy Exercise Acupuncture	-	Infant harms (neonatal syndrome , colic, drowsiness, or lethargy)

Abbreviations: CAM, complementary and alternative medicine; RCTs, randomised controlled trials; SAME, S-adenosyl-methionine; SR, systematic review.

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in this Review.

Table AppD2-27 Studies included in systematic reviews of St John's wort¹²⁰

Assessment type		Qualitative Assessment		
Included studies	Study type	Dante 2014	Budzynska 2012	Freeman 2009
Search date	-	Oct 2013	Nov 2010	NR
Interventions	-	<i>St John's wort</i> or other CAMs	<i>St John's wort</i> or other CAMs	<i>St John's wort</i> or other CAMs
Outcomes	-	Fetal outcomes	Maternal and fetal outcomes	Safety and efficacy of intervention on postpartum depressed women
Moretti 2009	Cohort	✓		
Lee 2003	Cohort	✓	✓	✓
Klier 2006	Case report	✓	✓	✓
Klier 2002	Case report		✓	✓
Grush 1998	Case report	✓		

Abbreviations: CAM, complementary and alternative medicine; NR, not reported; SR, systematic review.

¹²⁰ Only studies that were noted as reporting infant harms in general, or harms of specific interest to this review, are included here.

AppD2.2.2.2 Individual studies – St John's wort

Due to the lack of 'higher quality' SR evidence, an assessment of individual studies was undertaken. Studies were identified via the included SRs and the updated search for individual observational studies. **Table AppD2-28** provides a summary of the two individual comparative studies that were identified. Full data extraction for these studies can be found in **Section AppD3.2.2.2** of this Appendix.

Table AppD2-28 Characteristics of the included comparative observational studies of St John's wort harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Kolding 2015	Prospective cohort study Denmark (Danish National Birth Cohort) 1996 – 2003	Pregnant women who had singleton live births (N=90,166)	St John's wort	No exposure	Malformation Gestational age Preterm birth Birth weight Apgar scores
Moretti 2009	Cohort Canada (Mother-risk program) 1993 – 2007	Pregnant women (N=162)	St John's wort	Depressed women exposed to pharmacological therapies Healthy women not exposed to any teratogens	Malformation Live birth Miscarriage Elective abortion Gestational age Preterm delivery Birthweight

Note: Exposure/s, comparator/s and outcome/s shown in bold are those relevant to this Review.

AppD2.2.3 **Gingko biloba***AppD2.2.3.1* *Systematic reviews – gingko biloba*

No SRs were identified that assessed the effect of perinatal exposure to gingko biloba on infant harms.

AppD2.2.3.2 *Individual studies – gingko biloba*

No individual studies were identified that assessed the effect of perinatal exposure to gingko biloba on infant harms.

AppD2.3 **PHYSICAL****AppD2.3.1** **Electroconvulsive therapy***AppD2.3.1.1* *Systematic reviews – ECT*

The scoping and updated searches identified four SRs assessing harms to the infant resulting from maternal use of ECT during pregnancy. A summary of the characteristics of the identified SRs is presented in **Table AppD2-29**. One SR provides a quantitative assessment of the included studies while the remaining three provide a narrative assessment of the individual studies/cases only. **Table AppD2-30** presents a list of the individual studies included in each identified SR.

Table AppD2-29 Characteristics of the included systematic reviews of ECT harms

Study ID	Study characteristics	Population	Exposure (subgroups)	Comparator/s	Outcomes	Analysis
Quantitative assessment						
Leikness 2015	SR 67 case reports/series	Pregnant women with depression/bipolar disorder (including psychotic depression)	ECT	-	Various fetal and maternal adverse events	Pooled data
Qualitative assessment						
Calaway 2016	SR 13 studies; 9 case series/ 4 case reports	Pregnant women	ECT in first trimester	-	Various fetal adverse events	-
Pompili 2014	SR 31 case reports, 1 retrospective study, 1 observational study, 2 SRs, 2 narrative reviews	Pregnant women with major depressive disorder	ECT	-	Various fetal and maternal adverse events	-
Anderson 2009	SR 57 case reports/series	Pregnant women with MDD, bipolar disorder, schizophrenia or psychotic depression	ECT	-	Various fetal and maternal adverse events	_ ¹²¹

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: ECT, electro convulsive therapy; PPD, postpartum depression; PP, postpartum psychosis; SR, systematic review.

¹²¹ Pooled data for efficacy assessment only.

Table AppD2-30 Studies included in systematic reviews of ECT harms

Assessment type	Study type	Quantitative SRs	Qualitative SRs		
Included studies	-	Leikness 2015	Calaway 2016	Pompili 2014	Anderson 2009
Search date		Nov 2012	Oct 2015	2013	NR
Interventions	-	ECT	ECT	ECT	ECT
Outcomes	-	Infant and maternal harms	Infant harms	Infant and maternal harms	Infant and maternal harms
Leikness 2013	SR (non-comparative)			✓	
Anderson 2009	SR (non-comparative)			✓	
Miller 1993	SR (non-comparative)			✓	
Halmo 2014	Case report		✓		
De Asis 2013	Case report	✓		✓	
Bulbul 2013	Case report			✓	
Bulut 2013	Case report		✓	✓	
Gahr 2012	Case report	✓		✓	
Levy 2012	Case report				
Strain 2012	Case report				
Lovas 2011	Case report	✓	✓	✓	
O'Reardon 2011	Case report	✓		✓	
Salzbrenner 2011	Case report	✓		✓	
Yang 2011	Case report	✓		✓	
Pesiridou 2010	Case report	✓		✓	
Serim 2010	Case report	✓			
Ghanizadeh 2009	Case report	✓	✓	✓	
Ceccaldi 2008	Case report	✓		✓	
Malhotra 2008	Case report	✓			
Bozkurt 2007	Case report	✓		✓	✓
Espinola 2007	Case report	✓		✓	✓
Forray 2007	Case report				
Kasar 2007	Case report	✓		✓	✓
Pinette 2007	Case report	✓		✓	✓
Balki 2006	Case report	✓		✓	✓
Prieto 2006	Case report	✓		✓	✓
Kisa 2005	Case report				
Maletzky 2004	Case report	✓		✓	✓
DeBattista 2003	Case report	✓		✓	✓
Fukuchi 2003	Case report	✓		✓	✓
Iwasaki 2002	Case report	✓			✓
Ishikawa 2001	Case report	✓		✓	✓
Bhatia 1999	Case report	✓		✓	✓

Assessment type	Study type	Quantitative SRs	Qualitative SRs		
Gilot 1999	Case report	✓		✓	✓
Polster 1999	Case report	✓		✓	✓
Moreno 1998	Case report		✓	✓	✓
Livingston 1994	Case report	✓		✓	✓
Walker 1992	Case report				✓
Sherer 1991	Case report	✓		✓	✓
Vanelle 1991	Case report	✓			✓
LaGrone 1990	Case report	✓			✓
Yellowlees 1990	Case report	✓		✓	✓
Griffiths 1989	Case report	✓		✓	✓
Mynors-Wallis 1989	Case report				✓
Dorn 1985	Case report	✓	✓		✓
Varan 1985	Case report	✓		✓	✓
Repke 1984	Case report	✓		✓	✓
Wise 1984	Case report	✓		✓	✓
Loke 1983	Case report	✓		✓	✓
O'Reagan 1981	Case report				
Levine 1975	Case report			✓	✓
Impastato 1964	Case report	✓	✓		✓
Barten 1961	Case report	✓			✓
Sobel 1960	Case report	✓			✓
Impastato 1957	Case report				
Smith 1956	Case report	✓	✓		✓
Forssman 1955	Case report		✓		✓
Laird, 1955	Case report	✓	✓		✓
Monod, 1955	Case report	✓			
Russell, 1955	Case report				✓
Charatan, 1954	Case report	✓			✓
Yamamoto 1953	Case report	✓			✓
Forman 1952	Case report	✓			✓
Porot 1949	Case report	✓			✓
Boyd 1948	Case report	✓			✓
Doan 1948	Case report	✓	✓		✓
Simon 1948	Case report	✓			✓
Kent 1947	Case report	✓			✓
Moore 1947	Case report		✓		✓
Gralnick 1946	Case report	✓			✓
Sands 1946	Case report		✓		✓

Assessment type	Study type	Quantitative SRs	Qualitative SRs		
Polatin 1945	Case report	✓			✓
Leroux 1944	Case report				✓
Rondepierre 1943	Case report				✓

Abbreviations: ECT, electroconvulsive therapy; NR, not reported; SR, systematic review.

AppD2.3.1.2 Individual studies – ECT

No individual studies provide ‘higher quality’ evidence; i.e. based on analyses adjusted for potential confounders and compared to an untreated population with depression or a psychiatric condition, or adjusted for indication-related confounders. One study did provide comparative evidence of infant harms following postpartum exposure to ECT, although it should be noted that this study represents low quality evidence because there was no adjustment for potential confounders. A summary of the characteristics of this study is presented in **Table AppD2-31**.

Table AppD2-31 Characteristics of the included observational studies of ECT harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Babu 2013	Prospective cohort study India March 2006- September 2007	Women with postpartum psychosis Mean age=23 years (N=78)	ECT	No ECT	Adverse effects (anterograde amnesia, prolonged seizures, infant harms)

Abbreviations: ECT, electro convulsive therapy.

AppD2.3.2 Transcranial magnetic stimulation**AppD2.3.2.1** *Systematic reviews – TMS*

No systematic reviews or meta-analyses were identified that addressed the potential fetal or infant harms of the use of TMS in the antenatal or postnatal period.

AppD2.3.2.2 *Individual studies – TMS*

Due to the lack of SR evidence, an assessment of individual studies was undertaken. **Table AppD2-32** provides a summary of one cohort study, identified via the updated search for individual comparative and observational studies; this did not meet the inclusion criteria because it did not have a concurrent control group.

Table AppD2-32 Characteristics of the included observational studies of TMS harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Eryilmaz 2015	Prospective cohort study (non-concurrent control) Turkey 2008–2013	Pregnant patients with a diagnosis of major depressive disorder Mean age=33 (N=44)	rTMS	Untreated/depression	Low birth weight, fetal anomalies , feeding problems, respiratory complications , metabolic disorders, cardiac problems , hematologic problems, and central nervous system (CNS) problems

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: MDD, major depressive disorder; NR, not reported; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation, TMS, transcranial magnetic stimulation.

Appendix D3 DATA EXTRACTION

AppD3.1 PHARMACOLOGICAL

AppD3.1.1 Antidepressants

AppD3.1.1.1 Systematic reviews – antidepressants

AppD3.1.1.1.1 Malformations – antidepressants

Table AppD3-1 Antidepressant infant harms data extraction from systematic reviews – malformations

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Major malformations										
NICE 2015	Major congenital malformations	Any ADs	Unexposed – any	1 (CC)	13,615	-	OR 1.14 (0.85, 1.53)	NA	✖	✖
NICE 2015	Major congenital malformations	SSRIs	Unexposed – any	11 (cohort)	1,250,471	-	OR 1.15 (0.98, 1.35)	0.10 (37%)	✖	✖
NICE 2015	Major congenital malformations	Paroxetine	Unexposed – any	5 (cohort)	1,234,083	-	OR 1.34 (1.01, 1.70)	0.13 (44%)	✖	✖
NICE 2015	Major congenital malformations	Citalopram	Unexposed – any	5 (cohort)	1,233,776	-	OR 1.11 (0.89, 1.40)	0.31 (16%)	✖	✖
NICE 2015	Major congenital malformations	Fluoxetine	Unexposed – any	6 (cohort)	1,234,835	-	OR 1.27 (1.06, 1.51)	0.70 (0%)	✖	✖
NICE 2015	Major congenital malformations	Sertraline	Unexposed – any	4 (cohort)	1,231,765	-	OR 1.15 (0.91, 1.47)	0.59 (0%)	✖	✖
NICE 2015	Major congenital malformations	Fluvoxamine	Unexposed – any	3 (cohort)	737,266	-	OR 0.80 (0.44, 1.46)	0.74 (0%)	✖	✖
NICE 2015	Major congenital malformations	Escitalopram	Unexposed – any	2 (cohort)	629,048	-	OR 1.09 (0.67, 1.77)	NA ¹²²	✖	✖
NICE 2015	Major congenital malformations	Venlafaxine	Unexposed – any	2 (cohort)	108,652	-	OR 0.64 (0.32, 1.30)	0.41 (0%)	✖	✖

¹²² The risk estimate for one study was not estimable due to zero events in the exposure group.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
McDonagh 2014	Major malformations	SSRIs	Unexposed – disease	1 (cohort)	72	-	No events	-	✗	✗
McDonagh 2014	Major malformations	SSRIs	Unexposed – any	6 (OBS)	2,421,444	OR 1.08 (0.95, 1.22)	-	NR (67%)	✗	✓
McDonagh 2014	Major malformations	SSRIs	Unexposed – prior SSRIs	8 (OBS)	NR	-	OR 1.07 (0.78, 1.47) ¹²³	0.59 (NE)	✓	✓
McDonagh 2014	Major malformations	Citalopram/escitalopram	Unexposed – any	8 (OBS)	4,091,225	OR 1.06 (0.97, 1.16)	-	NR (0%)	✗	✓
McDonagh 2014	Major malformations	Fluoxetine	Unexposed – any	7 (OBS)	3,397,479	OR 1.14 (1.01, 1.30)	-	NR (0%)	✗	✓
McDonagh 2014	Major malformations	Paroxetine	Unexposed – any	11 (OBS)	4,192,613	OR 1.17 (1.02, 1.35)	-	NR (0%)	✗	✓
McDonagh 2014	Major malformations	Sertraline	Unexposed – any	7 (OBS)	4,020,791	OR 1.17 (1.02, 1.35)	-	NR (23%)	✗	✓
McDonagh 2014	Major malformations	Fluvoxamine	Unexposed – any	2 (OBS)	1,492,881	OR 0.76 (0.38, 1.50)	-	0.68 (NE)	✗	✓
McDonagh 2014	Major malformations	TCAs	Unexposed – any	2 (OBS)	NR	OR 1.31 (1.04, 1.65)	-	NR	✗	✓
McDonagh 2014	Major malformations	SSRIs	TCAs – any	2 (cohort)	17,810	-	OR 0.77 (0.60, 0.98)	NR	✗	✗
McDonagh 2014	Major malformations	Paroxetine	Fluoxetine – condition	9 (OBS)	NR	-	OR 1.14 (0.95, 1.37)	≥ 0.1 (NR)	✓	✗
McDonagh 2014	Major malformations	Citalopram or escitalopram	Fluoxetine or paroxetine – condition	8 (OBS)	NR	-	OR 0.94 (0.82, 1.07)	NR (0%)	✓	✗
McDonagh 2014	Major malformations	Sertraline	Fluoxetine or paroxetine – condition	8 (OBS)	NR	-	OR 0.59 (0.38, 0.90)	NR (0%)	✓	✗
McDonagh 2014	Major malformations	SSRIs + psychotherapy	Psychotherapy – condition	1 (cohort)	44	-	OR 0.40 (0.02, 6.93)	NA	✓	✗

¹²³ In the McDonagh publication this is included in the table with pooled adjusted analyses. However, in the table for cardiac malformations, this has been shown as being based on unadjusted data. This is assumed here also due to the fact this analysis has a greater number of studies than the overall adjusted analysis.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Grigoriadis 2013a	Major malformations	Any ADs	Unexposed (± ADs) – any	18 (OBS)	1,943,538	-	RR 1.09 (1.01, 1.18) ¹²⁴	0.67 (0%)	✖	✖
Grigoriadis 2013a	Major malformations	Any ADs	Unexposed (± ADs) – any	11 ¹²⁵ (OBS)	1,940,124	-	RR 1.07 (0.99, 1.17) ¹²⁴	0.86 (0%)	✖	✖
Grigoriadis 2013a	Major malformations	Any ADs	Unexposed (no ADs) – any	8 ¹²⁵ (OBS)	1,817,081	-	RR 1.10 (1.01, 1.21) ¹²⁴	0.99 (0%)	✖	✖
Grigoriadis 2013a	Major malformations	Any ADs	Unexposed (± ADs) – any	11 ¹²⁵ (OBS)	1,940,124	RR 1.07 (0.99, 1.17)	-	0.86 (0%)	✖	✓
Grigoriadis 2013a	Major malformations	Paroxetine	Unexposed (± ADs) – any	6 (OBS)	1,902,571	-	RR 1.20 (0.91, 1.57) ¹²⁴	0.14 (40%)	✖	✖
Grigoriadis 2013a	Major malformations	Paroxetine	Unexposed (± ADs) – any	5 ¹²⁵ (OBS)	1,900,864	-	RR 1.11 (0.88, 1.39) ¹²⁴	0.32 (14%)	✖	✖
Grigoriadis 2013a	Major malformations	Paroxetine	Unexposed (no ADs) – any	3 ¹²⁵ (OBS)	1,785,889	-	RR 1.21 (0.94, 1.56) ¹²⁴	0.40 (0%)	✖	✖
Grigoriadis 2013a	Major malformations	Paroxetine	Unexposed (± ADs) – any	5 ¹²⁵ (OBS)	1,900,864	RR 1.11 (0.88, 1.39)	-	0.32 (14%)	✖	✓
Grigoriadis 2013a	Major malformations	Fluoxetine	Unexposed (± ADs) – any	7 (OBS)	1,901,183	-	RR 1.25 (1.03, 1.51) ¹²⁴	0.59 (0%)	✖	✖
Grigoriadis 2013a	Major malformations	Fluoxetine	Unexposed (± ADs) – any	4 ¹²⁵ (OBS)	1,898,925	-	RR 1.20 (0.98, 1.48) ¹²⁴	0.38 (4%)	✖	✖
Grigoriadis 2013a	Major malformations	Fluoxetine	Unexposed (no ADs) – any	3 ¹²⁵ (OBS)	1,786,981	-	RR 1.29 (1.03, 1.61) ¹²⁴	0.52 (0%)	✖	✖
Grigoriadis 2013a	Major malformations	Fluoxetine	Unexposed (± ADs) – any	4 ¹²⁵ (OBS)	1,898,925	RR 0.98 (0.98, 1.48)	-	0.38 (4%)	✖	✓
Myles 2013	Major malformations	Fluoxetine	Unexposed – any	9 (OBS)	NR	-	OR 1.14 (1.01, 1.30)	0.33 (12%)	✖	✖
Myles 2013	Major malformations	Fluoxetine	Unexposed – any	5 ¹²⁶ (OBS)	NR	OR 1.22 (1.01, 1.47) ¹²⁷	-	0.51 (0%)	✖	✓

¹²⁴ Adjusted results included preferentially where available.¹²⁵ Studies above quality threshold.¹²⁶ Includes higher quality studies only (scored ≥ 4/6 in the quality assessment).¹²⁷ Controlled for at least one of the potential confounders of interest: (i) tobacco, alcohol or illicit drug use, (ii) maternal age and (iii) maternal parity.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Myles 2013	Major malformations	Paroxetine	Unexposed – any	8 (OBS)	NR	-	OR 1.29 (1.11, 1.49)	0.54 (0%)	✗	✗
Myles 2013	Major malformations	Paroxetine	Unexposed – any	4 ¹²⁸ (OBS)	NR	OR 1.40 (1.11, 1.78)¹²⁹	-	0.38 (3%)	✗	✓
Myles 2013	Major malformations	Sertraline	Unexposed – any	6 (OBS)	NR	-	OR 1.01 (0.88, 1.17)	0.78 (0%)	✗	✗
Myles 2013	Major malformations	Citalopram	Unexposed – any	7 (OBS)	NR	-	OR 1.04 (0.92, 1.17)	0.86 (0%)	✗	✗
Myles 2013	Major malformations	SSRIs	Unexposed – any	23 (cohort)	NR	-	OR 1.10 (1.03, 1.17)	0.52 (0%)	✗	✗
Myles 2013	Major malformations	SSRIs	Unexposed – any	13 (CC)	NR	-	OR 1.08 (0.94, 1.25)	0.61 (0%)	✗	✗
Myles 2013	Major malformations	SSRIs (early)	Unexposed – any	22 (OBS)	NR	-	OR 1.10 (1.02, 1.18)	0.43 (2%)	✗	✗
Myles 2013	Major malformations	SSRIs (continuous)	Unexposed – any	14 (OBS)	NR	-	OR 1.10 (0.99, 1.21)	0.73 (0%)	✗	✗
Myles 2013	Major malformations	SSRIs	Unexposed – any	27 (OBS)	NR	OR 1.11 (1.04, 1.19)¹³⁰	-	0.94 (0%)	✗	✓
Myles 2013	Major malformations	SSRIs	Unexposed – any	9 (OBS)	NR	-	OR 1.06 (0.95, 1.19) ¹³¹	0.06 (46%)	✗	✗
Myles 2013	Major malformations	SSRIs	Unexposed – any	32 (OBS)	NR	OR 1.10 (1.04, 1.17)¹³²	-	0.75 (0%)	✗	✓
Myles 2013	Major malformations	SSRIs	Unexposed – any	4 (OBS)	NR	-	OR 1.03 (0.84, 1.27) ¹³³	0.16 (43%)	✗	✗
Myles 2013	Major malformations	SSRIs	Unexposed – any	25 (OBS)	NR	OR 1.12 (1.05, 1.20)¹³⁴	-	0.62 (0%)	✗	✓

¹²⁸ Includes higher quality studies only (scored ≥ 4/6 in the quality assessment).

¹²⁹ Controlled for at least one of the potential confounders of interest: (i) tobacco, alcohol or illicit drug use, (ii) maternal age and (iii) maternal parity.

¹³⁰ Includes studies that controlled for tobacco, alcohol or illicit drug use.

¹³¹ Includes studies that did not control for tobacco, alcohol or illicit drug use.

¹³² Includes studies that controlled for maternal age.

¹³³ Includes studies that did not control for maternal age.

¹³⁴ Includes studies that controlled for maternal parity.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Myles 2013	Major malformations	SSRIs	Unexposed – any	11 (OBS)	NR	-	OR 1.04 (0.92, 1.16) ¹³⁵	0.58 (0%)	✖	✖
Myles 2013	Major malformations ¹³⁶	SSRIs	Unexposed – any	22 (OBS)	NR	-	OR 1.07 (1.00, 1.15)	0.96 (0%)	✖	✖
Myles 2013	Major malformations ¹³⁷	SSRIs	Unexposed – any	14 (OBS)	NR	-	OR 1.20 (1.05, 1.36)	0.16 (28%)	✖	✖
Cardiac malformations										
NICE 2015	Cardiac malformations	SSRIs	Unexposed – any	10 (cohort)	261,216	-	OR 1.32 (1.01, 1.73)	0.001 (67%)	✖	✖
NICE 2015	Cardiac malformations	TCAs	Unexposed – any	2 (cohort)	50,257	-	OR 0.50 (0.15, 1.66)	1.00 (0%)	✖	✖
NICE 2015	Cardiac malformations	Paroxetine	Unexposed – any	7 (cohort)	2,371,687	-	OR 1.46 (1.12, 1.90)	0.51 (0%)	✖	✖
NICE 2015	Cardiac malformations	Paroxetine	Unexposed – any	1 (CC)	1,282	-	OR 1.53 (0.55, 4.22)	NA	✖	✖
NICE 2015	Cardiac malformations	Citalopram	Unexposed – any	5 (cohort)	2,323,347	-	OR 1.41 (0.86, 2.29)	0.006 (72%)	✖	✖
NICE 2015	Cardiac malformations	Fluoxetine	Unexposed – any	6 (cohort)	2,322,442	-	OR 1.58 (1.08, 2.32)	0.12 (42%)	✖	✖
NICE 2015	Cardiac malformations	Sertraline	Unexposed – any	5 (cohort)	2,230,622	-	OR 1.29 (0.67, 2.49)	0.003 (75%)	✖	✖
NICE 2015	Cardiac malformations	Fluvoxamine	Unexposed – any	2 (cohort)	628,847	-	OR 0.64 (0.16, 2.58)	NA ¹³⁸	✖	✖
NICE 2015	Cardiac malformations	Escitalopram	Unexposed – any	2 (cohort)	842,848	-	OR 2.54 (0.67, 9.59)	0.05 (75%)	✖	✖
NICE 2015	Cardiac malformations	Venlafaxine	Unexposed – any	1 (cohort)	107,570	-	OR 0.84 (0.12, 5.98)	NA	✖	✖
Wang 2015	Cardiac malformations	SSRIs	Unexposed – any	4 (cohort)	2,010,180	OR 1.06 (0.94, 1.18)	-	0.24 (28%)	✖	✓

¹³⁵ Includes studies that did not control for maternal parity.¹³⁶ Includes chromosomal or genetic abnormalities.¹³⁷ Excludes chromosomal or genetic abnormalities.¹³⁸ The risk estimate for one study was not estimable due to zero events in the exposure group.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Wang 2015	Cardiac malformations	Paroxetine	Unexposed – any	3 (cohort)	NR	OR 0.97 (0.75, 1.19)	-	0.50 (0%)	✖	✓
Wang 2015	Cardiac malformations	Sertraline	Unexposed – any	3 (cohort)	NR	OR 1.00 (0.81, 1.20)	-	0.17 (43%)	✖	✓
Wang 2015	Cardiac malformations	Fluoxetine	Unexposed – any	3 (cohort)	NR	OR 1.11 (0.87, 1.35)	-	0.76 (0%)	✖	✓
Wang 2015	Cardiac malformations	Citalopram	Unexposed – any	3 (cohort)	NR	OR 0.86 (0.56, 1.16)	-	0.44 (0%)	✖	✓
McDonagh 2014	Cardiac malformations	SSRIs	Unexposed – any	5 (OBS)	NR	OR 1.29 (0.96, 1.72)	-	NR (84%)	✖	✓
McDonagh 2014	Cardiac malformations	SSRIs	Unexposed – prior SSRIs	NR	NR	-	OR 1.07 (0.94, 1.20)	NR (0%)	✖	✖
McDonagh 2014	Cardiac malformations	Citalopram/escitalopram	Unexposed – any	6 (OBS)	NR	OR 1.05 (0.84, 1.39)	-	NR (5%)	✖	✓
McDonagh 2014	Cardiac malformations	Fluoxetine	Unexposed – any	8 (OBS)	NR	OR 1.31 (1.08, 1.58)	-	NR (0%)	✖	✓
McDonagh 2014	Cardiac malformations	Paroxetine	Unexposed – any	6 (OBS)	NR	OR 1.49 (1.20, 1.85)	-	NR (0%)	✖	✓
McDonagh 2014	Cardiac malformations	Sertraline	Unexposed – any	7 (OBS)	NR	OR 1.08 (0.70, 1.65)	-	NR (68%)	✖	✓
McDonagh 2014	Cardiac malformations	TCAs	Unexposed – any	2 (OBS)	NR	OR 1.58 (1.10, 2.29)	-	NR	✖	✓
McDonagh 2014	Cardiac malformations	Bupropion	Unexposed – any	1 (CC)	12,749	OR 1.4 (0.8, 2.5)	-	NA	✖	✓
McDonagh 2014	Cardiac malformations	SSRIs	TCAs – any	2 (cohort)	17,810	-	OR 0.66 (0.44, 0.99)	NR	✖	✖
McDonagh 2014	Cardiac malformations	Bupropion	Other ADs – any	1 (CC)	7,005	OR 0.95 (0.62, 1.45)	-	NA	✖	✓
McDonagh 2014	Cardiac malformations	Paroxetine	Fluoxetine – condition	8 (OBS)	NR	-	OR 1.10 (0.85, 1.43)	≥ 0.1 (NR)	✓	✖
McDonagh 2014	Cardiac malformations	Citalopram or escitalopram	Fluoxetine or paroxetine – condition	8 (OBS)	NR	-	OR 0.94 (0.60, 1.47)	NR (49%)	✓	✖

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
McDonagh 2014	Cardiac malformations	Sertraline	Fluoxetine or paroxetine – condition	8 (OBS)	NR	-	OR 0.59 (0.38, 0.93)	NR (42%)	✓	✗
Grigoriadis 2013a	Cardiac malformations	Any ADs	Unexposed (± ADs) – any	18 (OBS)	1,550,271	-	RR 1.26 (1.07, 1.47) ¹³⁹	0.31 (12%)	✗	✗
Grigoriadis 2013a	Cardiac malformations	Any ADs	Unexposed (± ADs) – any	13 ¹⁴⁰ (OBS)	1,547,012	-	RR 1.36 (1.08, 1.71) ¹³⁹	0.13 (31%)	✗	✗
Grigoriadis 2013a	Cardiac malformations	Any ADs	Unexposed (no ADs) – any	9 ¹⁴⁰ (OBS)	1,338,913	-	RR 1.33 (1.02, 1.75) ¹³⁹	0.15 (34%)	✗	✗
Grigoriadis 2013a	Cardiac malformations	Any ADs	Unexposed (± ADs) – any	10 ¹⁴⁰ (OBS)	1,450,406	RR 1.35 (1.07, 1.70)	-	0.18 (29%)	✗	✓
Grigoriadis 2013a	Cardiac malformations	Paroxetine	Unexposed (± ADs) – any	8 (OBS)	1,640,772	-	RR 1.47 (1.12, 1.93) ¹³⁹	0.87 (0%)	✗	✗
Grigoriadis 2013a	Cardiac malformations	Paroxetine	Unexposed (± ADs) – any	7 ¹⁴⁰ (OBS)	1,639,065	-	RR 1.43 (1.08, 1.88) ¹³⁹	0.90 (0%)	✗	✗
Grigoriadis 2013a	Cardiac malformations	Paroxetine	Unexposed (no ADs) – any	5 ¹⁴⁰ (OBS)	1,527,305	-	RR 1.45 (1.06, 1.99) ¹³⁹	0.73 (0%)	✗	✗
Grigoriadis 2013a	Cardiac malformations	Paroxetine	Unexposed (± ADs) – any	6 ¹⁴⁰ (OBS)	1,635,544	RR 1.46 (1.09, 1.94)	-	0.86 (0%)	✗	✓
Grigoriadis 2013a	Cardiac malformations	Fluoxetine	Unexposed (± ADs) – any	6 (OBS)	1,585,725	-	RR 1.33 (0.92, 1.90) ¹³⁹	0.21 (30%)	✗	✗
Grigoriadis 2013a	Cardiac malformations	Fluoxetine	Unexposed (± ADs) – any	4 ¹⁴⁰ (OBS)	1,583,857	-	RR 1.17 (0.89, 1.55) ¹³⁹	0.42 (0%)	✗	✗
Grigoriadis 2013a	Cardiac malformations	Fluoxetine	Unexposed (no ADs) – any	3 ¹⁴⁰ (OBS)	1,474,754	-	RR 1.19 (0.83, 1.72) ¹³⁹	0.25 (29%)	✗	✗
Grigoriadis 2013a	Cardiac malformations	Fluoxetine	Unexposed (± ADs) – any	4 ¹⁴⁰ (OBS)	1,583,857	RR 1.17 (0.89, 1.55)	-	0.42 (0%)	✗	✓
Myles 2013	Cardiac malformations	Fluoxetine	Unexposed – any	6 (OBS)	NR	-	OR 1.25 (0.98, 1.60)	0.19 (33%)	✗	✗
Myles 2013	Cardiac malformations	Paroxetine	Unexposed – any	8 (OBS)	NR	-	OR 1.44 (1.12, 1.86)	0.82 (0%)	✗	✗

¹³⁹ Adjusted data included preferentially where available.¹⁴⁰ Studies above quality threshold.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Myles 2013	Cardiac malformations	Paroxetine	Unexposed – any	5 ¹⁴¹ (OBS)	NR	OR 1.41 (1.06, 1.87) ¹⁴²	-	0.65 (0%)	✗	✓
Myles 2013	Cardiac malformations	Sertraline	Unexposed – any	5 (OBS)	NR	-	OR 0.93 (0.70, 1.24)	0.03 (63%)	✗	✗
Myles 2013	Cardiac malformations	Citalopram	Unexposed – any	6 (OBS)	NR	-	OR 1.03 (0.80, 1.32)	0.58 (0%)	✗	✗
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	17 (cohort)	NR	-	OR 1.14 (0.95, 1.36)	0.02 (45%)	✗	✗
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	9 (CC)	NR	-	OR 1.18 (0.92, 1.52)	0.39 (6%)	✗	✗
Myles 2013	Cardiac malformations	SSRIs (early)	Unexposed – any	17 (OBS)	NR	-	OR 1.22 (1.01, 1.48)	0.27 (15%)	✗	✗
Myles 2013	Cardiac malformations	SSRIs (continuous)	Unexposed – any	9 (OBS)	NR	-	OR 1.06 (0.85, 1.33)	0.03 (54%)	✗	✗
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	25 (OBS)	NR	OR 1.17 (1.01, 1.34) ¹⁴³	-	0.07 (31%)	✗	✓
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	1 (OBS)	NR	-	OR 0.44 (0.13, 1.47) ¹⁴⁴	NA	✗	✗
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	24 (OBS)	NR	OR 1.17 (1.01, 1.35) ¹⁴⁵	-	0.05 (34%)	✗	✓
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	2 (OBS)	NR	-	OR 0.72 (0.32, 1.64) ¹⁴⁶	0.25 (26%)	✗	✗
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	20 (OBS)	NR	OR 1.15 (0.98, 1.34) ¹⁴⁷	-	0.04 (38%)	✗	✓
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	6 (OBS)	NR	-	OR 1.21 (0.76, 1.93) ¹⁴⁸	0.25 (24%)	✗	✗

¹⁴¹ Includes higher quality studies only (scored ≥ 4/6 in the quality assessment).

¹⁴² Controlled for at least one of the potential confounders of interest: (i) tobacco, alcohol or illicit drug use, (ii) maternal age and (iii) maternal parity.

¹⁴³ Includes studies that controlled for tobacco, alcohol or illicit drug use.

¹⁴⁴ Includes studies that did not control for tobacco, alcohol or illicit drug use.

¹⁴⁵ Includes studies that controlled for maternal age.

¹⁴⁶ Includes studies that did not control for maternal age.

¹⁴⁷ Includes studies that controlled for maternal parity.

¹⁴⁸ Includes studies that did not control for maternal parity.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Myles 2013	Cardiac malformations ¹⁴⁹	SSRIs	Unexposed – any	15 (OBS)	NR	-	OR 1.09 (0.91, 1.31)	0.08 (36%)	✗	✗
Myles 2013	Cardiac malformations ¹⁵⁰	SSRIs	Unexposed – any	11 (OBS)	NR	-	OR 1.27 (1.00, 1.62)	0.15 (37%)	✗	✗
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	2 ¹⁵¹ (OBS)	NR	-	OR 1.32 (0.80, 2.18)	0.69 (0%)	✗	✗
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	6 ¹⁵² (OBS)	NR	-	OR 1.14 (1.14, 1.90)	0.65 (0%)	✗	✗
Wurst 2010	Cardiac malformations	Paroxetine	Unexposed – any	11 (OBS)	NR	OR 1.48 (1.17, 1.86)¹⁵³	-	1.00 (NR)	✗	✓
Wurst 2010	Cardiac malformations	Paroxetine	Unexposed – any	3 (OBS)	NR	-	OR 1.21 (0.51, 2.84) ¹⁵⁴	0.1 (NR)	✗	✗
Wurst 2010	Cardiac malformations	Paroxetine	No SSRI prescriptions – any	7 (OBS)	NR	-	OR 1.34 (0.98, 1.82) ¹⁵⁵	0.7 (NR)	✗	✗
Wurst 2010	Cardiac malformations	Paroxetine	Untreated or treated with other antidepressants/ depression	2 (OBS)	NR	-	OR 1.44 (0.81, 2.54) ¹⁵⁵	0.9 (NR)	✓	✗
Wurst 2010	Cardiac malformations	Paroxetine	Nonteratogenic medications/any	4 (OBS)	NR	-	OR 1.89 (0.84, 4.23) ¹⁵⁵	0.5 (NR)	✗	✗
Septal malformations										
Grigoriadis 2013a	Septal heart defects	Any ADs	Unexposed (± ADs) – any	12 (OBS)	1,704,652	-	RR 1.37 (1.11, 1.69) ¹⁵⁶	0.17 (28%)	✗	✗
Grigoriadis 2013a	Septal heart defects	Any ADs	Unexposed (± ADs) – any	9 ¹⁵⁷ (OBS)	1,703,561	-	RR 1.40 (1.10, 1.77) ¹⁵⁶	0.08 (44%)	✗	✗

¹⁴⁹ Includes chromosomal or genetic abnormalities.¹⁵⁰ Excludes chromosomal or genetic abnormalities.¹⁵¹ Sensitivity analysis to check for publication bias: includes studies with funding only.¹⁵² Sensitivity analysis to check for publication bias: includes studies with no funding only.¹⁵³ Adjusted for at least one of the nine potential confounders identified a priori as being important: parity, maternal age, use of tobacco and/or alcohol, pregnancy outcome history, other diagnoses, family history of defects, body mass index, vitamin use and use of other medications.¹⁵⁴ Adjusted for none of the nine potential confounders identified a priori as being important: parity, maternal age, use of tobacco and/or alcohol, pregnancy outcome history, other diagnoses, family history of defects, body mass index, vitamin use and use of other medications.¹⁵⁵ May include some adjusted results.¹⁵⁶ Adjusted data included preferentially where available.¹⁵⁷ Studies above quality threshold.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Grigoriadis 2013a	Septal heart defects	Any ADs	Unexposed (no ADs) – any	5 ¹⁵⁷ (OBS)	1,494,368	-	RR 1.17 (1.03, 1.33) ¹⁵⁶	0.53 (0%)	✖	✖
Grigoriadis 2013a	Septal heart defects	Any ADs	Unexposed (± ADs) – any	7 ¹⁵⁷ (OBS)	1,608,759	RR 1.35 (1.08, 1.68)	-	0.11 (43%)	✖	✓
Grigoriadis 2013a	Septal heart defects	Paroxetine	Unexposed (± ADs) – any	3 (OBS)	226,272	-	RR 0.97 (0.47, 2.03) ¹⁵⁶	0.67 (0%)	✖	✖
Grigoriadis 2013a	Septal heart defects	Paroxetine	Unexposed (± ADs) – any	3 ¹⁵⁷ (OBS)	226,272	-	RR 0.97 (0.47, 2.03) ¹⁵⁶	0.67 (0%)	✖	✖
Grigoriadis 2013a	Septal heart defects	Paroxetine	Unexposed (no ADs) – any	2 ¹⁵⁷ (OBS)	224,773	-	RR 0.78 (0.32, 1.88) ¹⁵⁶	0.90 (0%)	✖	✖
Grigoriadis 2013a	Septal heart defects	Paroxetine	Unexposed (± ADs) – any	3 ¹⁵⁷ (OBS)	226,272	RR 0.97 (0.47, 2.03)	-	0.67 (0%)	✖	✓
Grigoriadis 2013a	Septal heart defects	Fluoxetine	Unexposed (± ADs) – any	2 (OBS)	225,193	-	RR 1.18 (0.65, 2.14) ¹⁵⁶	0.46 (0%)	✖	✖
Grigoriadis 2013a	Septal heart defects	Fluoxetine	Unexposed (± ADs) – any	2 ¹⁵⁷ (OBS)	224,937	-	RR 1.18 (0.65, 2.14) ¹⁵⁶	0.46 (0%)	✖	✖
Grigoriadis 2013a	Septal heart defects	Fluoxetine	Unexposed (no ADs) – any	2 ¹⁵⁷ (OBS)	224,937	-	RR 1.18 (0.65, 2.14) ¹⁵⁶	0.46 (0%)	✖	✖
Grigoriadis 2013a	Septal heart defects	Fluoxetine	Unexposed (± ADs) – any	2 ¹⁵⁷ (OBS)	224,937	RR 1.18 (0.65, 2.14)	-	0.46 (0%)	✖	✓

Abbreviations: AD, antidepressant; CC, case control; CI, confidence interval; NA, not applicable; NE, not estimable; OBS, observational study/studies; OR, odds ratio; RE, risk estimate; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. Data shown in grey hatching is either (i) adjusted for potential confounders or (ii) limited/adjusted for psychiatric illness. Data shown in grey shading is (i) adjusted for potential confounders and (ii) limited/adjusted for psychiatric illness. Only shaded data is carried into **Section AppD4.1.1**.

AppD3.1.1.1.2 Pregnancy and birth outcomes – antidepressants

Table AppD3-2 Antidepressant infant and maternal harms data extraction from systematic reviews – pregnancy and birth outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Neonatal mortality										
McDonagh 2014	Early neonatal mortality	SNRIs	Unexposed – any	1 (cohort)	NR	RR 1.3 (0.5, 2.8)	-	NA	✗	✓
McDonagh 2014	Late neonatal mortality	SNRIs	Unexposed – any	1 (cohort)	NR	RR 0.00 (0.0, 4.4)	-	NA	✗	✓
Miscarriage										
NICE 2015	Miscarriage/ spontaneous abortion	SSRIs	Unexposed – any	9 (cohort)	5,688	-	OR 1.60 (1.01, 2.53)	0.28 (22%)	✗	✗
Ross 2013	Miscarriage/ spontaneous abortion	Any ADs	Unexposed – any	11 (OBS)	NR	-	OR 1.45 (0.11, 1.72)	0.40 (4%)	✗	✗
Ross 2013	Miscarriage/ spontaneous abortion	Any ADs	Unexposed – any	3 ¹⁶¹ (OBS)	NR	-	OR 1.47 (0.99, 2.17)	0.37 (0%)	✗	✗
Ross 2013	Miscarriage/ spontaneous abortion	Any ADs	Unexposed – any	2 ¹⁶¹ (OBS)	NR	OR 1.49 (0.71, 3.13)	-	0.16 (50%)	✗	✓
Preterm birth										
Saccone 2016a	Preterm birth	SSRIs	Unexposed – any	8 (OBS)	1,237,669	-	OR 1.45 (1.24, 1.68)	<0.001 (86%)	✗	✗
NICE 2015	Preterm delivery	SSRIs	Unexposed – any	9 (cohort)	225,371	-	OR 1.38 (0.99, 1.92)	<0.001 (74%)	✗	✗
NICE 2015	Preterm delivery	TCAs	Unexposed – any	1 (cohort)	418	-	OR 2.01 (0.94, 4.28)	NA	✗	✗
Huang 2014	Preterm birth	Any ADs	Unexposed – any	28 (OBS)	NR	-	RR 1.69 (1.52, 1.88)	0.005 (45%)	✗	✗
Huang 2014	Preterm birth	SSRIs	Unexposed – any	18 (OBS)	NR	-	RR 1.74 (1.52, 2.00)	0.006 (52%)	✗	✗
Huang 2014	Preterm birth	Other/mixed ADs	Unexposed – any	10 (OBS)	NR	-	RR 1.63 (1.38, 1.93)	0.14 (33%)	✗	✗

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Huang 2014	Preterm birth	Any ADs	Unexposed – any	13 (OBS – retrospective)	NR	-	RR 1.59 (1.42, 1.78)	0.02 (50%)	✗	✗
Huang 2014	Preterm birth	Any ADs	Unexposed – any	15 (OBS – prospective)	NR	-	RR 1.91 (1.57, 2.32)	0.20 (23%)	✗	✗
Huang 2014	Preterm birth	Any ADs	Unexposed – depressed	4 (OBS)	NR	-	RR 2.85 (2.00, 4.07)	0.57 (0%)	✗	✗
Huang 2014	Preterm birth	Any ADs	Unexposed – mixed	11 (OBS)	NR	-	RR 1.55 (1.39, 1.73)	0.07 (43%)	✗	✗
Huang 2014	Preterm birth	Any ADs	Unexposed – non–depressed	11 (OBS)	NR	-	RR 1.84 (1.50, 2.27)	0.11 (34%)	✗	✗
Huang 2014	Preterm birth	Any ADs	Unexposed – any	6 (OBS)	NR	-	RR 1.90 (1.07, 3.38) ¹⁵⁸	0.07 (50%)	✗	✗
Huang 2014	Preterm birth	Any ADs	Unexposed – any	22 (OBS)	NR	-	RR 1.70 (1.53, 1.89) ¹⁵⁹	0.01 (46%)	✗	✗
Huybrechts 2014b	Preterm birth	Any ADs (early)	Unexposed – any	6/8 (OBS)	NR	-	OR 1.57 (1.30, 1.90)	0.32 (14%)	✗	✗
Huybrechts 2014b	Preterm birth	Any ADs (any time)	Unexposed – any	4/4 (OBS)	NR	-	OR 1.44 (1.34, 1.56)	0.41 (0%)	✗	✗
Huybrechts 2014b	Preterm birth	Any ADs (early)	Unexposed – any	4/8 (OBS)	NR	OR 1.16 (0.92, 1.45)	-	<0.001 (85%)	✗	✓
Huybrechts 2014b	Preterm birth	Any ADs (late)	Unexposed – any	8/12 (OBS)	NR	OR 1.96 (1.62, 2.38)	-	<0.001 (84%)	✗	✓
Huybrechts 2014b	Preterm birth	Any ADs (any time)	Unexposed – any	11/17 (OBS)	NR	OR 1.53 (1.40, 1.66)	-	0.23 (19%)	✗	✓
Huybrechts 2014b	Preterm birth	Any ADs	Unexposed – psychiatric illness	10/12 (OBS)	NR	-	OR 1.61 (1.26, 2.05)	0.04 (46%)	✓	✗
Huybrechts 2014b	Preterm birth	Any ADs	Unexposed – no psychiatric illness	10/12 (OBS)	NR	-	OR 1.88 (1.48, 2.40)	0.28 (20%)	✓	✗

¹⁵⁸ Controlled for depression severity.¹⁵⁹ Not controlled for depression severity.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Ross 2013	Preterm birth	Any ADs	Unexposed – any	19 (OBS)	NR	-	OR 1.52 (1.39, 1.66)	0.34 (9%)	✖	✖
Ross 2013	Preterm birth	Any ADs	Unexposed – any	13 ¹⁶¹ (OBS)	NR	-	OR 1.55 (1.38, 1.74)	0.28 (16%)	✖	✖
Ross 2013	Preterm birth	Any ADs	Unexposed – disease	5 ¹⁶¹ (OBS)	NR	-	OR 1.58 (0.97, 2.56)	0.001 (75%)	✖	✖
Ross 2013	Preterm birth	Any ADs	Unexposed – any	9 ¹⁶¹ (OBS)	NR	OR 1.70 (1.35, 2.14)	-	0.21 (25%)	✖	✖
Ross 2013	Preterm birth	Any ADs	Unexposed – disease	2 ¹⁶¹ (OBS)	NR	OR 1.79 (0.77, 4.14)	-	0.007 (80%)	✓	✓
Lopez-Yarto 2012	Preterm birth	SSRIs	Unexposed – disease	1 (cohort)	62	-	RR 0.97 (0.31, 3.05)	NA	✓	✖
PNAS										
NICE 2015	PNAS	Any ADs	Unexposed – any	6 (cohort)	1,954	-	OR 4.13 (2.14, 7.98)	0.02 (62%)	✖	✖
NICE 2015	PNAS	Paroxetine	Unexposed – any	1 (cohort)	82	-	OR 2.23 (0.57, 8.70)	NA	✖	✖
Grigoriadis 2013b	PNAS	Any ADs	Unexposed – any	8 (OBS)	959	-	OR 5.07 (3.25, 7.90) ¹⁶⁰	0.62 (0%)	✖	✖
Grigoriadis 2013b	PNAS	Any ADs	Unexposed – any	7 ¹⁶¹ (OBS)	813	-	OR 4.34 (2.53, 7.45) ¹⁶⁰	0.63 (0%)	✖	✖
Grigoriadis 2013b	PNAS	Any ADs (exposed late)	Unexposed – any	5 (OBS)	794	-	OR 5.13 (2.86, 9.21) ¹⁶⁰	0.29 (20%)	✖	✖
Grigoriadis 2013b	PNAS	Any ADs (unsure/not exposed late)	Unexposed – any	3 (OBS)	165	-	OR 5.20 (1.86, 14.6) ¹⁶⁰	0.83 (0%)	✖	✖
Grigoriadis 2013b	PNAS	Any ADs	Unexposed – any	2 (OBS)	312	OR 4.74 (2.14, 10.5)	-	0.17 (48%)	✖	✓
Persistent pulmonary hypertension										
NICE 2015	Persistent pulmonary hypertension	SSRIs	Unexposed – any	1 (cohort)	1,599,154	-	OR 2.51 (1.78, 3.54)	NA	✖	✖

¹⁶⁰ Includes adjusted estimates preferentially where available.¹⁶¹ Above quality threshold (excludes very low quality studies).

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Grigoriadis 2014	Persistent pulmonary hypertension	SSRIs (any time)	Unexposed – any	2 (OBS)	NR	-	OR 1.55 (0.79, 3.04) ¹⁶⁰	0.71 (0%)	✗	✗
Grigoriadis 2014	Persistent pulmonary hypertension	SSRIs (most or all of pregnancy)	Unexposed – any	2 (OBS)	NR	-	OR 3.33 (1.58, 7.02) ¹⁶⁰	0.67 (0%)	✗	✗
Grigoriadis 2014	Persistent pulmonary hypertension	SSRIs (early pregnancy)	Unexposed – any	3 (OBS)	NR	-	OR 1.23 (0.58, 2.60) ¹⁶⁰	0.01 (78%)	✗	✗
Grigoriadis 2014	Persistent pulmonary hypertension	SSRIs (late pregnancy)	Unexposed – any	5 (OBS)	NR	-	OR 2.50 (1.32, 4.73) ¹⁶⁰	0.08 (52%)	✗	✗
Grigoriadis 2014	Persistent pulmonary hypertension	SSRIs	Unexposed – any	2 (CC)	NR	-	OR 5.31 (1.94, 14.6) ¹⁶⁰	0.03 (78%)	✗	✗
Grigoriadis 2014	Persistent pulmonary hypertension	SSRIs	Unexposed – any	3 (cohort)	NR	-	OR 2.14 (1.57, 2.92) ¹⁶⁰	0.61 (0%)	✗	✗
Grigoriadis 2014	Persistent pulmonary hypertension (infants with congenital malformations excluded)	SSRIs	Unexposed – any	2 (OBS)	NR	-	OR 5.31 (1.94, 14.6) ¹⁶⁰	0.03 (78%)	✗	✗
Grigoriadis 2014	Persistent pulmonary hypertension (uncontrolled for congenital malformations)	SSRIs	Unexposed – any	3 (OBS)	NR	-	OR 2.14 (1.57, 2.92) ¹⁶⁰	0.61 (0%)	✗	✗
Grigoriadis 2014	Persistent pulmonary hypertension (controlled for meconium aspiration)	SSRIs	Unexposed – any	2 (OBS)	NR	-	OR 2.07 (1.46, 2.93)	0.06 (71%)	✗	✗

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Grigoriadis 2014	Persistent pulmonary hypertension (uncontrolled for meconium aspiration)	SSRIs	Unexposed – any	3 (OBS)	NR	-	OR 3.12 (1.77, 5.48)	0.19 (40%)	✗	✗
McDonagh 2014	Persistent pulmonary hypertension	SSRIs	Unexposed – any	4 (OBS)	NR	OR 2.41 (1.347, 3.95)	-	NR (14%)	✗	✓
McDonagh 2014	Persistent pulmonary hypertension	SSRIs in early pregnancy ¹⁶²	Unexposed – any	4 (OBS)	NR	OR 1.45 (0.84, 2.49)	-	NR (69%)	✗	✓
McDonagh 2014	Persistent pulmonary hypertension	SSRIs in late pregnancy ¹⁶³	Unexposed – any	3 (OBS)	NR	OR 2.72 (1.63, 4.54)	-	NR (48%)	✗	✓
McDonagh 2014	Persistent pulmonary hypertension	Fluoxetine in late pregnancy - ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 2.0 (1.0, 3.8)	-	NA	✗	✓
McDonagh 2014	Persistent pulmonary hypertension	Citalopram in late pregnancy - ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 2.3 (1.2, 4.1)	-	NA	✗	✓
McDonagh 2014	Persistent pulmonary hypertension	Paroxetine in late pregnancy - ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 2.8 (1.2, 6.7)	-	NA	✗	✓
McDonagh 2014	Persistent pulmonary hypertension	Sertraline in late pregnancy - ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 2.3 (1.3, 4.4)	-	NA	✗	✓
McDonagh 2014	Persistent pulmonary hypertension	Escitalopram in late pregnancy - ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 1.3 (0.2, 9.5)	-	NA	✗	✓
McDonagh 2014	Persistent pulmonary hypertension	Fluoxetine in early pregnancy - ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	1.3 (0.6, 2.8)	-	NA	✗	✓
McDonagh 2014	Persistent pulmonary hypertension	Citalopram in early pregnancy - ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	1.8 (1.1, 3.0)	-	NA	✗	✓

¹⁶² Not defined¹⁶³ Mostly > 20 weeks

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
McDonagh 2014	Persistent pulmonary hypertension	Paroxetine in early pregnancy - ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	1.3 (0.5, 3.5)	-	NA	✖	✓
McDonagh 2014	Persistent pulmonary hypertension	Sertraline in early pregnancy - ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	1.9 (1.0, 3.6)	-	NA	✖	✓
McDonagh 2014	Persistent pulmonary hypertension	Escitalopram in early pregnancy - ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	0.3 (0, 2.2)	-	NA	✖	✓
Respiratory distress										
NICE 2015	Respiratory distress	Any ADs	Unexposed – any	8 (cohort)	754,011	-	OR 2.07 (1.79, 2.39)	0.29 (18%)	✖	✖
McDonagh 2014	Respiratory distress	SSRIs	Unexposed – disease	3 (cohort)	15,793		OR 1.91 (1.63, 2.24)	NR (0%)	✓	✖
McDonagh 2014	Respiratory distress	SSRIs	Unexposed – any	4 (OBS)	748,658	OR 1.79 (1.64, 1.97)	-	NR (0%)	✖	✓
McDonagh 2014	Respiratory distress	TCAs	Unexposed – any	2 (OBS)	NR	OR 2.11 (1.57, 2.83)	-	0.78 (NR)	✖	✓
McDonagh 2014	Respiratory distress	SSRIs	Nortriptyline – disease	1 (cohort)	21	-	-	-	✓	✖
McDonagh 2014	Respiratory distress	SSRIs	SSRIs – disease	1 (cohort)	20	-	-	-	✓	✖
Grigoriadis 2013b	Respiratory distress	Any ADs	Unexposed – any	9 (OBS)	676,186	-	OR 2.20 (1.81, 2.66) ¹⁶⁰	0.12 (38%)	✖	✖
Grigoriadis 2013b	Respiratory distress	Any ADs	Unexposed – any	8 ¹⁶¹ (OBS)	676,040	-	OR 2.20 (1.79, 2.72) ¹⁶⁰	0.08 (45%)	✖	✖
Grigoriadis 2013b	Respiratory distress	Any ADs (exposed late)	Unexposed – any	6 (OBS)	76,657	-	OR 2.64 (1.69, 4.14) ¹⁶⁰	0.16 (37%)	✖	✖
Grigoriadis 2013b	Respiratory distress	Any ADs (unsure/not exposed late)	Unexposed – any	3 (OBS)	599,529	-	OR 2.14 (1.60, 2.86) ¹⁶⁰	0.09 (59%)	✖	✖
Grigoriadis 2013b	Respiratory distress	Any ADs	Unexposed – any	2 (OBS)	583,939	OR 2.24 (1.75, 2.86)	-	0.77 (0%)	✖	✓

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Tremors										
NICE 2015	Tremors	Any ADs	Unexposed – any	4 (cohort)	482	-	OR 8.14 (4.23, 15.7)	0.27 (24%)	✖	✖
Grigoriadis 2013b	Tremors	Any ADs (exposed late)	Unexposed – any	4 (OBS)	482	-	OR 7.89 (3.33, 18.7)	0.14 (45%)	✖	✖
Grigoriadis 2013b	Tremors	Any ADs	Unexposed – any	3 ¹⁶¹ (OBS)	336	-	OR 6.74 (2.39, 19.0)	0.13 (51%)	✖	✖
Convulsions										
McDonagh 2014	Neonatal convulsions	SSRIs	Unexposed – disease	1 (CC)	15,685	-	RD 0.0005 (-0.0015, 0.0025)	NA	✓	✖
McDonagh 2014	Neonatal convulsions	SSRIs	Unexposed – any	1 (CC)	NR	-	NR	NA	✖	✖
McDonagh 2014	Neonatal convulsions	SSRIs	Unexposed – any	7 (OBS)	NR	-	OR 4.11 (1.78, 9.48)	NR	✖	✖
McDonagh 2014	Neonatal convulsions	TCAs	Unexposed – any	1 (CC)	582,796	OR 6.8 (2.2, 16.0)	-	NR	✖	✓

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
McDonagh 2014	Neonatal convulsions	TCA	Unexposed – any	2 (OBS)	583,214	-	OR 7.82 (2.81, 21.8)	NR	✗	✗
Postpartum haemorrhage										
Jiang 2016	Postpartum haemorrhage	ADs (any time)	Unexposed - adjusted ¹⁶⁴	8 (17) ¹⁶⁵ (OBS)	NR	RR 1.32 (1.17, 1.48)	-	<0.001 (85%)	✓	✓
Jiang 2016	Postpartum haemorrhage	ADs (any time)	Unexposed - adjusted ¹⁶⁴	8 (17) ¹⁶⁶ (OBS)	NR	OR 1.25 (1.1, 1.5)	-	<0.001 (87%)	✓	✓
Jiang 2016	Postpartum haemorrhage – <u>similar definition of PPH</u>	ADs (any time)	Unexposed - adjusted ¹⁶⁴	3 (11) ¹⁶⁶	NR	OR 1.24 (1.09, 1.41)	-	<0.001 (90%)	✓	✓
Jiang 2016	Postpartum haemorrhage – <u>vaginal delivery</u>	ADs (any time)	Unexposed - adjusted ¹⁶⁴	2 (3) ¹⁶⁶	NR	OR 1.43 (1.15, 1.78)	-	0.32 (1%)	✓	✓
Jiang 2016	Postpartum haemorrhage – <u>caesarean section</u>	ADs (any time)	Unexposed - adjusted ¹⁶⁴	2 (3) ¹⁶⁶	NR	OR 2.02 (1.61, 2.54)	-	0.31 (12%)	✓	✓
Jiang 2016	Postpartum haemorrhage	ADs (any time)	Unexposed – <u>adjusted for disease severity</u>	5 (13) ¹⁶⁶	NR	OR 1.31 (1.14, 1.50)	-	0.31 (88%)	✓	✓
Jiang 2016	Postpartum haemorrhage	ADs (past users)	Unexposed - adjusted ¹⁶⁴	2 (3) ¹⁶⁶	NR	OR 1.08 (0.88, 1.31)	-	0.46 (68%)	✓	✓
Jiang 2016	Postpartum haemorrhage	ADs (recent users)	Unexposed - adjusted ¹⁶⁴	5 (11) ¹⁶⁶	NR	OR 1.32 (1.15, 1.51)	-	<0.01 (81%)	✓	✓
Jiang 2016	Postpartum haemorrhage	ADs (recent users)	Unexposed - adjusted ¹⁶⁴	4 (6) ¹⁶⁶	NR	OR 1.37 (1.09, 1.71)	-	<0.001 (83%)	✓	✓
Jiang 2016	Postpartum hemorrhage	SRI ¹⁶⁷ (any time)	Unexposed - adjusted ¹⁶⁴	4(10) ¹⁶⁶	NR	OR 1.23 (1.06, 1.44)	-	<0.001 (87%)	✓	✓
Jiang 2016	Postpartum hemorrhage	SRI ¹⁶⁷ (recent users)	Unexposed - adjusted ¹⁶⁴	3 (7) ¹⁶⁶	NR	OR 1.30 (1.06, 1.60)	-	<0.001 (84%)	✓	✓
Jiang 2016	Postpartum hemorrhage	SRI ¹⁶⁷ (current users)	Unexposed - adjusted ¹⁶⁴	2 (4) ¹⁶⁶	NR	OR 1.39 (0.96, 1.61)	-	<0.001 (89%)	✓	✓
Jiang 2016	Postpartum hemorrhage	Non-SRI (any time)	Unexposed - adjusted ¹⁶⁴	2 (4) ¹⁶⁶	NR	OR 1.31 (1.10, 1.56)	-	0.33 (12%)	✓	✓
Jiang 2016	Postpartum hemorrhage	SSRI (any time)	Unexposed - adjusted ¹⁶⁴	5 (10) ¹⁶⁶	NR	OR 1.20 (1.04, 1.38)	-	<0.001 (86%)	✓	✓

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Jiang 2016	Postpartum hemorrhage	SSRI (recent users)	Unexposed - adjusted ¹⁶⁴	3 (5) ¹⁶⁶	NR	OR 1.19 (1.02, 1.37)	-	<0.001 (78%)	✓	✓
Jiang 2016	Postpartum hemorrhage	SSRI (current users)	Unexposed - adjusted ¹⁶⁴	2 (2) ¹⁶⁶	NR	OR 1.24 (1.02, 1.37)	-	<0.001 (92%)	✓	✓
Jiang 2016	Postpartum hemorrhage	SNRI (any time)	Unexposed - adjusted ¹⁶⁴	2 (6) ¹⁶⁶	NR	OR 1.62 (1.41, 1.85)	-	0.26 (24%)	✓	✓
Jiang 2016	Postpartum hemorrhage	SNRI (recent users)	Unexposed - adjusted ¹⁶⁴	2 (4) ¹⁶⁶	NR	OR 1.73 (1.50, 2.00)	-	0.66 (0%)	✓	✓
Jiang 2016	Postpartum hemorrhage	SNRI (current users)	Unexposed - adjusted ¹⁶⁴	2 (2) ¹⁶⁶	NR	OR 1.79 (1.53, 2.10)	-	0.68 (0%)	✓	✓

Abbreviations: AD, antidepressant; CC, case control; CI, confidence interval; NA, not applicable; NR, not reported; OBS, observational study/studies; OR, odds ratio; PNAS, poor neonatal adaptation syndrome; RE, risk estimate; RR, relative risk; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. Data shown in grey hatching is either (i) adjusted for potential confounders or (ii) limited/adjusted for psychiatric illness. Data shown in grey shading is (i) adjusted for potential confounders and (ii) limited/adjusted for psychiatric illness. Only shaded data is carried into **Section AppD4.1.1**.

¹⁶⁴ Most included studies included adjustment for depression/psychiatric illness.

¹⁶⁵ Number of estimates included in meta-analysis.

¹⁶⁶ Number of estimates included in meta-analysis.

¹⁶⁷ Includes SSRIs and SNRIs.

AppD3.1.1.1.3 Neurodevelopmental outcomes – antidepressants

Table AppD3-3 Antidepressant infant harms data extraction from systematic reviews – neurodevelopmental outcomes

Study ID (quality)	Outcome (age at outcome measurement)	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Kaplan 2016	ASD (≥0 years)	SSRIs	Unexposed – any	5 (CC)	1,225,692	OR 1.66 (1.23, 2.23)	-	0.18 (37%)	✗	✓
Kaplan 2016	ASD (≥0 years)	Non-SSRIs	Unexposed - any	3 (CC)	596,318	OR 2.05 (1.20, 3.49)	-	0.77 (0%)	✗	✓
Kaplan 2016	ASD (≥2 years)	SSRIs (preconception)	Unexposed – any	3 (CC)	635,612	OR 1.84 (1.48, 2.28)	-	0.40 (0%)	✗	✓
Kaplan 2016	ASD (≥2 years)	SSRIs (first trimester)	Unexposed – any	4 (CC)	636,578	OR 1.90 (1.28, 2.83)	-	0.16 (42%)	✗	✓
Kaplan 2016	ASD (≥2 years)	SSRIs (second trimester)	Unexposed – any	4 (CC)	636,578	OR 1.73 (1.15, 2.61)	-	0.24 (29%)	✗	✓
Kaplan 2016	ASD (≥2 years)	SSRIs (third trimester)	Unexposed – any	4 (CC)	636,578	OR 1.64 (0.83, 3.24)	-	0.02 (68%)	✗	✓
Kaplan 2016	ASD (≥2 years)	SSRIs (third trimester – sensitivity 1)	Unexposed – any	3 (CC)	631,179	OR 2.48 (1.73, 3.57)	-	0.45 (0%)	✗	✓
Kaplan 2016	ASD (≥2 years)	SSRIs (third trimester – sensitivity 2)	Unexposed – any	3 (CC)	8,170	OR 1.11 (0.66, 1.88)	-	0.36 (3%)	✗	✓
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs (Study set A) ¹⁶⁸	Unexposed (other ADs or no ADs) - any	7 (cohort/ CC)	988,245	OR 1.45 (1.15, 1.82)	-	0.19 (31%)	✗	✓
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs (Study set A)	Unexposed (other ADs or no ADs) - any	5 (CC)	355,394	OR 1.37 (1.08, 1.74)	-	0.53 (0%)	✗	✓
Kobayashi 2016	ASD (Unknown)	SSRIs (Study set A)	Unexposed (other ADs or no ADs) - any	2 (cohort)	632,851	OR 1.69 (0.80, 3.57)	-	0.02 (82%)	✗	✓
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs (Study set B) ¹⁶⁹	Unexposed (other ADs or no ADs) - any	7 (cohort/ CC)	1,015,658	OR 1.55 (1.28, 1.88)	-	0.29 (19%)	✗	✓

¹⁶⁸ Includes Hviid 2013 for Danish dataset.¹⁶⁹ Includes Sørensen 2013 for Danish dataset.

Study ID (quality)	Outcome (age at outcome measurement)	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs (Study set B)	Unexposed (other ADs or no ADs) - any	5 (CC)	355,394	OR 1.37 (1.08, 1.74)	-	0.53 (0%)	✗	✓
Kobayashi 2016	ASD (unknown)	SSRIs (Study set B)	Unexposed (other ADs or no ADs) - any	2 (cohort)	660,264	OR 1.89 (1.21, 2.95)	-	0.12 (58%)	✗	✓
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs	Unexposed (other ADs) – disease	3 (cohort/ CC)	703,799	OR 1.14 (0.67, 1.96)	-	0.74 (0%)	✓	✓
Kobayashi 2016	ASD (≥0 years)	SSRIs	Unexposed (other ADs) – disease	2 (CC)	49,511	OR 0.98 (0.39, 2.43)	-	0.52 (0%)	✓	✓
Kobayashi 2016	ASD (Unknown)	SSRIs	Unexposed (other ADs) – disease	1 (cohort)	654,288	OR 1.24 (0.63, 2.43)	-	NA	✓	✓
Kobayashi 2016	ASD (Unknown or ≥2 years)	SSRIs (Study set A)	Unexposed – disease	3 (cohort/ CC)	633,663	OR 0.96 (0.57, 1.63)	-	0.22 (35%)	✓	✓
Kobayashi 2016	ASD (≥2 years)	SSRIs (Study set A)	Unexposed – disease	1 (CC)	812	OR 1.86 (0.76, 4.58)	-	NA	✓	✓
Kobayashi 2016	ASD (Unknown)	SSRIs (Study set A)	Unexposed – disease	2 (cohort)	632,851	OR 0.79 (0.51, 1.23)	-	0.58 (0%)	✓	✓
Kobayashi 2016	ASD (Unknown or ≥2 years)	SSRIs (Study set B)	Unexposed – disease	3 (cohort/ CC)	661,076	1.22 (0.72, 2.08)	-	0.22 (34%)	✓	✓
Kobayashi 2016	ASD (≥2 years)	SSRIs (Study set B)	Unexposed – disease	1 (CC)	812	OR 1.86 (0.76, 4.58)	-	NA	✓	✓
Kobayashi 2016	ASD (unknown)	SSRIs (Study set B)	Unexposed – disease	2 (cohort)	660,264	OR 1.03 (0.49, 2.15)	-	0.15 (52%)	✓	✓
Man 2015	ASD (≥0 years)	SSRIs	Unexposed – any	4 (cohort/ CC)	107,688	OR 1.81 (1.47, 2.24)	OR 2.12 (1.65, 2.71)	0.90 (0%) 0.87 (0%)	✗	✓
Man 2015	ASD (≥0 years)	SSRIs (sensitivity) ¹⁷⁰	Unexposed – any	4 (cohort/ CC)	233,560	-	OR 2.40 (1.70, 3.39)	0.23 (30%)	✗	✗

Abbreviations: AD, antidepressant; ASD, Autism Spectrum Disorder; CC, case control; CI, confidence interval; NA, not applicable; OR, odds ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. Data shown in grey hatching is either (i) adjusted for potential confounders or (ii) limited/adjusted for psychiatric illness. Data shown in grey shading is (i) adjusted for potential confounders and (ii) limited/adjusted for psychiatric illness. Only shaded data is carried into **Section AppD4.1.1**.

¹⁷⁰ Replaces Rai 2013 with Eriksson 2012.

AppD3.1.1.2 Individual studies – antidepressants

AppD3.1.1.2.1 Malformations – antidepressants

Table AppD3-4 Antidepressant infant harms data extraction from observational studies – malformations

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Major malformations						
Bérard 2015	Major congenital malformations	Sertraline (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	15,234	RR 1.11 (0.81, 1.52)
Bérard 2015	Major congenital malformations	Non-sertraline SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,831	RR 1.08 (0.93, 1.25)
Bérard 2015	Major congenital malformations	Non-SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,164	RR 1.12 (0.94, 1.33)
Ban 2014a	Major congenital anomalies	SSRIs (first trimester)	Unexposed – depression	1 (cohort)	31,516	OR 0.93 (0.78, 1.11)
Ban 2014a	Major congenital anomalies	TCAs (first trimester)	Unexposed – depression	1 (cohort)	26,261	OR 1.02 (0.79, 1.32)
Ban 2014a	Major congenital anomalies	SSRIs & TCAs (first trimester)	Unexposed – depression	1 (cohort)	24,123	OR 0.94 (0.46, 1.92)
Ban 2014a	Major congenital anomalies	Fluoxetine (first trimester)	Unexposed – depression	1 (cohort)	27,022	OR 0.85 (0.66, 1.09)
Ban 2014a	Major congenital anomalies	Citalopram (first trimester)	Unexposed – depression	1 (cohort)	25,779	OR 0.97 (0.71, 1.31)
Ban 2014a	Major congenital anomalies	Paroxetine (first trimester)	Unexposed – depression	1 (cohort)	25,033	OR 1.01 (0.71, 1.44)
Ban 2014a	Major congenital anomalies	Sertraline (first trimester)	Unexposed – depression	1 (cohort)	24,590	OR 1.17 (0.78, 1.77)
Ban 2014a	Major congenital anomalies	Escitalopram (first trimester)	Unexposed – depression	1 (cohort)	24,166	OR 0.77 (0.36, 1.66)
Oberlander 2008a	Major congenital anomalies	SRIs (SSRIs or venlafaxine)	Unexposed – adjusted for depression	1 (cohort)	109,945	RD -0.0061 (-0.0144, 0.0021)
Oberlander 2008a	Major congenital abnormalities	SRIs (SSRIs or venlafaxine) + benzodiazepines	Unexposed – adjusted for depression	1 (cohort)	107,679	RD 0.0165 (-0.0049, 0.0379)
Oberlander 2008a	Major congenital anomalies	Citalopram	Unexposed – adjusted for depression	1 (cohort)	107,421	RD 0.0040 (-0.0313, 0.0393)

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Oberlander 2008a	Major congenital anomalies	Fluoxetine	Unexposed – adjusted for depression	1 (cohort)	107,958	RD -0.0026 (-0.068, 0.0117)
Oberlander 2008a	Major congenital anomalies	Fluvoxamine	Unexposed – adjusted for depression	1 (cohort)	107,439	RD -1.52 (-0.0402, 0.0098)
Oberlander 2008a	Major congenital anomalies	Paroxetine	Unexposed – adjusted for depression	1 (cohort)	108,313	RD -0.56 (-0.0170, 0.0059)
Oberlander 2008a	Major congenital anomalies	Sertraline	Unexposed – adjusted for depression	1 (cohort)	107,928	RD -0.41 (-0.0184, 0.0102)
Oberlander 2008a	Major congenital anomalies	Venlafaxine	Unexposed – adjusted for depression	1 (cohort)	107,570	RD -0.0118 (-0.0320, 0.0084)
Ramos 2008	Major congenital malformations	Any ADs (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.10 (0.75, 1.62)
Ramos 2008	Major congenital malformations	Any ADs for 1-30 days (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.23 (0.77, 1.98)
Ramos 2008	Major congenital malformations	Any ADs for 31-60 days (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.03 (0.63, 1.69)
Ramos 2008	Major congenital malformations	Any ADs for ≥ 61 days (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 0.92 (0.50, 1.69)
Ramos 2008	Major congenital malformations	Paroxetine (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.27 (0.78, 2.06)
Ramos 2008	Major congenital malformations	Non-paroxetine SSRIs (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.19 (0.71, 1.97)
Ramos 2008	Major congenital malformations	TCAs (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 0.78 (0.30, 2.02)
Ramos 2008	Major congenital malformations	New antidepressant (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 0.94 (0.51, 1.75)
Ramos 2008	Major congenital malformations	Co-exposure (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.03 (0.44, 2.41)
Ramos 2008	Major congenital malformations	Any ADs (second trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.13 (0.59, 2.17)
Ramos 2008	Major congenital malformations	Any ADs (third trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 0.86 (0.45, 1.65)
Djulus 2006	Major malformations	Mirtazapine	Other ADs	1 (cohort)	208	P=0.50

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Simon 2002	Major congenital malformations	SSRIs (any time)	Unexposed - matched	1 (cohort)	370	OR 1.36 (0.56, 3.30)
Simon 2002	Major congenital malformations	TCAs (any time)	Unexposed - matched	1 (cohort)	418	OR 0.82 (0.35, 1.95)
Cardiac malformations						
Petersen 2016	Congenital heart anomalies	SSRIs	Unexposed – halted treatment	1 (cohort)	7,930	OR 0.82 (0.48, 1.38)
Petersen 2016	Congenital heart anomalies	SSRIs	Non-SSRIs	1 (cohort)	3,768	OR 1.48 (0.58, 3.73)
Bérard 2015	Cardiac malformations	Sertraline (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	15,234	RR 1.16 (0.62, 2.19)
Bérard 2015	Cardiac malformations	Non-sertraline SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,831	RR 1.10 (0.82, 1.48)
Bérard 2015	Cardiac malformations	Non-SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,164	RR 0.91 (0.62, 1.34)
Furu 2015	Cardiac birth defects	SSRIs/venlafaxine (first trimester)	Unexposed – sibling-controlled	1 (cohort)	991	OR 0.92 (0.72, 1.17)
Ban 2014a	Cardiac anomalies	SSRIs (first trimester)	Unexposed – depression	1 (cohort)	31,516	OR 1.04 (0.76, 1.41)
Ban 2014a	Cardiac anomalies	TCAs (first trimester)	Unexposed – depression	1 (cohort)	26,261	OR 0.90 (0.54, 1.50)
Ban 2014a	Cardiac anomalies	SSRIs & TCAs (first trimester)	Unexposed – depression	1 (cohort)	24,123	OR 0.78 (0.19, 3.27)
Ban 2014a	Cardiac anomalies	Fluoxetine (first trimester)	Unexposed – depression	1 (cohort)	27,022	OR 0.79 (0.49, 1.26)
Ban 2014a	Cardiac anomalies	Citalopram (first trimester)	Unexposed – depression	1 (cohort)	25,779	OR 1.02 (0.61, 1.70)
Ban 2014a	Cardiac anomalies	Paroxetine (first trimester)	Unexposed – depression	1 (cohort)	25,033	OR 1.67 (1.00, 2.80)
Ban 2014a	Cardiac anomalies	Sertraline (first trimester)	Unexposed – depression	1 (cohort)	24,590	OR 1.39 (0.70, 2.74)
Ban 2014a	Cardiac anomalies	Escitalopram (first trimester)	Unexposed – depression	1 (cohort)	24,166	OR 1.09 (0.34, 3.50)

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Huybrechts 2014b	Cardiac malformation	Any AD (first trimester)	Unexposed – depression	1 (cohort)	NR	OR 1.02 (0.90, 1.15)
Huybrechts 2014b	Cardiac malformation	SSRIs (first trimester)	Unexposed – depression	1 (cohort)	217,342	OR 1.06 (0.93, 1.22)
Huybrechts 2014b	Cardiac malformation	Paroxetine (first trimester)	Unexposed – depression	1 (cohort)	189,312	OR 0.94 (0.73, 1.21)
Huybrechts 2014b	Cardiac malformation	Sertraline (first trimester)	Unexposed – depression	1 (cohort)	191,620	OR 1.09 (0.88, 1.34)
Huybrechts 2014b	Cardiac malformation	Fluoxetine (first trimester)	Unexposed – depression	1 (cohort)	189,227	OR 1.14 (0.90, 1.44)
Huybrechts 2014b	Cardiac malformation	TCAs (first trimester)	Unexposed – depression	1 (cohort)	183,876	OR 0.77 (0.52, 1.14)
Huybrechts 2014b	Cardiac malformation	SNRIs (first trimester)	Unexposed – depression	1 (cohort)	186,574	OR 1.20 (0.91, 1.57)
Huybrechts 2014b	Cardiac malformation	Bupropion (first trimester)	Unexposed – depression	1 (cohort)	187,254	OR 0.92 (0.69, 1.22)
Huybrechts 2014b	Cardiac malformation	Other (first trimester)	Unexposed – depression	1 (cohort)	186,585	OR 1.21 (0.91, 1.60)
Margulis 2013	Cardiac malformations (all patent ductus arteriosus included)	SSRIs (first trimester)	Unexposed – matched for mental health conditions	1 (cohort)	12,037	OR 1.00 (0.50, 2.00)
Margulis 2013	Cardiac malformations (surgical patent ductus arteriosus included only)	SSRIs (first trimester)	Unexposed – matched for mental health conditions	1 (cohort)	12,037	OR 0.86 (0.40, 1.85)
Oberlander 2008a	Cardiovascular congenital defects	SRI (SSRIs + venlafaxine)	Unexposed – adjusted for depression	1 (cohort)	109,945	RD 0.0021 (–0.0014, 0.0056)
Oberlander 2008a	Cardiovascular congenital defects	SRI (SSRIs + venlafaxine) + benzodiazepines	Unexposed – adjusted for depression	1 (cohort)	109,945	RD 0.0118 (0.0018, 0.0218)
Oberlander 2008a	Cardiovascular congenital defects	Citalopram	Unexposed – adjusted for depression	1 (cohort)	107,421	RD 0.0228 (0.0019, 0.0436)
Oberlander 2008a	Cardiovascular congenital defects	Fluoxetine	Unexposed – adjusted for depression	1 (cohort)	107,958	RD 0.0008 (–0.0054, 0.0070)
Oberlander 2008a	Cardiovascular congenital defects	Fluvoxamine	Unexposed – adjusted for depression	1 (cohort)	107,439	RD –0.0055 (–0.0145, 0.0036)

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Oberlander 2008a	Cardiovascular congenital defects	Paroxetine	Unexposed – adjusted for depression	1 (cohort)	108,313	RD 0.0012 (–0.0038, 0.0062)
Oberlander 2008a	Cardiovascular congenital defects	Sertraline	Unexposed – adjusted for depression	1 (cohort)	107,928	RD –0.0009 (–0.0065, 0.0047)
Oberlander 2008a	Cardiovascular congenital defects	Venlafaxine	Unexposed – adjusted for depression	1 (cohort)	107,570	RD 0.0001 (–0.0077, 0.0079)
Cole 2007a	Cardiovascular malformations	Other ADs (first trimester)	Bupropion monotherapy (first trimester)	1 (cohort)	5,381	OR 0.54 (0.19, 1.51) ¹⁷¹
Cole 2007b	Cardiovascular malformations	Paroxetine monotherapy (first trimester)	Other ADs monotherapy (first trimester)	1 (cohort)	5,013	OR 1.46 (0.74, 2.88)
Cole 2007b	Cardiovascular malformations	Paroxetine mono- or polytherapy	Other ADs mono- or polytherapy	1 (cohort)	5,956	OR 1.68 (0.95, 2.97)
Simon 2002	Major congenital malformations	TCAs (any time)	Unexposed - matched	1 (cohort)	418	OR 0.50 (0.05, 5.53)
Septal defects						
Bérard 2015	Cardiac malformations	Sertraline (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	15,234	RR 1.34 (1.02, 1.76)
Bérard 2015	Cardiac malformations	Non-sertraline SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,831	RR 1.13 (0.81, 1.58)
Bérard 2015	Cardiac malformations	Non-SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,164	RR 0.91 (0.59, 1.42)

Abbreviations: AD, antidepressant; CI, confidence interval; NR, not reported; OR, odds ratio; RD, risk difference; RE, risk estimate; RR, relative risk; SRI, selective reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. All included data was adjusted for potential confounders and limited/adjusted for psychiatric illness. All data is carried into **Section AppD 4.2.1**.

¹⁷¹ In the analysis, bupropion is used as the reference group.

AppD3.1.1.2.2 Pregnancy and birth outcomes – antidepressants

Table AppD3-5 Antidepressant infant harms data extraction from systematic reviews – pregnancy and birth outcomes

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Neonatal mortality						
Ban 2012	Perinatal death	SSRIs (first trimester)	Unexposed – unmedicated depression/anxiety	1 (cohort)	NR	RR 1.2 (0.6, 2.3)
Ban 2012	Perinatal death	TCAs (first trimester)	Unexposed – unmedicated depression/anxiety	1 (cohort)	NR	RR 1.2 (0.5, 2.7)
Miscarriage						
Almeida 2016	Miscarriage	Any ADs	Unexposed – depression	1 (cohort)	10,376	RR 1.2 (1.0, 1.4)
Almeida 2016	Miscarriage	SSRI monotherapy	Unexposed – depression	1 (cohort)	9,815	RR 1.2 (0.94, 1.5)
Almeida 2016	Miscarriage	SNRI monotherapy	Unexposed – depression	1 (cohort)	9,014	RR 1.7 (1.2, 2.6)
Almeida 2016	Miscarriage	TCA monotherapy	Unexposed – depression	1 (cohort)	9,024	RR 1.5 (0.96, 2.2)
Almeida 2016	Miscarriage	Other monotherapy	Unexposed – depression	1 (cohort)	8,966	RR 1.0 (0.53, 2.0)
Almeida 2016	Miscarriage	Polytherapy	Unexposed – depression	1 (cohort)	9,065	RR 1.5 (0.99, 2.1)
Kjaersgaard 2013	Spontaneous abortion	Any ADs	Unexposed – depression	1 (cohort)	315	RR 1.00 (0.80, 1.24)
Kjaersgaard 2013	Spontaneous abortion	Any ADs	Unexposed – adjusted for history of severe mental disorder	1 (cohort)	113,119	RR 1.14 (1.10, 1.18)
Ban 2012	Miscarriage	SSRIs (first trimester)	Unexposed – unmedicated depression/anxiety	1 (cohort)	NR	RR 1.4 (1.2, 1.7)
Ban 2012	Miscarriage	TCAs (first trimester)	Unexposed – unmedicated depression/anxiety	1 (cohort)	NR	RR 1.3 (1.1, 1.5)
Nakhai-Pour 2010	Spontaneous abortion	SSRIs (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	5,001	OR 1.61 (1.28, 2.04)

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Nakhai-Pour 2010	Spontaneous abortion	TCAs (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,876	OR 1.27 (0.85, 1.91)
Nakhai-Pour 2010	Spontaneous abortion	SNRIs (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,873	OR 2.11 (1.34, 3.30)
Nakhai-Pour 2010	Spontaneous abortion	Other ADs ¹⁷² (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,858	OR 1.53 (0.86, 2.72)
Nakhai-Pour 2010	Spontaneous abortion	≥ 2 AD classes (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,876	OR 3.51 (2.20, 5.61)
Nakhai-Pour 2010	Spontaneous abortion	Paroxetine (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,924	OR 1.75 (1.31, 2.34)
Nakhai-Pour 2010	Spontaneous abortion	Sertraline (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,868	OR 1.33 (0.85, 2.08)
Nakhai-Pour 2010	Spontaneous abortion	Fluoxetine (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,862	OR 1.44 (0.86, 2.43)
Nakhai-Pour 2010	Spontaneous abortion	Citalopram (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,859	OR 1.55 (0.89, 2.68)
Nakhai-Pour 2010	Spontaneous abortion	Fluvoxamine (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,845	OR 2.19 (0.79, 6.08)

¹⁷² Includes serotonin modulators, monoamine oxidase inhibitors, tetracyclic piperazino-azepines, and dopamine and norepinephrine reuptake inhibitors.

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Nakhai-Pour 2010	Spontaneous abortion	Venlafaxine (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,873	OR 2.11 (1.34, 3.30)
Nakhai-Pour 2010	Spontaneous abortion	≥ 2 SSRIs (up to 20 weeks)	Unexposed – adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	1 (case control)	4,876	OR 2.47 (0.62, 9.83)
Djulus 2006	Spontaneous abortion	Mirtazapine	Other ADs	1 (cohort)	208	<i>P=0.86</i>
Stillbirth						
Djulus 2006	Stillbirth	Mirtazapine	Other ADs	1 (cohort)	208	<i>P=0.50</i>
Preterm birth						
Malm 2015	Preterm birth (32–36 weeks)	SSRIs (any time)	Unexposed – psychiatric diagnosis	1 (cohort)	25,381	OR 0.84 (0.74, 0.96)
Malm 2015	Preterm birth (<32 weeks)	SSRIs (any time)	Unexposed – psychiatric diagnosis	1 (cohort)	25,381	OR 0.52 (0.37, 0.74)
Grzeskowiak 2012	Preterm delivery (< 37 weeks)	SSRI (late gestation)	Unexposed – psychiatric illness	1 (cohort)	1,787	OR 2.68 (1.83, 3.93)
Oberlander 2008b	Gestational age < 37 weeks	SSRI (early exposure) ¹⁷³	SSRI (late exposure) ¹⁷⁴	1 (cohort)	858	10.3% vs 9.1%; <i>P</i> ≥0.05
Djulus 2006	Preterm birth (< 37 weeks)	Mirtazapine	Other ADs	1 (cohort)	208	<i>P=0.61</i>
Oberlander 2006	Preterm birth (<37 weeks)	SSRIs	Unexposed – depression	1 (cohort)	1,622	RD 0.007 (-0.018, 0.034)
Small for gestational age						
Malm 2015	Small for gestational age	SSRI (any time)	Unexposed – psychiatric diagnosis	1 (cohort)	25,381	OR 0.92 (0.77, 1.10)
Grzeskowiak 2012	Small for gestational age	SSRI (late gestation)	Unexposed – psychiatric illness	1 (cohort)	1,787	OR 1.13 (0.65, 1.94)

¹⁷³ Discontinued use in first or second trimester.¹⁷⁴ Continued use into third trimester.

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Oberlander 2008b	Birth weight < 10 th percentile for gestational age	SSRI (early exposure) ¹⁷⁵	SSRI (late exposure) ¹⁷⁶	1 (cohort)	858	7.0% vs 7.9%; $P \geq 0.05$
Oberlander 2006	Birthweight < 10 th percentile for gestational age	SSRI	Unexposed – depression	1 (cohort)	1,622	RD 0.033 (0.007, 0.059)
Respiratory distress						
Malm 2015	Breathing problems	SSRI	Unexposed – psychiatric diagnosis	1 (cohort)	25,381	OR 1.40 (1.20, 1.62)
Hayes 2012	Respiratory distress	Any ADs – 1 prescription (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Respiratory distress	Any ADs – 2 prescriptions (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Respiratory distress	Any ADs – ≥ 3 prescriptions (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Respiratory distress	Any ADs – 1 prescription (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 1.1 (0.9, 1.3)
Hayes 2012	Respiratory distress	Any ADs – 2 prescriptions (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 1.4 (1.1, 1.8)
Hayes 2012	Respiratory distress	Any ADs – ≥ 3 prescriptions (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 1.6 (1.2, 2.0)
Hayes 2012	Respiratory distress	Any ADs – 1 prescription (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 0.9 (0.7, 1.1)
Hayes 2012	Respiratory distress	Any ADs – 2 prescriptions (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 0.8 (0.6, 1.0)
Hayes 2012	Respiratory distress	Any ADs – ≥ 3 prescriptions (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 0.6 (0.5, 0.8)
Oberlander 2008b	Respiratory distress	SSRI (early exposure) ¹⁷⁷	SSRI (late exposure) ¹⁷⁸	1 (cohort)	858	9.3% vs 10.3%; $P \geq 0.05$
Oberlander 2006	Respiratory distress	SSRIs	Unexposed – depression	1 (cohort)	1,622	RD 0.044 (0.013, 0.077)

¹⁷⁵ Discontinued use in first or second trimester.¹⁷⁶ Continued use into third trimester.¹⁷⁷ Discontinued use in first or second trimester.¹⁷⁸ Continued use into third trimester.

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Oberlander 2006	Respiratory distress, infants born by vaginal birth	SSRIs	Unexposed – depression	1 (cohort)	NR	RD 0.049 (0.017, 0.088)
PNAS						
Kieviet 2015	Poor neonatal adaptation (≥ 1 Finnegan score ≥ 4 during admission)	SSRIs	SNRIs	1 (cohort)	247	OR 2.75 (1.13, 6.71)
Kieviet 2015	Poor neonatal adaptation (≥ 1 Finnegan score ≥ 4 during admission) – admitted to maternity ward	SSRIs	SNRIs	1 (cohort)	194	OR 4.12 (1.32, 12.8)
Persistent pulmonary hypertension						
Huybrechts 2015	Persistent pulmonary hypertension	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	722,830	OR 1.12 (0.95, 1.31) ¹⁷⁹
Huybrechts 2015	Persistent pulmonary hypertension	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	722,831	OR 1.10 (0.94, 1.29) ¹⁸⁰
Huybrechts 2015	Persistent pulmonary hypertension (full-term deliveries)	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	621,398	OR 1.32 (1.04, 1.68)¹⁷⁹
Huybrechts 2015	Persistent pulmonary hypertension (full-term deliveries)	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	621,399	OR 1.27 (1.00, 1.61)¹⁸⁰
Huybrechts 2015	Persistent pulmonary hypertension without cardiac malformation or lung hypoplasia	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	722,830	OR 1.12 (0.95, 1.32) ¹⁷⁹
Huybrechts 2015	Persistent pulmonary hypertension without cardiac malformation or lung hypoplasia	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	722,830	OR 1.08 (0.92, 1.27) ¹⁸⁰
Huybrechts 2015	Primary persistent pulmonary hypertension (without cardiac malformation or lung hypoplasia in full-term deliveries)	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	621,398	OR 1.33 (1.04, 1.70)¹⁷⁹
Huybrechts 2015	Primary persistent pulmonary hypertension (without cardiac malformation or lung hypoplasia in full-term deliveries)	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	621,399	OR 1.28 (1.01, 1.64)¹⁸⁰
Huybrechts 2015	Persistent pulmonary hypertension	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	673,789	OR 1.01 (0.76, 1.35) ¹⁷⁹
Huybrechts 2015	Persistent pulmonary hypertension	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	673,789	OR 1.02 (0.77, 1.35) ¹⁸⁰
Huybrechts 2015	Persistent pulmonary hypertension (full-term deliveries)	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	580,466	OR 1.25 (0.82, 1.90) ¹⁷⁹

¹⁷⁹ Propensity score stratified¹⁸⁰ High-dimensional propensity score stratified

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Huybrechts 2015	Persistent pulmonary hypertension (full-term deliveries)	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	580,471	OR 1.19 (0.79, 1.79) ¹⁸⁰
Huybrechts 2015	Persistent pulmonary hypertension without cardiac malformation or lung hypoplasia	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	673,789	OR 0.95 (0.70, 1.30) ¹⁷⁹
Huybrechts 2015	Persistent pulmonary hypertension without cardiac malformation or lung hypoplasia	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	673,789	OR 0.96 (0.71, 1.30) ¹⁸⁰
Huybrechts 2015	Primary persistent pulmonary hypertension (without cardiac malformation or lung hypoplasia in full-term deliveries)	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	580,466	OR 1.21 (0.78, 1.86) ¹⁷⁹
Huybrechts 2015	Primary persistent pulmonary hypertension (without cardiac malformation or lung hypoplasia in full-term deliveries)	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	580,471	OR 1.14 (0.74, 1.74) ¹⁸⁰
Kieler 2012	Persistent pulmonary hypertension	SSRIs (early pregnancy) ¹⁸¹	Unexposed – previous psychiatric hospital admission	1 (cohort)	63,615	OR 1.3 (1.0, 1.6)
Kieler 2012	Persistent pulmonary hypertension and no meconium aspiration	SSRIs (early pregnancy) ¹⁸²	Unexposed – previous psychiatric hospital admission	1 (cohort)	NR	OR 1.3 (1.1, 1.7)
Kieler 2012	Persistent pulmonary hypertension	SSRIs (late pregnancy) ¹⁸³	Unexposed – previous psychiatric hospital admission	1 (cohort)	63,615	OR 3.1 (1.9, 4.9)
Convulsions						
Hayes 2012	Convulsions	SSRIs – one prescription filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – two prescriptions filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – three+ prescription filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – one prescription filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – two prescriptions filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – three+ prescription filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS

¹⁸¹ Filled a prescription three months before the start of pregnancy to day 55.¹⁸² Filled a prescription three months before the start of pregnancy to day 55.¹⁸³ Filled a prescription from 140 days after the start of pregnancy to birth.

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Hayes 2012	Convulsions	SSRIs – one prescription filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 1.4 (0.7, 2.8)
Hayes 2012	Convulsions	SSRIs – two prescriptions filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 2.8 (1.9, 5.5)
Hayes 2012	Convulsions	SSRIs – three+ prescription filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 4.9 (2.6, 9.5)
Hayes 2012	Convulsions	Non-SSRIs – one prescription filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – two prescriptions filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – three+ prescription filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – one prescription filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – two prescriptions filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – three+ prescription filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – one prescription filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – two prescriptions filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – three+ prescription filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Oberlander 2006	Convulsions	SSRI	Unexposed – depression	1 (cohort)	1,622	RD 0.00077 (-0.0010, 0.0036)

Abbreviations: AD, antidepressant; CI, confidence interval; NR, not reported; NS, not statistically significant; OR, odds ratio; PNAS, poor neonatal adaptation syndrome; RD, risk difference; RE, risk estimate; RR, relative risk; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. All included data was adjusted for potential confounders and limited/adjusted for psychiatric illness. All data is carried into **Section AppD 4.2.1**.

AppD3.1.1.2.3 Neurodevelopmental outcomes – antidepressants

Table AppD3-6 Antidepressant infant harms data extraction from systematic reviews – neurodevelopmental outcomes

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Autism spectrum disorder						
Bérard 2016 ¹⁸⁴	Autism spectrum disorder – full-term delivery (median 4 years)	Citalopram (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	143,137	HR 2.23 (1.01, 4.92)
Bérard 2016 ¹⁸⁴	Autism spectrum disorder – full-term delivery (median 4 years)	Fluoxetine (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	142,887	HR 4.99 (1.45, 17.1)
Bérard 2016 ¹⁸⁴	Autism spectrum disorder – full-term delivery (median 4 years)	Fluvoxamine (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	142,751	HR 7.30 (0.30, 178)
Bérard 2016 ¹⁸⁴	Autism spectrum disorder – full-term delivery (median 4 years)	Paroxetine (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	143,460	HR 1.99 (1.00, 3.96)
Bérard 2016 ¹⁸⁴	Autism spectrum disorder – full-term delivery (median 4 years)	Sertraline (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	143,008	HR 0.45 (0.05, 4.26)
Bérard 2016 ¹⁸⁴	Autism spectrum disorder – full-term delivery (median 4 years)	SNRI/TCA/MAOI, other ¹⁸⁵ (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	143,495	HR 0.85 (0.28, 2.54)
Bérard 2016 ¹⁸⁴	Autism spectrum disorder – full-term delivery (median 4 years)	≥ 2 ADs (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	142,799	HR 4.95 (0.66, 36.8)
Boukhris 2016	Autism spectrum disorder (mean 4 years)	Any ADs (second and/or third trimester)	Unexposed – depression	1 (cohort)	16,442	HR 1.75 (1.03, 2.97)
Boukhris 2016 ¹⁸⁶	Autism spectrum disorder – full-term delivery (median 4 years)	SSRIs (2 nd or 3 rd trimester)	Unexposed – adjusted for prior AD use and other psychiatric disorders	1 (cohort)	144,507	HR 2.17 (1.20, 3.93)
Boukhris 2016 ¹⁸⁶	Autism spectrum disorder – full-term delivery (median 4 years)	SNRIs (2 nd or 3 rd trimester)	Unexposed – adjusted for prior AD use and other psychiatric disorders	1 (cohort)	143,371	HR 1.04 (0.20, 5.46)
Boukhris 2016 ¹⁸⁶	Autism spectrum disorder – full-term delivery (median 4 years)	TCAs (2 nd or 3 rd trimester)	Unexposed – adjusted for prior AD use and other psychiatric disorders	1 (cohort)	143,153	HR 1.03 (0.23, 4.61)
Boukhris 2016 ¹⁸⁶	Autism spectrum disorder – full-term delivery (median 4 years)	≥ 2 ADs (2 nd or 3 rd trimester)	Unexposed – adjusted for prior AD use and other psychiatric disorders	1 (cohort)	143,091	HR 4.39 (1.44, 13.3)
Johnson 2016	Pervasive developmental disorder (mother-rated) (2.5 – 5.5 years)	SSRIs (any time)	Unexposed – attended mental health clinic	1 (cohort)	178	OR 1.05 (1.01, 1.08)

¹⁸⁴ Includes the same study cohort as Boukhris 2016.¹⁸⁵ Other includes bupropion, amoxapine, maprotiline, mirtazapine, trazodone and nefazodone.¹⁸⁶ Includes the same cohort as Bérard 2016.

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Johnson 2016	Pervasive developmental disorder (alternate caregiver-rated) (2.5 – 5.5 years)	SSRIs (any time)	Unexposed – attended mental health clinic	1 (cohort)	178	OR 1.01 (0.98, 1.05)
Malm 2016	Autism spectrum disorder (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – psychiatric disorder	1 (cohort)	25,380	HR 0.88 (0.65, 1.20)
Malm 2016	Autism spectrum disorder (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – previous SSRIs	1 (cohort)	23,709	HR 1.30 (0.88, 1.92)
Clements 2015	Autism spectrum disorder (2-19 years)	Any ADs (first trimester)	Unexposed – adjusted for major depression	1 (case control)	5,399	OR 1.43 (0.85, 2.38)
Clements 2015	Autism spectrum disorder (2-19 years)	Any ADs (second trimester)	Unexposed – adjusted for major depression	1 (case control)	5,399	OR 1.34 (0.77, 2.27)
Clements 2015	Autism spectrum disorder (2-19 years)	Any ADs (third trimester)	Unexposed – adjusted for major depression	1 (case control)	5,399	OR 1.08 (0.61, 1.88)
Clements 2015	Autism spectrum disorder (2-19 years)	Any ADs (any time)	Unexposed – adjusted for major depression	1 (case control)	5,399	OR 1.10 (0.70, 1.70)
El Marroun 2014	Pervasive developmental problems ¹⁸⁷ (1.5–6 years)	SSRIs (any time)	Unexposed – depression	1 (cohort)	445	OR 1.33 (0.68, 2.57)
Gidaya 2014	Autism spectrum disorder (2-14 years)	SSRIs (any time)	Unexposed – adjusted for history of maternal depression	1 (case control)	57,365	OR 1.8 (1.4, 2.3)
Gidaya 2014	Autism spectrum disorder (2-14 years)	SSRIs (first trimester)	Unexposed – adjusted for history of maternal depression	1 (case control)	57,360	OR 2.0 (1.5, 2.6)
Gidaya 2014	Autism spectrum disorder (2-14 years)	SSRIs (second trimester)	Unexposed – adjusted for history of maternal depression	1 (case control)	57,333	OR 2.1 (1.5, 3.0)
Gidaya 2014	Autism spectrum disorder (2-14 years)	SSRIs (third trimester)	Unexposed – adjusted for history of maternal depression	1 (case control)	57,328	OR 2.5 (1.7, 3.7)
Harrington 2014	Autism spectrum disorder (mean 3.8 years at diagnosis)	SSRIs (any time)	Unexposed – history of mood/anxiety disorder	1 (case control)	229	OR 1.86 (0.76, 4.58)
Harrington 2014	Autism spectrum disorder – boys only (mean 3.8 years at diagnosis)	SSRIs (any time)	Unexposed – history of mood/anxiety disorder	1 (case control)	NR	OR 3.17 (0.91, 11.00)
Harrington 2014	Autism spectrum disorder (mean 3.8 years at diagnosis)	SSRIs (first trimester)	Unexposed – history of mood/anxiety disorder	1 (case control)	229	OR 1.70 (0.66, 4.37)
Harrington 2014	Autism spectrum disorder – boys only (mean 3.8 years at diagnosis)	SSRIs (first trimester)	Unexposed – history of mood/anxiety disorder	1 (case control)	NR	OR 3.52 (0.93, 13.34)

¹⁸⁷ Now known as autism spectrum disorder.

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Harrington 2014	Autism spectrum disorder (mean 3.8 years at diagnosis)	SSRIs (second trimester)	Unexposed – history of mood/anxiety disorder	1 (case control)	229	OR 1.12 (0.40, 3.11)
Harrington 2014	Autism spectrum disorder – boys only (mean 3.8 years at diagnosis)	SSRIs (second trimester)	Unexposed – history of mood/anxiety disorder	1 (case control)	NR	OR 1.80 (0.39, 8.37)
Harrington 2014	Autism spectrum disorder (mean 3.8 years at diagnosis)	SSRIs (third trimester)	Unexposed – history of mood/anxiety disorder	1 (case control)	229	OR 1.43 (0.52, 3.95)
Harrington 2014	Autism spectrum disorder – boys only (mean 3.8 years at diagnosis)	SSRIs (third trimester)	Unexposed – history of mood/anxiety disorder	1 (case control)	NR	OR 2.45 (0.54, 11.22)
Hviid 2013	Autism spectrum disorder (up to 10 years – median age 5.6 years)	SSRIs (–4 weeks pregnancy to delivery)	Unexposed – adjusted for psychiatric diagnoses before delivery	1 (cohort)	4,991,303 py	RR 1.20 (0.90, 1.61)
Hviid 2013	Autism spectrum disorder (up to 10 years – median age 5.6 years)	SSRIs (any time)	Unexposed – adjusted for psychiatric diagnoses before delivery	1 (cohort)	4,965,867 py	RR 1.40 (0.92, 2.13)
Hviid 2013	Autism spectrum disorder (up to 10 years – median age 5.6 years)	SSRIs (first trimester)	Unexposed – adjusted for psychiatric diagnoses before delivery	1 (cohort)	4,977,850 py	RR 1.35 (0.97, 1.87)
Rai 2013	Autism spectrum disorder (> 3 years)	Any ADs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (case control)	18,524	OR 1.90 (1.15, 3.14)
Rai 2013	Autism spectrum disorder – <u>with</u> intellectual disability (> 3 years)	Any ADs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (case control)	NR	OR 1.09 (0.41, 2.88)
Rai 2013	Autism spectrum disorder – <u>without</u> intellectual disability (> 3 years)	Any ADs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (case control)	NR	OR 2.54 (1.37, 4.68)
Rai 2013	Autism spectrum disorder (> 3 years)	SSRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (case control)	18,524	OR 1.65 (0.90, 3.03)
Rai 2013	Autism spectrum disorder – <u>with</u> intellectual disability (> 3 years)	SSRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (case control)	NR	OR 1.01 (0.34, 2.98)
Rai 2013	Autism spectrum disorder – <u>without</u> intellectual disability (> 3 years)	SSRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (case control)	NR	OR 2.34 (1.09, 5.06)
Rai 2013	Autism spectrum disorder (> 3 years)	Non-selective MRIs ¹⁸⁸ (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (case control)	18,524	OR 2.69 (1.04, 6.96)
Rai 2013	Autism spectrum disorder – <u>with</u> intellectual disability (> 3 years)	Non-selective MRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (case control)	NR	OR 1.72 (0.20, 15.03)

¹⁸⁸ Defined as tricyclic antidepressants (TCAs) in Rai 2013.

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Rai 2013	Autism spectrum disorder – <u>without</u> intellectual disability (> 3 years)	Non-selective MRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (case control)	NR	OR 2.93 (0.98, 8.82)
Sørensen 2013	Autism spectrum disorder (mean 8.8 years)	Any ADs (any time)	Unexposed – hospital-diagnosed affective disorder	1 (cohort)	6,080	HR 1.2 (0.7, 2.1)
Sørensen 2013	Autism spectrum disorder (mean 8.8 years)	Any ADs (any time)	Unexposed – sibling study	1 (cohort)	6,142	HR 1.1 (0.5, 2.3)
Sørensen 2013	Autism spectrum disorder (mean 8.8 years)	SSRIs (any time)	Unexposed – hospital-diagnosed affective disorder	1 (cohort)	5,799	HR 1.4 (0.8, 2.4)
Sørensen 2013	Autism spectrum disorder (mean 8.8 years)	SSRIs (any time)	Unexposed – sibling study	1 (cohort)	6,117	HR 0.9 (0.4, 2.0)
Croen 2011	Autism spectrum disorder (median 4 years)	Any ADs (first trimester)	Unexposed – adjusted for history of any mental health disorder in year before delivery	1 (case control)	1,799	OR 3.5 (1.5, 7.9)
Croen 2011	Autism spectrum disorder (median 4 years)	Any ADs (second trimester)	Unexposed – adjusted for history of any mental health disorder in year before delivery	1 (case control)	1,774	OR 1.5 (0.5, 5.0)
Croen 2011	Autism spectrum disorder (median 4 years)	Any ADs (third trimester)	Unexposed – adjusted for history of any mental health disorder in year before delivery	1 (case control)	1,775	OR 2.2 (0.7, 6.9)
Croen 2011	Autism spectrum disorder (median 4 years)	Any ADs (year before delivery)	Unexposed – adjusted for history of any mental health disorder in year before delivery	1 (case control)	1,805	OR 2.1 (1.0, 4.4)
Childhood autism						
Sørensen 2013	Childhood autism (mean 8.8 years)	Any ADs (any time)	Unexposed – hospital-diagnosed affective disorder	1 (cohort)	6,080	HR 0.8 (0.3, 2.1)
Sørensen 2013	Childhood autism (mean 8.8 years)	SSRIs (any time)	Unexposed – hospital-diagnosed affective disorder	1 (cohort)	5,799	HR 1.0 (0.4, 2.6)
Autistic traits						
El Marroun 2014	Autistic traits (6 years)	SSRIs (any time)	Unexposed – depression	1 (cohort)	445	β 0.10 (0.02, 0.18)
Social cognition						
El Marroun 2014	Social cognition (6 years)	SSRIs (any time)	Unexposed – depression	1 (cohort)	445	β 0.10 (-0.02, 0.22)
Social communication						
El Marroun 2014	Social communication (6 years)	SSRIs (any time)	Unexposed – depression	1 (cohort)	445	β 0.12 (0.03, 0.21)

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Autistic mannerism						
El Marroun 2014	Autistic mannerism (6 years)	SSRIs (any time)	Unexposed – depression	1 (cohort)	445	β 0.09 (0.01, 0.17)
ADHD						
Malm 2016	ADHD (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – psychiatric disorder	1 (cohort)	25,380	OR 0.98 (0.77, 1.24)
Malm 2016	ADHD (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – previous SSRIs	1 (cohort)	23,709	OR 0.98 (0.75, 1.27)
Clements 2015	ADHD (2-19 years)	Any ADs (first trimester)	Unexposed – adjusted for major depression	1 (case control)	7,874	OR 2.03 (1.19, 3.44)
Clements 2015	ADHD (2-19 years)	Any ADs (second trimester)	Unexposed – adjusted for major depression	1 (case control)	7,874	OR 0.98 (0.56, 1.68)
Clements 2015	ADHD (2-19 years)	Any ADs (third trimester)	Unexposed – adjusted for major depression	1 (case control)	7,874	OR 1.29 (0.76, 2.15)
Clements 2015	ADHD (2-19 years)	Any ADs (any time)	Unexposed – adjusted for major depression	1 (case control)	7,874	OR 1.81 (1.22, 2.70)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Any ADs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	877,778	HR 1.2 (1.1, 1.4)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Any ADs (first semester)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	NR	HR 1.2 (1.0, 1.4)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Any ADs (second semester)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	NR	HR 1.5 (0.9, 2.4)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Any ADs (third semester)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	NR	HR 0.8 (0.3, 2.0)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	SSRIs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	874,491	HR 1.2 (1.0, 1.5)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	SNRIs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	863,533	HR 1.0 (0.4, 2.5)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	TCAs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	863,486	HR 1.1 (0.6, 2.0)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Other ADs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	863,374	HR 1.6 (0.8, 3.0)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Combined ADs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	863,974	HR 0.8 (0.4, 1.7)

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Figueroa 2010	ADHD (up to 5 years)	SSRIs (any time)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.91 (0.51, 1.60)
Figueroa 2010	ADHD (up to 5 years)	SSRIs (first trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 1.62 (0.79, 3.32)
Figueroa 2010	ADHD (up to 5 years)	SSRIs (second trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 1.59 (0.58, 4.35)
Figueroa 2010	ADHD (up to 5 years)	SSRIs (third trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.38 (0.14, 1.03)
Figueroa 2010	ADHD (up to 5 years)	SSRIs (after pregnancy)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 2.04 (1.43, 2.91)
Figueroa 2010	ADHD (up to 5 years)	Bupropion (any time)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 3.63 (1.20, 11.0)
Figueroa 2010	ADHD (up to 5 years)	Bupropion (first trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 2.06 (0.35, 12.2)
Figueroa 2010	ADHD (up to 5 years)	Bupropion (second trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 14.66 (3.27, 65.73)
Figueroa 2010	ADHD (up to 5 years)	Bupropion (third trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.00 (0.00, 1.00)
Figueroa 2010	ADHD (up to 5 years)	Bupropion (after pregnancy)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.90 (0.32, 2.53)
Figueroa 2010	ADHD (up to 5 years)	Other ADs ¹⁸⁹ (any time)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.65 (0.09, 4.79)
Other disorders						
Brown 2016	Speech/language disorder ¹⁹⁰ (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	25,133	HR 1.20 (0.97, 1.49)
Brown 2016	Speech/language disorder ³⁹⁵ – 1 purchase (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 0.86 (0.67, 1.10)
Brown 2016	Speech/language disorder ³⁹⁵ – ≥ 2 purchases (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 1.37 (1.11, 1.70)
Brown 2016 <i>High</i>	Speech/language disorder ³⁹⁵ – ≥ 2 purchases (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with <u>monotherapy</u> SSRI use	1 (cohort)	NR	HR 1.34 (1.07, 1.68)

¹⁸⁹ Tricyclic antidepressants, tetracyclic antidepressants, mirtazapine and venlafaxine). NR¹⁹⁰ ICD-10.

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Brown 2016 <i>High</i>	Speech/language disorder ³⁹⁵ – ≥ 2 purchases (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use <u>and adjusted for maternal suicidal behavior</u>	1 (cohort)	NR	HR 1.34 (1.07, 1.68)
Brown 2016	Scholastic disorder ³⁹⁵ (mean 3.6 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	25,133	HR 1.00 (0.63, 1.59)
Brown 2016	Scholastic disorder ³⁹⁵ – one purchase (mean 3.6 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 0.86 (0.52, 1.42)
Brown 2016	Scholastic disorder ³⁹⁵ – ≥ 2 purchases (mean 3.6 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 1.15 (0.72, 1.84)
Brown 2016	Motor disorder ³⁹⁵ (mean 7.7 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	25,133	HR 1.18 (0.81, 1.72)
Brown 2016	Motor disorder ³⁹⁵ – 1 purchase (mean 7.7 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 0.86 (0.57, 1.30)
Brown 2016	Motor disorder ³⁹⁵ – ≥ 2 purchases (mean 7.7 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 1.33 (0.93, 1.91)
IQ						
Nulman 2015	Full Scale IQ (WPPSI-III)	SRIs ¹⁹¹ (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05
Nulman 2015	Verbal IQ (WPPSI-II)	SRIs (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05
Nulman 2015	Performance IQ (WPPSI-II)	SRIs (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05
Behavioural problems						
Grzeskowiak 2015	Total difficulties – abnormal score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	441	RR 0.54 (0.23, 1.30)
Grzeskowiak 2015	Total difficulties – abnormal score (SDQ)	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.84 (0.31, 2.31)
Grzeskowiak 2015	Internalising problems – abnormal emotional symptoms score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	441	RR 0.74 (0.47, 1.14)
Grzeskowiak 2015	Internalising problems – abnormal emotional symptoms score (SDQ)	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.80 (0.50, 1.28)
Grzeskowiak 2015	Internalising problems – abnormal peer problems score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	441	RR 0.65 (0.30, 1.42)

¹⁹¹ Includes SSRIs and SNRIs.

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Grzeskowiak 2015	Internalising problems – abnormal peer problems score (SDQ)	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.76 (0.32, 1.85)
Grzeskowiak 2015	Externalising problems – abnormal conduct problems score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	441	RR 0.82 (0.47, 1.43)
Grzeskowiak 2015	Externalising problems – abnormal conduct problems score (SDQ)	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.90 (0.49, 1.67)
Grzeskowiak 2015	Externalising problems – abnormal hyperactivity-inattention score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	441	RR 0.57 (0.28, 1.19)
Grzeskowiak 2015	Externalising problems – abnormal hyperactivity-inattention problems score (SDQ)	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.75 (0.34, 1.64)
Grzeskowiak 2015	Other measures – abnormal pro-social score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	441	RR 0.23 (0.05, 1.18)
Grzeskowiak 2015	Other measures – abnormal pro-social score (SDQ)	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.19 (0.05, 0.77)
Grzeskowiak 2015	Other measures – abnormal impact score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	441	RR 0.66 (0.36, 1.20)
Grzeskowiak 2015	Other measures – abnormal impact score (SDQ)	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.76 (0.40, 1.46)
Nulman 2015	Total problems (CBCL)	SRI ¹⁹² (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05
Pedersen 2013	Total difficulties – abnormal score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	225	OR 1.3 (0.3, 6.0)
Pedersen 2013	Internalising problems – abnormal emotional symptoms score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	225	OR 1.6 (0.8, 8.9)
Pedersen 2013	Internalising problems – abnormal conduct problems score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	225	OR 0.6 (0.3, 1.3)
Pedersen 2013	Externalising problems – abnormal hyperactivity-inattention score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	225	OR 1.8 (0.6, 5.6)
Pedersen 2013	Internalising problems – abnormal peer problems score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	225	OR 0.9 (0.2, 4.8)
Pedersen 2013	Other measures – abnormal pro-social score (SDQ)	Any ADs (any time)	Unexposed – depression	1 (cohort)	225	OR 0.5 (0.2, 1.7)

¹⁹² Includes SSRIs and SNRIs.

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Internalising behaviours						
Brandlistuen 2015	Internalising behaviour (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.16 (-0.14, 0.46)
Brandlistuen 2015	Internalising behaviour – anxiety (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.14 (-0.19, 0.47)
Brandlistuen 2015	Internalising behaviour – emotional reactivity (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.05 (-0.28, 0.38)
Brandlistuen 2015	Internalising behaviour – somatic (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β -0.05 (-0.41, 0.30)
Brandlistuen 2015	Internalising behaviour - sleep (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.20 (-0.11, 0.51)
Brandlistuen 2015	Internalising behaviour (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β 0.34 (-0.01, 0.68)
Brandlistuen 2015	Internalising behaviour - anxiety (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β 0.64 (0.26, 1.02)
Brandlistuen 2015	Internalising behaviour – emotional reactivity (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β -0.06 (-0.42, 0.30)
Brandlistuen 2015	Internalising behaviour - somatic (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β 0.04 (-0.36, 0.43)
Brandlistuen 2015	Internalising behaviour - sleep (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β 0.25 (-0.11, 0.60)
Nulman 2015	Internalising behaviour (CBCL)	SRIs ¹⁹³ (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	\geq 0.05
Externalising behaviours						
Brandlistuen 2015	Externalising behaviour (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.26 (-0.05, 0.56)
Brandlistuen 2015	Externalising behaviour - attention (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.15 (-0.16, 0.47)
Brandlistuen 2015	Externalising behaviour – aggression (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.30 (-0.03, 0.64)
Brandlistuen 2015	Externalising behaviour (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β -0.08 (-0.44, 0.27)

¹⁹³ Includes SSRIs and SNRIs.

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Brandlistuen 2015	Externalising behaviour - attention (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β -0.01 (-0.38, 0.36)
Brandlistuen 2015	Externalising behaviour – aggression (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β -0.11 (-0.49, 0.27)
Nulman 2015	Externalising behaviour (CBCL)	SRI ¹⁹⁴ (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	\geq 0.05
Depression						
Malm 2016	Depression (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – psychiatric disorder	1 (cohort)	25,380	HR 1.78 (1.12, 2.82)
Malm 2016	Depression (up to 14 years)	SSRIs (monotherapy only)	Unexposed – psychiatric disorder	1 (cohort)	NR	HR 1.85 (1.15, 2.98)
Malm 2016	Depression (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – previous SSRIs	1 (cohort)	23,709	HR 1.84 (1.14, 2.97)
Anxiety						
Malm 2016	Depression (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – psychiatric disorder	1 (cohort)	25,380	HR 1.30 (0.84, 2.01)
Malm 2016	Depression (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – previous SSRIs	1 (cohort)	23,709	HR 1.53 (0.94, 2.50)

Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CBCL, Child behaviour Checklist; CI, confidence interval; HR, hazard ratio; ICD, International Statistical Classification of Diseases; MAOI, monoamine oxidase inhibitor; MRI, non-selective, monoamine reuptake inhibitor; NR, not reported; OR, odds ratio; RE, risk estimate; RR, relative risk; SDQ, Strengths and Difficulties Questionnaire; SNRI, serotonin and noradrenaline reuptake inhibitor; SRI, selective reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. All included data was adjusted for potential confounders and limited/adjusted for psychiatric illness. All data is carried into **Section AppD 4.2.1**.

¹⁹⁴ Includes SSRIs and SNRIs.

AppD3.1.2 Antipsychotics

AppD3.1.2.1 Systematic reviews – antipsychotics

AppD3.1.2.1.1 Malformations – antipsychotics

Table AppD3-7 Antipsychotic infant harms data extraction from systematic reviews – malformation outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	No. studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Major malformations										
Coughlin 2015	Major malformations	Antipsychotics	Unexposed	7 (cohort)	1,640,357	-	OR 2.12 (1.25, 3.57)	<0.00001 (84%)	✗	✗
Coughlin 2015	Major malformations	Typical antipsychotics ¹⁹⁵	Unexposed	5 (cohort)	NR	-	OR 1.55 (1.21, 1.99)	NR	✗	✗
Coughlin 2015	Major malformations	Atypical antipsychotics	Unexposed	3 (cohort)	NR	-	OR 1.39 (0.66, 2.93)	NR	✗	✗
Ennis 2015	Major malformations ¹⁹⁶	Olanzapine	Unexposed	9 (cohort) ¹⁹⁷	1090 ¹⁹⁸	-	RR 1.0 (0.7–1.4)	NR	✗	✗
Ennis 2015	Major malformations ¹⁹⁶	Quetiapine	Unexposed	10 (cohort) ¹⁹⁷	443 ¹⁹⁸	-	RR 1.0 (0.6–1.7)	NR	✗	✗
Ennis 2015	Major malformations ¹⁹⁶	Risperidone	Unexposed	9 (cohort) ¹⁹⁷	432 ¹⁹⁸	-	RR 1.5 (0.9–2.2)	NR	✗	✗
Ennis 2015	Major malformations ¹⁹⁶	Aripiprazole	Unexposed	6 (cohort) ¹⁹⁷	100 ¹⁹⁸	-	RR 1.4 (0.5–3.1)	NR	✗	✗
NICE 2015	Major congenital malformations	Any antipsychotics	Unexposed	4 (cohort)	977,062	-	OR 1.62 (1.18, 2.22)	0.35 (8%)	✗	✗
Terrana 2015	Major malformations	SGAs	Unexposed	8 (cohort)	962,587	-	OR 2.03 (1.41, 2.93)¹⁹⁹	<0.001 (0%)	✗	✗

¹⁹⁵ Difference between typical and atypical antipsychotics not statistically significant (p = 0.79).¹⁹⁶ Unclear whether this review intended to restrict events to ‘major’ malformations. The outcome is inconsistently referred to as ‘major’ or, more frequently, ‘congenital’ malformations, and this systematic review appears to have extracted data for ‘any’ malformations from at least some studies (e.g. hip dysplasia for olanzapine from Kulkarni 2014).¹⁹⁷ Studies were a mixture of non-comparative and comparative cohort studies. However, rates were determined from exposed groups only, pooled and compared with a published population incidence of 3.5%.¹⁹⁸ Number exposed (compared to population incidence, for which n is not reported).¹⁹⁹ For only one of the eight studies was non-adjusted data used in this analysis, contributing 18% of the total weight.

Study ID	Outcome	Exposure (subgroup)	Comparator population	No. studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Cardiac malformations										
Coughlin 2015	Cardiac malformations	Antipsychotics	Unexposed	4 (cohort)	1,628,021	-	OR 2.09 (1.50, 2.91)	0.48 (0%)	✗	✗

Abbreviations: CI, confidence interval; NICE, National Institute of Health and Care Excellence; NR, not reported; OR, odds ratio; RE, risk estimate; RR, risk ratio; SGA, second generation antipsychotic; SR, systematic review.

AppD3.1.2.1.2 Pregnancy and birth outcomes – antipsychotics

Table AppD3-8 Antipsychotic infant harms data extraction from systematic reviews – pregnancy and birth outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	No. studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Neonatal mortality										
Coughlin 2015	Stillbirth, late pregnancy loss prior to completion of delivery	Antipsychotics	Unexposed	5 (cohort)	1,018,795	-	OR 1.18 (0.88, 1.57)	0.47 (0%)	✗	✗
NICE 2015	Stillbirth	Antipsychotics	Unexposed	5 (cohort)	1,335,661	-	OR 1.45 (0.70, 3.01)	0.47 (0%)	✗	✗
Terrana 2015	Stillbirth	SGAs	Unexposed	2 (cohort)	NR	-	OR 0.79 (0.22, 2.83)	0.452 (0%)	✗	✗
Miscarriage										
Coughlin 2015	Spontaneous abortion, early pregnancy loss	Antipsychotics	Unexposed	4 (cohort)	3788	-	OR 1.05 (0.61, 1.81)	0.02 (70%)	✗	✗
NICE 2015	Miscarriage	Antipsychotics	Unexposed	3 (cohort)	3,115	-	OR 1.26 (0.71, 2.24)	0.03 (72%)	✗	✗
Terrana 2015	Miscarriage	SGAs	Unexposed	6 (cohort)	4722	-	OR 1.10 (0.74, 1.64)	0.152 (38%)	✗	✗
Preterm delivery (<37 weeks)										
Coughlin 2015	Preterm (<37 weeks)	Antipsychotics	Unexposed	7 (cohort)	1,534,350	-	OR 1.86 (1.45, 2.39)	0.08 (46%)	✗	✗
Coughlin 2015	Preterm (<37 weeks)	Typical antipsychotics ²⁰⁰	Unexposed	NR	NR	-	OR 2.03 (1.47, 2.80)	NR	✗	✗

²⁰⁰ Difference between typical and atypical antipsychotics not statistically significant (p = 0.79).

Study ID	Outcome	Exposure (subgroup)	Comparator population	No. studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Coughlin 2015	Preterm (<37 weeks)	Atypical antipsychotics	Unexposed	NR	NR	-	OR 1.61 (1.15, 2.25)	NR	✗	✗
NICE 2015	Preterm (not defined)	Antipsychotics	Unexposed, excluding psychiatric population	6 (cohort)	950,255	-	OR 1.90 (1.40, 2.57)	0.03 (60%)	✗	✗
NICE 2015	Preterm (not defined)	Antipsychotics	Unexposed, restricted to psychiatric population	2 (cohort)	1,570	-	OR 1.58 (0.75, 3.33)	0.03 (78%)	✗	✗
NICE 2015	Preterm (not defined)	Antipsychotics	Unexposed, all	8 (cohort)	951,825	-	OR 1.81 (1.39, 2.36)	0.01 (60%)	✗	✗
Terrana 2015	Preterm (<37 weeks)	Antipsychotics	Unexposed	7 (cohort)	NR	-	OR 1.85 (1.20, 2.86) ²⁰¹	0.103 (43%)	✗	✗
Small for gestational age										
Coughlin 2015	Small for gestational age	Antipsychotics	Unexposed	4 (cohort)	1,578,906	-	OR 2.44 (1.22, 4.86)	0.001 (81%)	✗	✗
NICE 2015	Small for gestational age	Antipsychotics	Unexposed, excluding psychiatric population	5 (cohort)	943,127	-	OR 2.30 (1.76, 3.01)	0.08 (51%)	✗	✗
NICE 2015	Small for gestational age	Antipsychotics	Unexposed, restricted to psychiatric population	2 (cohort)	1,566	-	OR 1.15 (0.82, 1.62)	0.08 (51%)	✗	✗
NICE 2015	Small for gestational age	Antipsychotics	Unexposed, all	7 (cohort)	944,783	-	OR 1.77 (1.43, 2.18)	0.003 (69%)	✗	✗
Large for gestational age										
NICE 2015	Large for gestational age	Antipsychotics	Unexposed, excluding psychiatric population	4 (cohort)	942,917	-	OR 0.82 (0.63, 1.06)	0.0006 (83%)	✗	✗
NICE 2015	Large for gestational age	Antipsychotics	Unexposed, restricted to psychiatric population	2 (cohort)	1,566	-	OR 0.82 (0.52, 1.28)	0.08 (51%)	✗	✗
NICE 2015	Large for gestational age	Antipsychotics	Unexposed, all	6 (cohort)	944,483	-	OR 0.82 (0.65, 1.03)	0.004 (72%)	✗	✗
Terrana 2015	Small for gestational age	SGAs	Unexposed	6 (cohort)	NR	-	OR 1.58 (0.91, 2.74)	0.530 (0%)	✗	✗

Abbreviations; CI, confidence interval; NICE, National Institute of Health and Care Excellence; NR, not reported; OR, odds ratio; RE, risk estimate; RR, risk ratio; SGA, second generation antipsychotic; SR, systematic review.

²⁰¹ When publication bias accounted for, this estimate was OR 1.34 (0.85, 2.11).

AppD3.1.2.1.3 Neurodevelopmental outcomes – antipsychotics

Table AppD 3-9 Antipsychotic infant harms data extraction from systematic reviews – neurodevelopmental outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	No. studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
INFANIB										
NICE 2015	INFANIB, mean score at 6 months	Antipsychotics	Unexposed	1 (cohort)	107	-	SMD -0.67, (-1.15, -0.19)	N/A	✗	✗
Bayley scales of infant development										
NICE 2015	Bayley cognitive functioning scale, score <85	Antipsychotics	Unexposed	1 (cohort)	152	-	OR 1.67 (0.52, 5.36)	N/A	✗	✗
NICE 2015	Bayley language scale, score <85	Antipsychotics	Unexposed	1 (cohort)	152	-	OR 1.13 (0.43, 2.95)	N/A	✗	✗
NICE 2015	Bayley motor functioning scale, score <85	Antipsychotics	Unexposed	1 (cohort)	152	-	OR 1.67 (0.52, 5.36)	N/A	✗	✗
NICE 2015	Bayley social/emotional functioning scale, score <85	Antipsychotics	Unexposed	1 (cohort)	152	-	OR 2.19 (0.78, 6.17)	N/A	✗	✗
NICE 2015	Bayley adaptive behaviour scale, score <85	Antipsychotics	Unexposed	1 (cohort)	152	-	OR 2.15 (0.70, 6.62)	N/A	✗	✗
NICE 2015	All Bayley scales, score <85	Antipsychotics	Unexposed	1 (cohort)	152 x 5 (760)	-	OR 1.68 (1.04, 2.73)	N/A	✗	✗

Abbreviations: INFANIB, Infant Neurological International Battery; NICE, National Institute of Health and Care Excellence; SMD, standardized mean difference.

AppD3.1.2.2 Individual studies – antipsychotics

AppD3.1.2.2.1 Malformations – antipsychotics

Table AppD3-10 Antipsychotic infant harms data extraction from observational studies – malformations

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
STUDIES REPORTING AN ESTIMATE OF EFFECT SIZE (UNADJUSTED RESULTS SHADED)						
Major Malformations						
Cohen 2016	Major malformations	SGAs (1 st trimester)	Unexposed, partially restricted by psychiatric illness	Prospective cohort	Infants exposed: 214 Unexposed, diagnosis: 89	OR 1.25 (0.13, 12.19).

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Cohen 2016	Major malformations	SGAs (1 st trimester)	Unexposed, partially restricted by psychiatric illness	Prospective cohort	Infants exposed: 214 Unexposed, diagnosis: 89	AOR 0.69 (0.06, 8.09) ²⁰²
Huybrechts 2016	Major congenital malformations	SGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 9,258 Unexposed: 1,331,910	Unadjusted RR 1.36 (1.24, 1.50)
Huybrechts 2016	Major congenital malformations	SGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 9,240 Unexposed: 1,331,896	Adjusted for psychiatric indication and assoc. meds RR 1.12 (1.02, 1.23)
Huybrechts 2016	Major congenital malformations	SGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 9,237 Unexposed: 1,289,826	Fully adjusted RR 1.05 (0.96, 1.16)
Huybrechts 2016	Major congenital malformations	SGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 9,236 Unexposed: 1,324,021	Adjusted for hdPS RR 1.08 (0.98, 1.19)
Huybrechts 2016	Major congenital malformations	SGAs <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 3,995 Unexposed: 11,606	Fully adjusted RR 1.16 (0.99, 1.35)
Huybrechts 2016	Major congenital malformations	SGAs, <u>≥2 scripts during 1st trimester</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 3,798 Unexposed: 1,226,901	Fully adjusted RR 1.09 (0.94, 1.25)
Huybrechts 2016	Major congenital malformations	FGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 733 Unexposed: 1,331,910	Unadjusted RR 1.17 (0.81, 1.68)
Huybrechts 2016	Major congenital malformations	FGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 668 Unexposed: 1,331,449	Adjusted for psychiatric indication and assoc. meds RR 1.00 (0.69, 1.45)
Huybrechts 2016	Major congenital malformations	FGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 727 Unexposed: 1,297,638	Fully adjusted RR 0.90 (0.62, 1.31)
Huybrechts 2016	Major congenital malformations	FGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 726 Unexposed: 1,137,048	Adjusted for hdPS RR 0.93 (0.64, 1.35)
Huybrechts 2016	Major congenital malformations	FGAs, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 381 Unexposed: 10,418	Fully adjusted RR 0.93 (0.57, 1.51)
Huybrechts 2016	Major congenital malformations	FGAs, <u>≥2 scripts during 1st trimester</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 212 Unexposed: 860,458	Fully adjusted RR 0.80 (0.39, 1.66)
Huybrechts 2016	Major congenital malformations	Aripiprazole (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,756 Unexposed: 1,331,910	Unadjusted RR 1.31 (1.05, 1.63)

²⁰² This estimate was derived from a sensitivity analysis using a hypothetical propensity score-adjusted model (the propensity score predicting exposure was calculated using first-trimester exposure to 10 medication classes and a primary diagnosis of bipolar disorder) However, due to rarity of outcome, authors interpreted only the crude analysis (unadjusted OR 1.25 (0.13, 12.19), and noted that adjusting for confounders indicated an upward bias in the results.

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Huybrechts 2016	Major congenital malformations	Aripiprazole (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,750 Unexposed: 1,325,710	Adjusted for psychiatric indication and assoc. meds RR 1.04 (0.83, 1.30)
Huybrechts 2016	Major congenital malformations	Aripiprazole (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,752 Unexposed: 957,012	Fully adjusted RR 0.95 (0.76, 1.19)
Huybrechts 2016	Major congenital malformations	Aripiprazole, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 949 Unexposed: 10,174	Fully adjusted RR 1.13 (0.86, 1.50)
Huybrechts 2016	Major congenital malformations	Olanzapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,394 Unexposed: 1,331,910	Unadjusted RR 1.3 (1.01, 1.66)
Huybrechts 2016	Major congenital malformations	Olanzapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,335 Unexposed: 1,329,948	Adjusted for psychiatric indication and assoc. meds RR 1.05 (0.82, 1.36)
Huybrechts 2016	Major congenital malformations	Olanzapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,392 Unexposed: 1,231,441	Fully adjusted RR 1.09 (0.85, 1.41)
Huybrechts 2016	Major congenital malformations	Olanzapine, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 648 Unexposed: 10,949	Fully adjusted RR 1.19 (0.84, 1.67)
Huybrechts 2016	Major congenital malformations	Quetiapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 4,221 Unexposed: 1,331,910	Unadjusted RR 1.32 (1.15, 1.52)
Huybrechts 2016	Major congenital malformations	Quetiapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 4,213 Unexposed: 1,331,557	Adjusted for psychiatric indication and assoc. meds RR 1.09 (0.95, 1.26)
Huybrechts 2016	Major congenital malformations	Quetiapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 4,213 Unexposed: 1,161,955	Fully adjusted RR 1.01 (0.88, 1.17)
Huybrechts 2016	Major congenital malformations	Quetiapine, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 1,747 Unexposed: 11,440	Fully adjusted RR 1.13 (0.92, 1.41)
Huybrechts 2016	Major congenital malformations	Risperidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,566 Unexposed: 1,331,910	Unadjusted RR 1.56 (1.26, 1.94)
Huybrechts 2016	Major congenital malformations	Risperidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,472 Unexposed: 1,331,674	Adjusted for psychiatric indication and assoc. meds RR 1.31 (1.05, 1.63)
Huybrechts 2016	Major congenital malformations	Risperidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,565 Unexposed: 1,290,485	Fully adjusted RR 1.26 (1.02, 1.56)

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Huybrechts 2016	Major congenital malformations	Risperidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,563 Unexposed: 1,266,615	Adjusted for hdPS RR 1.36 (1.10, 1.69)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 740 Unexposed: 11,497	Fully adjusted RR 1.19 (0.86, 1.64)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>≥2 scripts during 1st trimester</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 473 Unexposed: 933,940	Fully adjusted RR 1.46 (1.01, 2.10)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>≥2 scripts during 1st trimester</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 477 Unexposed: 1,244,862	Adjusted for hdPS RR 1.5 (1.04, 2.16)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>low dose</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 407 Unexposed: 988,963	Fully adjusted RR 1.42 (0.96, 2.09)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>medium dose</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 532 Unexposed: 1,126,638	Fully adjusted RR 1.13 (0.76, 1.67)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>high dose</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 609 Unexposed: 1,094,959	Fully adjusted RR 1.36 (0.97, 1.90)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	<u>Discontinued</u> : no Rx from start of pregnancy	Retrospective, Medicaid cohort	Exposed: 895 Unexposed: 1,737	PS-adjusted RR 1.00 (0.70, 1.43)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	<u>Discontinued</u> : no Rx from 4 weeks before pregnancy	Retrospective, Medicaid cohort	Exposed: 882 Unexposed: 1,089	PS-adjusted RR 1.13 (0.75, 1.71)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	<u>Discontinued</u> : no Rx from 6 weeks before pregnancy	Retrospective, Medicaid cohort	Exposed: 878 Unexposed: 799	PS-adjusted RR 1.12 (0.71, 1.75)
Huybrechts 2016	Major congenital malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	<u>Discontinued</u> : no Rx from 8 weeks before pregnancy	Retrospective, Medicaid cohort	Exposed: 866 Unexposed: 496	PS-adjusted RR 1.64 (0.90, 2.98)
Huybrechts 2016	Major congenital malformations	Ziprasidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 697 Unexposed: 1,331,910	Unadjusted RR 1.14 (0.78, 1.67)
Huybrechts 2016	Major congenital malformations	Ziprasidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 695 Unexposed: 1,270,722	Adjusted for psychiatric indication and assoc. meds RR 0.9 (0.61, 1.31)
Huybrechts 2016	Major congenital malformations	Ziprasidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 696 Unexposed: 979,614	Fully adjusted RR 0.88 (0.60, 1.28)

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Huybrechts 2016	Major congenital malformations	Ziprasidone, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 425 Unexposed: 10,971	Fully adjusted RR 0.84 (0.51, 1.39)
Petersen 2016a	Major congenital malformations	Any antipsychotics (early)	Discontinued antipsychotics	Retrospective, general practice cohort	Exposed: 290 Unexposed: 492	ARR 1.79 (0.72, 4.47)
Petersen 2016a	Major congenital malformations	Any antipsychotics (early)	Unexposed	Retrospective, general practice cohort	Exposed: 290 Unexposed: 210,966	ARR 1.59 (0.84, 3.00)
Bellet 2015	Major malformations	Aripiprazole (embryogenesis: 4-10 weeks)	Unexposed, matched ²⁰³	Prospective cohort, matched controls	Exposed: 86 Unexposed: 172	OR 2.30 (0.32, 16.7)
Habermann 2013	Major congenital malformations	SGAs (pregnancy)	Unexposed, matched	Prospective, cohort, matched controls	Exposed: 561 Unexposed: 1122	AOR 2.17 (1.20, 3.91)
Habermann 2013	Major congenital malformations	FGAs (pregnancy)	Unexposed, not matched	Prospective, cohort, matched controls	Exposed: 284 Unexposed: 1122	AOR 1.71 (0.78, 3.76)
Habermann 2013	Major congenital malformations	SGAs (pregnancy)	FGAs, not matched	Prospective, cohort, matched controls	SGAs: 561 FGAs: 284	AOR 1.27 (0.57, 2.82)
Källén 2013	Relatively severe malformations	Antipsychotics or lithium ²⁰⁴ (early)	Unexposed	Population-based cohort	Infant exposure <u>instances</u> : 1,344 Total: 1,575,847	AOR 1.48 (1.13, 1.92)
Källén 2013	Relatively severe malformations	haloperidol (early)	Unexposed	Population-based cohort	Exposed: 115 Total: 1,575,847	ARR 1.21 (0.39, 2.83) ²⁰⁵
Källén 2013	Relatively severe malformations	flupenthixol (early)	Unexposed	Population-based cohort	Exposed: 154 Total: 1,575,847	ARR 1.94 (1.00, 3.40) ²⁰⁵
Källén 2013	Relatively severe malformations	olanzapine (early)	Unexposed	Population-based cohort	Exposed: 205 Total: 1,575,847	ARR 0.93 (0.40, 1.84) ²⁰⁵
Reis 2008	Relatively severe malformations	Antipsychotics (early)	Unexposed	Population-based cohort	Exposed: 576 Total: 973,767	AOR 1.52 (1.05, 2.19)
Reis 2008	Relatively severe malformations	Antipsychotics, excluding anticonvulsants (early)	Unexposed	Population-based cohort	Exposed: NR Excluded 18 women	AOR 1.45 (0.99, 1.41) ²⁰⁶
Slone 1977	Major congenital malformations	Phenothiazines (1 st four months)	Unexposed	Prospective cohort	Exposed: 1,309 Unexposed: 48,973	RR 1.16 (CI NR) not significant ²⁰⁷

²⁰³ For maternal age and gestational age at contact with service.

²⁰⁴ Data aggregated for antipsychotics (excluding dixyrazine and prochlorperazine) and lithium, which is most common subgroup (17% of infants exposed) and confounds the data for antipsychotics.

²⁰⁵ As the expected number of events in the exposed group was less than 10, a RR was calculated instead of OR, using the observed over expected number with 95% CI from exact Poisson distributions.

²⁰⁶ Upper CI reported in Reis 2008 is less than the point estimate. Using RevMan 5.3 and the reported p value of 0.055, the upper CI was estimated post hoc as 2.12.

²⁰⁷ Inferred from text.

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Slone 1977	Major congenital malformations	Phenothiazines, heavy exposure (not defined) (1 st four months)	Unexposed	Prospective cohort	Exposed: 403 Unexposed: 48,973	RR 1.05 (0.56, 1.77)
Cardiac malformations						
Huybrechts 2016	Cardiac malformations	SGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 9,258 Unexposed: 1,331,910	Unadjusted RR 1.40 (1.19, 1.64)
Huybrechts 2016	Cardiac malformations	SGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 9,240 Unexposed: 1,331,896	Adjusted for psychiatric indication and assoc. meds RR 1.15 (0.98, 1.35)
Huybrechts 2016	Cardiac malformations	SGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 9,237 Unexposed: 1,289,826	Fully adjusted RR 1.06 (0.90, 1.24)
Huybrechts 2016	Cardiac malformations	SGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 9,236 Unexposed: 1,324,021	Adjusted for hdPS RR 1.10 (0.94, 1.30)
Huybrechts 2016	Cardiac malformations	SGAs, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 3,995 Unexposed: 11,606	Fully adjusted RR 1.21 (0.93, 1.57)
Huybrechts 2016	Cardiac malformations	SGAs, <u>≥2 scripts during 1st trimester</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 3,798 Unexposed: 1,226,901	Fully adjusted RR 1.17 (0.93, 1.47)
Huybrechts 2016	Cardiac malformations	FGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 733 Unexposed: 1,331,910	Unadjusted RR 1.18 (0.64, 2.18)
Huybrechts 2016	Cardiac malformations	FGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 668 Unexposed: 1,331,449	Adjusted for psychiatric indication and assoc. meds RR 0.94 (0.49, 1.80)
Huybrechts 2016	Cardiac malformations	FGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 727 Unexposed: 1,297,638	Fully adjusted RR 0.75 (0.39, 1.43)
Huybrechts 2016	Cardiac malformations	FGAs (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 726 Unexposed: 1,137,048	Adjusted for hdPS RR 0.86 (0.45, 1.65)
Huybrechts 2016	Cardiac malformations	FGAs, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 381 Unexposed: 10,418	Fully adjusted RR 0.91 (0.43, 1.91)
Huybrechts 2016	Cardiac malformations	FGAs, <u>≥2 scripts during 1st trimester</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 212 Unexposed: 860,458	Fully adjusted RR 0.74 (0.24, 2.29)
Huybrechts 2016	Cardiac malformations	Aripiprazole (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,756 Unexposed: 1,331,910	Unadjusted RR 1.33 (0.91, 1.93)
Huybrechts 2016	Cardiac malformations	Aripiprazole (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,750 Unexposed: 1,325,710	Adjusted for psychiatric indication and assoc. meds RR 1.06 (0.72, 1.55)

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Huybrechts 2016	Cardiac malformations	Aripiprazole (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,752 Unexposed: 957,012	Fully adjusted RR 0.93 (0.64, 1.37)
Huybrechts 2016	Cardiac malformations	Aripiprazole, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 949 Unexposed: 10,174	Fully adjusted RR 1.13 (0.71, 1.80)
Huybrechts 2016	Cardiac malformations	Olanzapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,394 Unexposed: 1,331,910	Unadjusted RR 1.24 (0.80, 1.92)
Huybrechts 2016	Cardiac malformations	Olanzapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,335 Unexposed: 1,329,948	Adjusted for psychiatric indication and assoc. meds RR 0.96 (0.61, 1.52)
Huybrechts 2016	Cardiac malformations	Olanzapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,392 Unexposed: 1,231,441	Fully adjusted RR 0.99 (0.64, 1.53)
Huybrechts 2016	Cardiac malformations	Olanzapine, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 648 Unexposed: 10,949	Fully adjusted RR 1.23 (0.69, 2.19)
Huybrechts 2016	Cardiac malformations	Quetiapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 4,221 Exposed: 1,331,910	Unadjusted RR 1.43 (1.14, 1.81)
Huybrechts 2016	Cardiac malformations	Quetiapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 4,213 Unexposed: 1,331,557	Adjusted for psychiatric indication and assoc. meds RR 1.18 (0.94, 1.49)
Huybrechts 2016	Cardiac malformations	Quetiapine (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 4,213 Unexposed: 1,161,955	Fully adjusted RR 1.07 (0.85, 1.35)
Huybrechts 2016	Cardiac malformations	Quetiapine, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 1,747 Unexposed: 11,440	Fully adjusted RR 1.17 (0.81, 1.67)
Huybrechts 2016	Cardiac malformations	Risperidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,566 Unexposed: 1,331,910	Unadjusted RR 1.60 (1.12, 2.30)
Huybrechts 2016	Cardiac malformations	Risperidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,472 Unexposed: 1,331,674	Adjusted for psychiatric indication and assoc. meds RR 1.39 (0.96, 2.01)
Huybrechts 2016	Cardiac malformations	Risperidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,565 Unexposed: 1,290,485	Fully adjusted RR 1.26 (0.88, 1.81)
Huybrechts 2016	Cardiac malformations	Risperidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 1,563 Unexposed: 1,266,615	Adjusted for hdPS RR 1.38 (0.96, 1.98)

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 740 unexposed: 11,497	Fully adjusted RR 1.64 (1.03, 2.62)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>≥2 scripts during 1st trimester</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 473 Unexposed: 933,940	Fully adjusted RR 1.87 (1.09, 3.19)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>≥2 scripts during 1st trimester</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 477 Unexposed: 1,244,862	Adjusted for hdPS RR 1.9 (1.11, 3.25)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>low dose</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 407 Unexposed: 988,963	Fully adjusted RR 0.95 (0.43, 2.10)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>medium dose</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 532 Unexposed: 1,126,638	Fully adjusted RR 0.67 (0.28, 1.60)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>high dose</u> (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 609 Unexposed: 1,094,959	Fully adjusted RR 2.08 (1.32, 3.28)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	Discontinued: no Rx from start of pregnancy	Retrospective, Medicaid cohort	Exposed: 895 Unexposed: 1,737	Fully adjusted RR 0.85 (0.49, 1.46)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	Discontinued: no Rx from 4 weeks before pregnancy	Retrospective, Medicaid cohort	Exposed: 882 Unexposed: 1,089	Fully adjusted RR 1.31 (0.64, 2.68)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	Discontinued: no Rx from 6 weeks before pregnancy	Retrospective, Medicaid cohort	Exposed: 878 Unexposed: 799	Fully adjusted RR 1.7 (0.72, 4.01)
Huybrechts 2016	Cardiac malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	Discontinued: no Rx from 8 weeks before pregnancy	Retrospective, Medicaid cohort	Risperidone: 866 Discontinued: 496	Fully adjusted RR 2.46 (0.77, 7.87)
Huybrechts 2016	Cardiac malformations	Ziprasidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Ziprasidone: 697 Exposed: 1,331,910	Unadjusted RR 1.12 (0.58, 2.14)
Huybrechts 2016	Cardiac malformations	Ziprasidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 695 Unexposed: 1,270,722	Adjusted for psychiatric indication and assoc. meds RR 0.88 (0.46, 1.69)
Huybrechts 2016	Cardiac malformations	Ziprasidone (1 st trimester)	Unexposed	Retrospective, Medicaid cohort	Exposed: 696 Unexposed: 979,614	Fully adjusted RR 0.85 (0.44, 1.63)

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Huybrechts 2016	Cardiac malformations	Ziprasidone, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed: psychosis, schizophrenia, bipolar disorder	Retrospective, Medicaid cohort	Exposed: 425 Unexposed: 10,971	Fully adjusted RR 0.75 (0.31, 1.81)
Habermann 2013	Cardiac malformations (post hoc analysis)	SGAs (pregnancy)	Unexposed, matched	Prospective, cohort, matched controls	Exposed: 561 Unexposed: 1122	OR 3.21 (1.34, 7.67)
Habermann 2013	Cardiac malformations (post hoc analysis)	FGAs (pregnancy)	Unexposed, not matched	Prospective, cohort, matched controls	Exposed: 284 Unexposed: 1122	OR 2.13 (0.65, 7.01)
Habermann 2013	Cardiac malformations (post hoc analysis)	SGAs (pregnancy)	FGAs, not matched	Prospective, cohort, matched controls	SGAs: 561 FGAs: 284	OR 1.50 (0.48, 4.71)
Källén 2013	Any cardiac defect	Antipsychotics or lithium ²⁰⁴ (early)	Unexposed	Population-based cohort	Infant exposure <u>instances</u> : 1,344 Total: 1,575,847	AOR 0.83 (0.48, 1.41)
Källén 2013	Septal cardiac defects	Antipsychotics or lithium ²⁰⁴ (early)	Unexposed	Population-based cohort	Infant exposure <u>instances</u> : 1,344 Total: 1,575,847	AOR 0.83 (0.44, 1.59)
Slone 1977	Cardiovascular malformations	Phenothiazines (1 st four months)	Unexposed	Prospective cohort	Exposed: 1,309 Unexposed: 48,973	RR 1.68 (1.0, upper CI NR)
STUDIES NOT REPORTING AN ESTIMATE OF EFFECT SIZE						%, p value
Habermann 2013	Major malformations for <u>1st trimester exposure</u>	SGAs (1st trimester)	Alternative SGA 1st trimester. Concomitant FGAs allowed.	Prospective, cohort, matched controls	Quetiapine: 5/139 Aripiprazole: 3/44 Amisulpride: 0/13 Zotepine: 0/2	Quetiapine 3.59% vs Aripiprazole 6.81% p>0.05
Peng 2013	Any malformations	SGAs (pregnancy)	Unexposed, no mental health disorder, matched	Prospective, longitudinal cohort	Exposed: 76 Unexposed: 76	Reported there were no malformations in either group (but the authors note this outcome is subject to bias ²⁰⁸)
Sadowski 2013	Major malformations	SGAs (pregnancy)	Unexposed, matched (age, contact time)	Prospective cohort, matched controls	Exposed: 133 Unexposed: 133	6.2% vs 2.6% p = 0.211
Diav-Citrin 2005	Major anomalies	Haloperidol or penfluridol (pregnancy)	Unexposed	Prospective cohorts, multicentre	Exposed: 215 Unexposed: 631	3.4% vs 3.8% p = 0.787
Diav-Citrin 2005	Major anomalies in live births with 1 st trimester exposure	Haloperidol or penfluridol (pregnancy)	Unexposed	Prospective cohorts, multicentre	Exposed: 215 Unexposed: 631	3.1% vs 3.8% p = 1.000

²⁰⁸ Participants were recruited close to the end of their pregnancy, and “since late abortion is allowed in China, it was very unlikely that any mother would carry an ultrasound detectable developmental deficit fetus to the end of pregnancy regardless if they have a mental illness or not”.

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
McKenna 2005	Major malformations	SGAs (1 st trimester)	Unexposed, matched	Prospective cohorts, matched controls	Exposed: N = 151 Unexposed: N = 151	0.9% vs 1.5% p = 1.0
Rumeau-Rouquette 1977	Congenital malformations	Phenothiazines (1 st trimester)	Unexposed ²⁰⁹	Prospective cohort	Exposed: 315 Unexposed: 11,099	1.6% vs 3.5% p < 0.01

Abbreviations: AOR, adjusted odds ratio; ARR, adjusted risk ratio; CI, confidence interval; FGAs, first generation antipsychotics; hdPS, high-dimensional propensity score; NR, not reported; OBS, observational studies; OR, odds ratio; PS, propensity score; RE, risk estimate; RR, risk ratio; Rx, prescription; SGA, second generation antipsychotic.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Shaded data is carried into **Section AppD4.1.2**. Data shown in grey hatching is either (i) adjusted for potential confounders OR (ii) limited to/adjusted for psychiatric illness. Data shown in grey shading is adjusted for potential confounders and limited to/adjusted for psychiatric illness. For some analyses, unadjusted data from Huybrechts 2016 is also carried through to Section AppD4.1.2 for the purpose of illustrating the impact on risk estimates of accounting for potential confounders (not shaded).

AppD3.1.2.2.2 Pregnancy and birth outcomes – antipsychotics

Table AppD3-11 Antipsychotic infant harms data extraction from observational studies – pregnancy and birth outcomes

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
STUDIES REPORTING AN ESTIMATE OF EFFECT SIZE (UNADJUSTED RESULTS SHADED)						
Miscarriage						
Bellet 2015	Miscarriage	Aripiprazole (embryogenesis: 4-10 weeks)	Unexposed, matched	Prospective, cohort matched controls	Exposed: 86 Unexposed: 172	OR 1.66 (0.63, 4.38)
Sorensen 2015	Miscarriage	Any antipsychotics (any time from 30 days before, to end of pregnancy)	Unexposed	Retrospective., linked, population-based cohort	Exposed: 1,881 Unexposed: 841,183	ARR 1.34 (1.22, 1.46)
Sorensen 2015	Miscarriage	Any antipsychotics, <u>high dose</u> and hospital diagnosis of severe mental disorder (any time from 30 days before, to end of pregnancy)	Unexposed, restricted to hospital diagnosis of severe mental disorder	Population-based cohort	Exposed: NR Unexposed: 839,846	Unadjusted RR 2.22 (1.67, 2.95)
Sorensen 2015	Miscarriage	Any antipsychotics, <u>high dose</u> ²¹⁰ (any time from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 117 Unexposed: 841,183	ARR 3.19 (2.65, 3.84)
Sorensen 2015	Miscarriage	Any antipsychotics, <u>low dose</u> , and hospital diagnosis of severe mental disorder (any time from 30 days before, to end of pregnancy)	Unexposed, restricted to hospital diagnosis of severe mental disorder	Population-based cohort	Exposed: NR Unexposed: 839,846	Unadjusted RR 2.95 (0.73, 1.26)

²⁰⁹ This study is presented as a comparison of groups defined by outcome (mothers with malformed infants versus mothers with normal infants – control group). However, results are stratified by exposure to phenothiazines.

²¹⁰ Only 85% of exposed cohort included in this subgroup analysis.

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Sorensen 2015	Miscarriage	Any antipsychotics, <u>low dose</u> ²¹⁰ (any time from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 1,487 Unexposed: 841,183	ARR 1.36 (1.22, 1.51)
Sorensen 2015	Miscarriage	Any antipsychotics (any time from 30 days before, to end of pregnancy)	Discontinued (used during preceding year but not from 30 days prior)	Population-based cohort	Exposed: 1,881 Unexposed: 2,745	ARR 1.04 (0.93; 1.17)
Sorensen 2015	Miscarriage	Any antipsychotics and hospital diagnosis of severe mental disorder ²¹¹ (any time from 30 days before, to end of pregnancy)	Unexposed, restricted to hospital diagnosis of severe mental disorder	Population-based cohort	Exposed: 461 Unexposed: 1,337	ARR 1.14 (0.94, 1.39)
Sorensen 2015	Miscarriage	Any antipsychotics, <u>without</u> a hospital diagnosis of severe mental disorder (any time from 30 days before, to end of pregnancy)	Unexposed, <u>without</u> a hospital diagnosis of severe mental disorder	Population-based cohort	Exposed: 1,420 Unexposed: 839,846	ARR 1.34 (1.21, 1.49)
Sorensen 2015	Miscarriage	Chlorprothixene ²¹² (any time from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 365 Unexposed: 841,183	ARR 1.65 (1.39, 1.95)
Sorensen 2015	Miscarriage	Flupenthixol (any time from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 233 Unexposed: 841,183	ARR 1.55 (1.22, 1.97)
Sorensen 2015	Miscarriage	Perphenazine (any time from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 229 Unexposed: 841,183	ARR 1.25 (0.95, 1.64)
Sorensen 2015	Miscarriage	Zuclopenthixol (any time from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 229 Unexposed: 841,183	ARR 1.26 (0.95, 1.66)
Sorensen 2015	Miscarriage	Levomepromazine ²¹³ (any time from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 200 Unexposed: 841,183	ARR 1.32 (1.01, 1.72)
Sorensen 2015	Miscarriage	Quetiapine (any time from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 174 Unexposed: 841,183	ARR 1.65 (1.28, 2.15)

²¹¹ "The Danish Psychiatric Central Register contains information on treatment at psychiatric hospital-based units in Denmark. However, data on diagnoses made by general practitioners or private psychiatrists are not included in the register. Only diagnoses recorded in the register can be adjusted for."

²¹² This intervention is not currently listed on the Australian Register of Therapeutic Goods, so while data is extracted here, it is not taken through to evidence profile tables.

²¹³ This intervention is not currently listed on the Australian Register of Therapeutic Goods, so while data is extracted here, it is not taken through to evidence profile tables.

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Sorensen 2015	Miscarriage	Olanzapine (any time from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 223 Unexposed: 841,183	ARR 1.10 (0.83, 1.46)
Preterm birth						
Bellet 2015	Preterm birth (<37 weeks)	Aripiprazole (embryogenesis: 4-10 weeks)	Unexposed, matched	Prospective, cohort matched controls	Exposed: 86 Unexposed: 172	OR 2.57 (1.06, 6.27)
Vigod 2015	Preterm birth (<37 weeks)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 1.51 (1.29, 1.78)
Vigod 2015	Preterm birth (<37 weeks)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 1.01 (0.81, 1.27)
Vigod 2015	Preterm birth (<37 weeks)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR 0.99 (0.78, 1.26)
Vigod 2015	Preterm birth (<37 weeks)	Any antipsychotic (1 st trimester)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 893 Unexposed: 893	hdPS-matched RR 1.01 (0.80, 1.29)
Vigod 2015	Preterm birth (<37 weeks)	Any antipsychotic (1 st trimester)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 893 Unexposed: 893	hdPS-matched, adjusted RR 0.99 (0.77, 1.27)
Vigod 2015	Preterm birth (<37 weeks)	Any antipsychotic (2 nd trimester)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 758 Unexposed: 758	hdPS-matched RR 1.10 (0.83, 1.44)
Vigod 2015	Preterm birth (<37 weeks)	Any antipsychotic (2 nd trimester)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 758 Unexposed: 758	hdPS-matched, adjusted RR 1.00 (0.75, 1.35)
Vigod 2015	Preterm birth (<37 weeks)	Any antipsychotic (3 rd trimester)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 614 Unexposed: 614	hdPS-matched RR 0.87 (0.64, 1.19)
Vigod 2015	Preterm birth (<37 weeks)	Any antipsychotic (3 rd trimester)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 614 Unexposed: 614	hdPS-matched, adjusted RR 0.83 (0.59, 1.16)
Vigod 2015	Preterm birth (<32 weeks)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 1.61 (1.19, 2.16)
Vigod 2015	Preterm birth (<32 weeks)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 0.89 (0.58, 1.36)
Vigod 2015	Preterm birth (<32 weeks)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR 0.85 (0.53, 1.36)
Vigod 2015	Preterm birth (<28 weeks)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 1.20 (0.80, 1.82)
Vigod 2015	Preterm birth (<28 weeks)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 0.59 (0.34, 1.02)
Vigod 2015	Preterm birth (<28 weeks)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS- matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR 0.48 (0.25, 0.93)

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Habermann 2013	Preterm birth (<37 weeks)	SGAs (pregnancy)	Unexposed, matched	Prospective, cohort, matched controls	Exposed: 561 Unexposed: 1,122	OR 1.06 (0.72, 1.56)
Habermann 2013	Preterm birth (<37 weeks)	FGAs (pregnancy)	Unexposed, not matched	Prospective, cohort, matched controls	Exposed: 284 Unexposed: 1,122	OR 1.96 (1.29, 2.98)
Habermann 2013	Preterm birth (<37 weeks)	SGAs (pregnancy)	FGAs, not matched	Prospective, cohort, matched controls	SGAs: 561 FGAs: 284	OR 0.54 (0.33, 0.87)
Källén 2013	Preterm birth (<37 weeks)	Antipsychotics or lithium ²¹⁴ (2 nd or 3 rd trimester)	Unexposed	Population-based cohort	Infant exposure <u>instances</u> : 1,344 Total: 1,575,847	AOR 1.02 (0.69, 1.51)
Bodén 2012b	Preterm birth (<37 weeks)	Olanzapine and/or clozapine (pregnancy)	Unexposed	Population-based cohort	Exposed: 169 Unexposed: 357,696	AOR 1.58 (0.91, 2.73) ²¹⁵
Bodén 2012b	Preterm birth (<37 weeks)	Antipsychotic (not olanzapine or clozapine) (pregnancy)	Unexposed	Population-based cohort	Exposed: 338 Unexposed: 357,696	AOR 1.94 (1.37, 2.77)²¹⁵
Lin 2010	Preterm birth (<37 weeks)	SGAs for schizophrenia (pregnancy)	Unexposed to FGAs or SGAs, schizophrenia	Population-based cohort	Exposed: 48 Unexposed: 454	AOR 1.61 (0.63, 4.12)
Lin 2010	Preterm birth (<37 weeks)	FGAs for schizophrenia (pregnancy)	Unexposed to FGAs or SGAs, schizophrenia	Population-based cohort	Exposed: 194 Unexposed: 454	AOR 2.46 (1.50, 4.11)
Reis 2008	Preterm birth (< 37 weeks)	Antipsychotics (early)	Unexposed	Population-based cohort	Exposed: 563 Total: 942,780	AOR 1.73 (1.31, 2.29)
Neonatal mortality						
Vigod 2015	Neonatal mortality (<90 days)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 1.64 (0.84, 3.20)
Vigod 2015	Neonatal mortality (<90 days)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 1.50 (0.53, 4.21)
Vigod 2015	Neonatal mortality (<90 days)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR NR
Sorensen 2015	Stillbirth	Any antipsychotics any time (from 30 days before, to end of pregnancy)	Unexposed	Population-based cohort	Exposed: 1,616 Unexposed: 726,727	Unadjusted RR 2.27 (1.45, 3.55)²¹⁶

²¹⁴ Data aggregated for antipsychotics (excluding dixyrazine and prochlorperazine) and lithium, which is most common subgroup (17% of infants exposed) and confounds the data for antipsychotics.

²¹⁵ Reported as OR in results section but the methods section implies the results for preterm birth are adjusted.

²¹⁶ Authors noted that estimates changed only slightly when adjustments were performed (for one variable at a time, due to small sample size) for maternal age, cohabitation, income, history of severe mental disorder or history of drug misuse.

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Sorensen 2015	Stillbirth	Any antipsychotics (any time from 30 days before, to end of pregnancy)	Discontinued (used during preceding year but not from 30 days prior)	Population-based cohort	Exposed: 1,474 Unexposed: 2,193	Unadjusted RR 2.06 (1.01, 4.19)
Vigod 2015	Stillbirth (>20 weeks gestation)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 1.15 (0.64, 2.05)
Vigod 2015	Stillbirth (>20 weeks gestation)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 0.56 (0.25, 1.27)
Vigod 2015	Stillbirth (>20 weeks gestation)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR NR
Reis 2008	Stillbirth	Antipsychotics (early)	Unexposed	Population-based cohort	Exposed: 576 Total: 973,767	ARR ²¹⁷ 1.48 (0.48, 3.47)
Small for gestational age						
Bellet 2015	Small for gestational age (<10 th percentile)	Aripiprazole (embryogenesis: 4-10 weeks)	Unexposed, matched	Prospective, cohort matched controls	Exposed: 86 Unexposed: 172	OR 2.97 (1.23, 7.16)
Vigod 2015	Small for gestational age (birth weight <3 rd centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 1.20 (0.95, 1.53)
Vigod 2015	Small for gestational age (birth weight <3 rd centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 1.22 (0.84, 1.77)
Vigod 2015	Small for gestational age (birth weight <3 rd centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR 1.21 (0.81, 1.82)
Vigod 2015	Small for gestational age (birth weight <3 rd centile)	Any antipsychotic (1 st trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 893 Unexposed: 893	hdPS-matched RR 1.33 (0.91, 1.96)
Vigod 2015	Small for gestational age (birth weight <3 rd centile)	Any antipsychotic (1 st trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 893 Unexposed: 893	hdPS-matched, adjusted RR 1.33 (0.88, 2.02)
Vigod 2015	Small for gestational age (birth weight <3 rd centile)	Any antipsychotic (2 nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 758 Unexposed: 758	hdPS-matched RR 1.22 (0.79, 1.88)
Vigod 2015	Small for gestational age (birth weight <3 rd centile)	Any antipsychotic (2 nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 758 Unexposed: 758	hdPS-matched, adjusted RR 1.21 (0.74, 1.96)
Vigod 2015	Small for gestational age (birth weight <3 rd centile)	Any antipsychotic (3 rd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 614 Unexposed: 614	hdPS-matched RR 1.25 (0.76, 2.06)

²¹⁷ Observed over expected numbers.

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Vigod 2015	Small for gestational age (birth weight <3 rd centile)	Any antipsychotic (3 rd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 614 Unexposed: 614	hdPS-matched, adjusted RR 1.24 (0.73, 2.10)
Vigod 2015	Small for gestational age (birth weight <10 th centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 1.33 (1.15 to 1.54)
Vigod 2015	Small for gestational age (birth weight <10 th centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 1.14 (0.93, 1.40)
Vigod 2015	Small for gestational age (birth weight <10 th centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR 1.20 (0.97, 1.50)
Källén 2013	Small for gestational age	Antipsychotics or lithium ²¹⁴ (2 nd or 3 rd trimester)	Unexposed	Population-based cohort	Exposed: 592 Unexposed: 1,575,255	AOR 1.72 (1.13, 2.95)
Bodén 2012b	Small for gestational age (by birth weight)	Olanzapine and/or clozapine (pregnancy)	Unexposed	Population-based cohort	Exposed: 169 Unexposed: 357,696	AOR 1.82 (0.91, 3.61)
Bodén 2012b	Small for gestational age (by birth length)	Olanzapine and/or clozapine (pregnancy)	Unexposed	Population-based cohort	Exposed: 169 Unexposed: 357,696	AOR 1.17 (0.54, 2.55)
Bodén 2012b	Small for gestational age (by head circumference)	Olanzapine and/or clozapine (pregnancy)	Unexposed	Population-based cohort	Exposed: 169 Unexposed: 357,696	AOR 0.62 (0.19, 2.01)
Bodén 2012b	Small for gestational age (by birth weight)	Antipsychotic (not olanzapine or clozapine) (pregnancy)	Unexposed	Population-based cohort	Exposed: 338 Unexposed: 357,696	AOR 1.24 (0.72, 2.15)
Bodén 2012b	Small for gestational age (by birth length)	Antipsychotic (not olanzapine or clozapine) (pregnancy)	Unexposed	Population-based cohort	Exposed: 338 Unexposed: 357,696	AOR 1.35 (0.79, 2.28)
Bodén 2012b	Small for gestational age (by head circumference)	Antipsychotic (not olanzapine or clozapine) (pregnancy)	Unexposed	Population-based cohort	Exposed: 338 Unexposed: 357,696	AOR 1.64 (0.97, 2.77)
Lin 2010	Small for gestational age	SGAs for schizophrenia (pregnancy)	Unexposed to FGAs or SGAs, schizophrenia	Population-based cohort	Exposed: 48 Unexposed: 454	AOR 1.15 (0.55, 2.41)
Lin 2010	Small for gestational age	FGAs for schizophrenia (pregnancy)	Unexposed to FGAs or SGAs, schizophrenia	Population-based cohort	Exposed: 194 Unexposed: 454	AOR 1.39 (0.93, 2.08)
Reis 2008	Small for gestational age	Antipsychotics (early)	Unexposed	Population-based cohort	Exposed: 561 Total: 938,318	AOR 1.46 (0.99, 2.15)

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Large for gestational age						
Vigod 2015	Large for gestational age (birth weight >97 th centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,209 Unmatched unexposed: 40,314	Unmatched RR 1.44 (1.06, 1.96)
Vigod 2015	Large for gestational age (birth weight >97 th centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Matched unexposed: 1,021	hdPS-matched RR 1.64 (0.96, 2.78)
Vigod 2015	Large for gestational age (birth weight >97 th centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Matched unexposed: 1,021	hdPS-matched, adjusted ARR 1.26 (0.69, 2.29)
Vigod 2015	Large for gestational age (birth weight >97 th centile)	Any antipsychotic (<u>1st trimester</u>)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 893 Unexposed: 893	hdPS-matched RR 1.47 (0.82, 2.64)
Vigod 2015	Large for gestational age (birth weight >97 th centile)	Any antipsychotic (<u>1st trimester</u>)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 893 Unexposed: 893	hdPS-matched, adjusted ARR 0.94 (0.46, 1.93)
Vigod 2015	Large for gestational age (birth weight >97 th centile)	Any antipsychotic (<u>2nd trimester</u>)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 758 Unexposed: 758	hdPS-matched RR 2.21 (1.18, 4.16)
Vigod 2015	Large for gestational age (birth weight >97 th centile)	Any antipsychotic (<u>2nd trimester</u>)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 758 Unexposed: 758	hdPS-matched, adjusted ARR 1.83 (0.89, 3.77)
Vigod 2015	Large for gestational age (birth weight >97 th centile)	Any antipsychotic (<u>3rd trimester</u>)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 614 Unexposed: 614	hdPS-matched RR 2.46 (1.22, 4.95)
Vigod 2015	Large for gestational age (birth weight >97 th centile)	Any antipsychotic (<u>3rd trimester</u>)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 614 Unexposed: 614	hdPS-matched, adjusted AR 2.39 (1.00, 5.75)
Vigod 2015	Large for gestational age (birth weight >90 th centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 1.18 (0.97, 1.45)
Vigod 2015	Large for gestational age (birth weight >90 th centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 1.15 (0.84, 1.56)
Vigod 2015	Large for gestational age (birth weight >90 th centile)	Any antipsychotic (≥2 consecutive scripts, one in the 1st or 2nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted ARR 1.07 (0.76, 1.51)
Källén 2013	Large for gestational age	Antipsychotics or lithium ²¹⁴ (2 nd or 3 rd trimester)	Unexposed	Population-based cohort	Exposed: 592 Unexposed: 1,575,255	AOR 2.03 (1.39, 2.95)

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Bodén 2012b	Large for gestational age (by birth weight)	Antipsychotic (not olanzapine or clozapine) (pregnancy)	Unexposed	Population-based cohort	Exposed: 338 Unexposed: 357,696	AOR 1.37 (0.69, 2.75)
Bodén 2012b	Large for gestational age (by birth weight)	Olanzapine and/or clozapine (pregnancy)	Unexposed	Population-based cohort	Exposed: 169 Unexposed: 357,696	AOR 0.55 (0.14, 2.11)
Bodén 2012b	Large for gestational age (by birth length)	Antipsychotic (not olanzapine or clozapine) (pregnancy)	Unexposed	Population-based cohort	Exposed: 338 Unexposed: 357,696	AOR 0.96 (0.40, 2.29)
Bodén 2012b	Large for gestational age (by birth length)	Olanzapine and/or clozapine (pregnancy)	Unexposed	Population-based cohort	Exposed: 169 Unexposed: 357,696	AOR 1.94 (0.87, 4.34)
Bodén 2012b	Large for gestational age (by head circumference)	Antipsychotic (not olanzapine or clozapine) (pregnancy)	Unexposed	Population-based cohort	Exposed: 338 Unexposed: 357,696	AOR 0.67 (0.25, 1.76)
Bodén 2012b	Large for gestational age (by head circumference)	Olanzapine and/or clozapine (pregnancy)	Unexposed	Population-based cohort	Exposed: 169 Unexposed: 357,696	AOR 3.02 (1.60, 5.71)
Lin 2010	Large for gestational age	FGAs for schizophrenia (pregnancy)	Unexposed, schizophrenia	Population-based cohort	Exposed: 194 Unexposed: 454	AOR 0.72 (0.39, 1.34)
Lin 2010	Large for gestational age	SGAs for schizophrenia (pregnancy)	Unexposed, schizophrenia	Population-based cohort	Exposed: 48 Unexposed: 454	AOR 0.55 (0.16, 1.85)
Reis 2008	Large for gestational age	Antipsychotics (early pregnancy)	Unexposed	Population-based cohort	Infants exposed: 561 Total: 938,318	AOR 1.04 (0.70, 1.55)
Seizures						
Vigod 2015	Seizure	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 4.30 (2.22, 8.33)
Vigod 2015	Seizure	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 1.29 (0.48, 3.45)
Vigod 2015	Seizure	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR NR
Respiratory distress						
Vigod 2015	Respiratory distress syndrome (not acute)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 1.87 (1.31, 2.66)
Vigod 2015	Respiratory distress syndrome (not acute)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 0.87 (0.51, 1.47)
Vigod 2015	Respiratory distress syndrome (not acute)	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR 0.82 (0.46, 1.43)

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Poor neonatal adaptation syndrome						
Vigod 2015	Poor neonatal adaptation syndrome	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,209 Unexposed: 40,314	Unmatched RR 7.06 (5.91, 8.45)
Vigod 2015	Poor neonatal adaptation syndrome	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched RR 1.19 (0.92, 1.53)
Vigod 2015	Poor neonatal adaptation syndrome	Any antipsychotic (pregnancy)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 1,021 Unexposed: 1,021	hdPS-matched, adjusted RR 1.15 (0.88, 1.50)
Vigod 2015	Poor neonatal adaptation syndrome	Any antipsychotic (only in 1 st or 2 nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 180 Unexposed: 40,314	Unmatched RR 5.49 (3.56, 8.46)
Vigod 2015	Poor neonatal adaptation syndrome	Any antipsychotic (only in 1 st or 2 nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 151 Unexposed: 151	hdPS-matched RR 1.50 (0.72, 3.11)
Vigod 2015	Poor neonatal adaptation syndrome	Any antipsychotic (only in 1 st or 2 nd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 151 Unexposed: 151	hdPS-matched, adjusted RR 1.65 (0.62, 4.39)
Vigod 2015	Poor neonatal adaptation syndrome	Any antipsychotic (only in 3 rd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 747 Unexposed: 40,314	Unmatched RR 6.29 (5.11, 7.74)
Vigod 2015	Poor neonatal adaptation syndrome	Any antipsychotic (only in 3 rd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 614 Unexposed: 614	hdPS-matched RR 1.25 (0.89, 1.75)
Vigod 2015	Poor neonatal adaptation syndrome	Any antipsychotic (only in 3 rd trimester)	Unexposed	Population-based, hdPS-matched cohort	Exposed: 614 Unexposed: 614	hdPS-matched, adjusted RR 1.31 (0.91, 1.90)
Källén 2013	Respiratory diagnosis (valid outcome?)	Antipsychotics or lithium ²¹⁴ (2 nd or 3 rd trimester)	Unexposed	Population-based cohort	Exposed: 592 Unexposed: 1,575,255	AOR 1.73 (1.24, 2.40)
STUDIES NOT REPORTING AN ESTIMATE OF EFFECT SIZE						%, p value
Miscarriage						
Habermann 2013	Miscarriage (Cumulative incidence)	SGAs (pregnancy)	Unexposed, matched	Prospective, cohort, matched controls	Exposed: 561 Unexposed: 1,122	24% (14, 39) vs 20% (15, 26) – not significant
Habermann 2013	Miscarriage (Cumulative incidence)	FGAs (pregnancy)	Unexposed, not matched	Prospective, cohort, matched controls	Exposed: 284 Unexposed: 1,122	16% (10, 26) vs 20% (15, 26) – not significant
Habermann 2013	Miscarriage (Cumulative incidence)	SGAs (pregnancy)	FGAs, not matched	Prospective, cohort, matched controls	SGAs: 561 FGAs: 284	24% (14, 39) vs 16% (10, 26) – not significant
Sadowski 2013	Miscarriage (<20 weeks)	SGAs (pregnancy)	Unexposed, matched (age, contact time)	Prospective cohort, matched controls	Exposed: 133 Unexposed: 133	13.2% vs NR not significant
Sadowski 2013	Foetal death (≥20 weeks)	SGAs (pregnancy)	Unexposed, matched (age, contact time)	Prospective cohort, matched controls	Exposed: 133 Unexposed: 133	1.5% vs NR not significant

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Neonatal mortality						
Bodén 2012b	Neonatal death	Any antipsychotic (pregnancy)	Unexposed	Population-based cohort	Exposed: 507 Unexposed: 357,696	0.2% (n=1) vs 0.2% (n=630)
Slone 1977	Neonatal death	Phenothiazines (1 st four months)	Unexposed	Prospective cohort	Exposed: 3,056 Unexposed: 38,281	1.2% vs 1.0%
Bodén 2012b	Stillbirth	Any antipsychotic (pregnancy)	Unexposed	Population-based cohort	Exposed: 507 Unexposed: 357,696	0.4% (n=2) vs 0.4% (n=1289)
Diav-Citrin 2005	Stillbirth	Haloperidol or penfluridol (pregnancy)	Unexposed	Prospective cohorts, multicentre	Exposed: 215 Unexposed: 631	0.0% vs 0.2% p = 1.000
McKenna 2005	Stillbirth	SGAs (1 st trimester)	Unexposed, matched	Prospective cohorts, matched controls	Exposed: N = 151 Unexposed: N = 151	2.6% vs 2.6% p = 1.0
Slone 1977	Stillbirth	Phenothiazines (1 st four months)	Unexposed	Prospective cohort	Exposed: 3,056 Unexposed: 38,281	1.3% vs 1.3%
Preterm birth						
Sadowski 2013	Preterm birth	SGAs (pregnancy)	Unexposed, matched (age, contact time)	Prospective cohort, matched controls	Exposed: 133 Unexposed: 133	10.6% vs 4.3% p = 0.071
Hironaka 2011	Preterm birth	Antipsychotics (pregnancy)	Healthy, unexposed	Retrospective cohort	Antipsychotics: 17 Unexposed: 278	0/17 vs 2/278
Hironaka 2011	Preterm birth	SGAs (pregnancy)	Healthy, unexposed	Retrospective cohort	Exposed: 15 Unexposed: 278	0/15 vs 2/278
Hironaka 2011	Preterm birth	SGAs, schizophrenia (pregnancy)	Healthy, unexposed	Retrospective cohort	Exposed: 9 Unexposed: 278	0/9 vs 2/278
Hironaka 2011	Preterm birth	SGAs, schizophrenia (pregnancy)	Schizophrenia, unexposed	Retrospective cohort	Exposed: 9 Unexposed: 3	0/9 vs 0/3
Newham 2008	Preterm birth (<37 weeks)	SGAs (pregnancy)	Unexposed	UK National TIS database review	Exposed: 5/30 Unexposed: 1/41	17% vs 2% p>0.5
Newham 2008	Preterm birth (<37 weeks)	FGAs (pregnancy)	Unexposed	UK National TIS database review	Exposed: 9/56 Unexposed: 1/41	16% vs 2% p>0.5
Diav-Citrin 2005	Preterm birth (≤37 weeks)	Haloperidol or penfluridol (pregnancy)	Unexposed	Prospective cohorts, multicentre	Exposed: 215 Unexposed: 631	13.9% vs 6.9% p = 0.006
Small for gestational age						
Sadowski 2013	Small for gestational age	SGAs (pregnancy)	Unexposed, matched (age, contact time)	Prospective cohort, matched controls	Exposed: 133 Unexposed: 133	11.6% vs 8.8% p = 0.495
Newham 2008	Small for gestational age (37-42 weeks)	SGAs (pregnancy)	Unexposed	UK National TIS database review	Exposed: 2/25 Unexposed: 0/38	8% vs 0% p>0.5

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N	RE (95% CI)
Newham 2008	Small for gestational age (37-42 weeks)	FGAs (pregnancy)	Unexposed	UK National TIS database review	Exposed: 7/45 Unexposed: 0/38	16% vs 0% p<0.05
Large for gestational age						
Newham 2008	Large for gestational age (37-42 weeks)	SGAs (pregnancy)	Unexposed	UK National TIS database review	Exposed: 5/25 Unexposed: 1/38	20% vs 3% p<0.05
Sadowski 2013	Large for gestational age	SGAs (pregnancy)	Unexposed, matched (age, contact time)	Prospective cohort, matched controls	Exposed: 133 Unexposed: 133	11.6% vs 3.5% p = 0.022
Newham 2008	Large for gestational age (37-42 weeks)	SGAs (pregnancy)	FGAs (during pregnancy)	UK National TIS database review	SGAs: 5/25 FGAs: 1/45	20% vs 2% p<0.05
Newham 2008	Large for gestational age (37-42 weeks)	Olanzapine or clozapine (pregnancy)	Unexposed	UK National TIS database review	Exposed: 5/16 Unexposed: 1/38	p<0.01 <i>unchanged by exclusion of mothers taking weight-altering medication</i>
Newham 2008	Large for gestational age (37-42 weeks)	Olanzapine or clozapine (pregnancy)	FGAs (during pregnancy)	UK National TIS database review	Exposed: 5/16 FGAs: 1/45	p<0.01 <i>p<0.05 when mothers taking weight-altering medication excluded</i>
McKenna 2005	Spontaneous abortion	SGAs (1 st trimester)	Unexposed, matched	Prospective cohorts, matched controls	Exposed: N = 151 Unexposed: N = 151	14.5% vs 8.6% p = 0.15

Abbreviations: AOR, adjusted odds ratio; ARR, adjusted risk ratio; CI, confidence interval; FGAs, first generation antipsychotics; hdPS, high-dimensional propensity score; NR, not reported; OBS, observational studies; OR, odds ratio; RE, risk estimate; RR, risk ratio; SGA, second generation antipsychotic; vs, versus.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. Shaded data is carried into

Section AppD4.1.2. Data shown in grey hatching is either (i) adjusted for potential confounders OR (ii) limited to/adjusted for psychiatric illness. Data shown in grey shading is either (i) adjusted for potential confounders AND limited to/adjusted for psychiatric illness OR (ii) matched using a high dimensional propensity score that includes indication. For some analyses, unadjusted data from Vigod 2015 is also carried through to Section AppD4.1.2 for the purpose of illustrating the impact on risk estimates of accounting for potential confounders (not shaded).

AppD3.1.2.2.3 Neurodevelopmental outcomes – antipsychotics

Table AppD3-12 Antipsychotic infant harms data extraction from observational studies – neurodevelopmental outcomes

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N ²¹⁸	RE (95% CI)
STUDIES REPORTING AN ESTIMATE OF EFFECT SIZE						
Petersen 2016a	Neurodevelopment/behavioural disorders ²¹⁹	Any antipsychotics (early; 31-105 days)	Discontinued antipsychotics	Retrospective, primary care database	Exposed: 290 Unexposed: 492	ARR 0.83 (0.49, 1.39)

²¹⁸ For Clements 2015, % reported rather than n, so estimates of n were calculated post hoc (ranges reported where rounding of % results in more than one possible integer).

²¹⁹ This outcome includes a broad range of Read codes describing developmental delay as well as behavioural problems recorded within the first 5 years of life. Read codes for neurodevelopmental and behavioural disorders were identified as those relating to conditions listed as neurodevelopmental or behavioural disorders in Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition.

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N ²¹⁸	RE (95% CI)
Petersen 2016a	Neurodevelopment/behavioural disorders	Any antipsychotics (early; 31-105 days)	Unexposed	Retrospective, primary care database	Exposed: 290 Unexposed: 210,966	ARR 1.22 (0.80, 1.84)
Clements 2015	Autism spectrum disorder (2-19 years)	Any antipsychotics (1 st trimester)	Unexposed – adjusted for major depression	Case control ²²⁰	Cases: 1,377 (0.3% exposed; n=4) Controls: 4,022 (0.0% exposed; n=0-1) ²²¹	AOR 3.66 (0.70, 26.82)
Clements 2015	Autism spectrum disorder (2-19 years)	Any antipsychotics (2 nd trimester)	Unexposed – adjusted for major depression	Case control	Cases: 1,377 (0.3% exposed; n=4) Controls: 4,022 (0.0% exposed; n=0-1)	Not estimable
Clements 2015	Autism spectrum disorder (2-19 years)	Any antipsychotics (3 rd trimester)	Unexposed – adjusted for major depression	Case control	Cases: 1,377 (0.1% exposed; n=1-2) Controls: 4,022 (0.1% exposed; n=3-6)	AOR 1.23 (0.15, 7.93)
Clements 2015	Autism spectrum disorder (2-19 years)	Any antipsychotics (pregnancy ²²²)	Unexposed – adjusted for major depression	Case control	Cases: 1,377 (0.5% exposed; n=7) Controls: 4,022 (0.1% exposed; n=3-6)	AOR 2.23 (0.65, 8.01)
Clements 2015	ADHD (2-19 years)	Any antipsychotics (1 st trimester)	Unexposed – adjusted for major depression	Case control ²²³	Cases: 2,243 (0.0% exposed; n=0-1) ²²¹ Controls: 5,631 (0.0% exposed; n=0-3)	AOR 0.72 (0.03, 7.80)
Clements 2015	ADHD (2-19 years)	Any antipsychotics (2 nd trimester)	Unexposed – adjusted for major depression	Case control	Cases: 2,243 (0.0% exposed; n=0-1) Controls: 5,631 (0.0% exposed; n=0-3)	Not estimable
Clements 2015	ADHD (2-19 years)	Any antipsychotics (3 rd trimester)	Unexposed – adjusted for major depression	Case control	Cases: 2,243 (0.2% exposed; n=4-5) Controls: 5,631 (0.1% exposed; n=3-8)	AOR 0.60 (0.08, 3.18)
Clements 2015	ADHD (2-19 years)	Any antipsychotics (pregnancy ²²²)	Unexposed – adjusted for major depression	Case control	Cases: 2,243 (0.2% exposed; n=4-5) Controls: 5,631 (0.1% exposed; n=3-8)	AOR 0.61 (0.13, 2.40)
Johnson 2012	INFANIB score at 6 months postpartum	Any antipsychotic (pregnancy)	Unexposed	Prospective cohort	Exposed: 22 Unexposed: 85	AOR 5.41 (1.22, 24.09) ²²⁴
Johnson 2012	INFANIB score at 6 months postpartum	Any antipsychotic (pregnancy)	Any antidepressant	Prospective cohort	Exposed to antipsychotics: 22 Exposed to antidepressants: 202	AOR 4.11 (1.05, 15.99) ²²⁵
STUDIES NOT REPORTING AN ESTIMATE OF EFFECT SIZE						%, p value
Shao 2015	Bayley-III adaptive behaviour scale At 2 months	Clozapine for schizophrenia (pregnancy)	SGAs (not clozapine) for schizophrenia	Subgroup analysis of exposure group from Peng 2013	Clozapine: 33 Other SGA: 30	p = 0.001 <i>Favours other SGAs</i>

²²⁰ Delivered at the MGH, BWH or NWH and matched 1:3 on birth year, hospital, sex, insurance type (as proxy for socioeconomic status), race/ethnicity and preterm/full-term status (for 81 of the 1,377 ASD cases, only 1 or 2 matched controls were found).

²²¹ As % only reported, estimates of n were calculated post hoc (ranges reported where rounding of % results in more than one possible integer).

²²² Including up to 30 days prior to conception.

²²³ Delivered at the MGH, BWH or NWH and matched 1:3 on birth year, hospital, sex, insurance type (as proxy for socioeconomic status), race/ethnicity and preterm/full-term status (for 726 of the 2,243 ADHD cases, only 1 or 2 matched controls were found).

²²⁴ Likelihood of a normal score in unexposed vs exposed group. Between-group difference in adjusted mean scores was significant (p<0.01) but continuous outcomes are not extracted for the current Review.

²²⁵ Likelihood of a normal score in the group exposed to antidepressants vs the group exposed to antipsychotics. Between-group difference in adjusted mean scores was significant (p<0.01) but continuous outcomes are not extracted for the current Review.

Study ID	Outcome	Exposure (Timing)	Comparator population	Study design	N ²¹⁸	RE (95% CI)
Shao 2015	Bayley-III all other scales At 2 months	Clozapine for schizophrenia (pregnancy)	SGAs (not clozapine) for schizophrenia	Subgroup analysis of exposure group from Peng 2013	Clozapine: 33 Other SGA: 30	No significant differences
Shao 2015	Bayley-III adaptive behaviour scale At 6 months	Clozapine for schizophrenia (pregnancy)	SGAs (not clozapine) for schizophrenia	Subgroup analysis of exposure group from Peng 2013	Clozapine: 33 Other SGA: 30	p = 0.011 <i>Favours other SGAs</i>
Shao 2015	Bayley-III all other scales At 6 months	Clozapine for schizophrenia (pregnancy)	SGAs (not clozapine) for schizophrenia	Subgroup analysis of exposure group from Peng 2013	Clozapine: 33 Other SGA: 30	No significant differences
Shao 2015	Bayley-III all scales At 12 months	Clozapine for schizophrenia (pregnancy)	SGAs (not clozapine) for schizophrenia	Subgroup analysis of exposure group from Peng 2013	Clozapine: 33 Other SGA: 30	No significant differences
Peng 2013	Bayley-III cognitive scale At 2 months	SGAs for schizophrenia (pregnancy)	No mental health disorder, unexposed, matched	Prospective, longitudinal, matched cohort	Exposed: 76 Unexposed: 76	p<0.001 <i>Favours unexposed group</i>
Peng 2013	Bayley-III language scale At 2 months	SGAs for schizophrenia (pregnancy)	No mental health disorder, unexposed, matched	Prospective, longitudinal, matched cohort	Exposed: 76 Unexposed: 76	p = 0.157 <i>Favours unexposed group</i>
Peng 2013	Bayley-III motor scale At 2 months	SGAs for schizophrenia (pregnancy)	No mental health disorder, unexposed, matched	Prospective, longitudinal, matched cohort	Exposed: 76 Unexposed: 76	p<0.001 <i>Favours unexposed group</i>
Peng 2013	Bayley-III social-emotional scale At 2 months	SGAs for schizophrenia (pregnancy)	No mental health disorder, unexposed, matched	Prospective, longitudinal, matched cohort	Exposed: 76 Unexposed: 76	p<0.001 <i>Favours unexposed group</i>
Peng 2013	Bayley-III adaptive behaviour At 2 months	SGAs for schizophrenia (pregnancy)	No mental health disorder, unexposed, matched	Prospective, longitudinal, matched cohort	Exposed: 76 Unexposed: 76	p<0.001 <i>Favours unexposed group</i>
Peng 2013	Bayley-III: At 6 months At 12 months	SGAs for schizophrenia (pregnancy)	No mental health disorder, unexposed, matched	Prospective, longitudinal, matched cohort	Exposed: 76 Unexposed: 76	No significant difference between groups for any Bayley-III scale at either time point
Gilad 2011	Speech (as assessed by mother)	Olanzapine (breast-feeding)	Olanzapine (NOT breast-feeding) Acetaminophen (breast-feeding)	Prospective cohort	Olanzapine (breast fed): 22 Olanzapine (bottle fed): 15 Acetaminophen (breast-fed): 51	No significant difference between groups
Gilad 2011	Motor developmental (as assessed by mother)	Olanzapine (breast-feeding)	Olanzapine (NOT breast-feeding) Acetaminophen (breast-feeding)	Prospective cohort	Olanzapine (breast fed): 22 Olanzapine (bottle fed): 15 Acetaminophen (breast-fed): 51	No significant difference between groups

Abbreviations: ADHD, attention-deficit hyperactivity disorder; AOR, adjusted odds ratio; ARR, adjusted risk ratio; CI, confidence interval; INFANIB, Infant Neurological International Battery; OBS, observational studies; RE, risk estimate; SGA, second generation antipsychotic; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Shaded data is carried into **Section AppD4.1.2**. Data shown in grey hatching is either (i) adjusted for potential confounders or (ii) limited to/adjusted for psychiatric illness. Data shown in grey shading is adjusted for potential confounders and limited to/adjusted for psychiatric illness.

AppD3.1.3 Anticonvulsants

AppD3.1.4 Systematic reviews – anticonvulsants

Table AppD3-13 Anticonvulsant infant harms data extraction from systematic reviews – malformations

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity I ² (P value)	Appropriate comparator population?	Adjusted analysis?
Major malformations										
Weston 2016	Major malformations	Carbamazepine	Unexposed – any	8 (OBS)	3,513	-	RR 2.01 (1.20, 3.36)	0% (0.99)		
Weston 2016	Major malformations	Carbamazepine	Unexposed – epilepsy (no medication)	17 (OBS)	4,345	-	RR 1.50 (1.03, 2.19)	0% (0.95)	✓	
Weston 2016	Major malformations	Lamotrigine	Unexposed – any	3 (OBS)	3,188	-	RR 1.68 (0.78, 3.65)	0% (0.65)		
Weston 2016	Major malformations	Lamotrigine	Unexposed – epilepsy (no medication)	3 (OBS)	3,181	-	RR 1.07 (0.64, 1.77)	0% (0.81)	✓	
Weston 2016	Major malformations	Sodium valproate	Unexposed – any	7 (OBS)	2,403	-	RR 5.69 (3.33, 9.73)	0% (0.54)		
Weston 2016	Major malformations	Sodium valproate	Unexposed – epilepsy (no medication)	14 (OBS)	3,182	-	RR 3.13 (2.16, 4.54)	0% (0.71)	✓	
Weston 2016	Major malformations	Carbamazepine	Lamotrigine	7 (OBS)	7,549	-	RR 1.34 (1.01, 1.76)	0% (0.74)	✓	
Weston 2016	Major malformations	Carbamazepine	Sodium valproate	25 (OBS)	7,078	-	RR 0.41 (0.34, 0.50)	0% (0.94)	✓	
Weston 2016	Major malformations	Sodium valproate	Lamotrigine	7 (OBS)	6,185	-	RR 3.56 (2.77, 4.58)	0% (0.44)	✓	
NICE 2015	Major congenital malformations	Carbamazepine	Unexposed – any	17 (cohort)	10,774	-	OR 1.89 (1.34, 2.65)	21% (0.21)		
NICE 2015	Major congenital malformations	Carbamazepine	Unexposed – epilepsy	12 (cohort)	6,669	-	OR 1.43 (1.04, 1.96)	0% (0.44)	✓	
NICE 2015	Major malformations	Lamotrigine	Unexposed – any	7 (cohort)	842,294	-	OR 1.48 (0.97, 2.27)	31% (0.19)		
NICE 2015	Major malformations	Lamotrigine	Unexposed – epilepsy	5 (cohort)	3,008	-	OR 1.41 (0.62, 3.21)	51% (0.09)	✓	
NICE 2015	Major malformations	Sodium valproate	Unexposed – any	14 (cohort)	108,500	-	OR 3.37 (2.5, 4.53)	0% (0.48)		

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity I ² (P value)	Appropriate comparator population?	Adjusted analysis?
NICE 2015	Major malformations	Sodium valproate	Unexposed – epilepsy	8 (cohort)	3,526	-	OR 2.6 (1.7, 3.97)	0% (0.64)	✓	
NICE 2015	Major malformations	Sodium valproate	Unexposed – any	1 (CC)	76,626	-	OR 2.89 (2.05, 4.06)²²⁶	NA		
Tanoshima 2015	Major congenital malformations	Sodium valproate	Carbamazepine – epilepsy	23 (OBS)	10,509	-	RR 2.21 (1.88, 2.59)	0% (NR)	✓	
Tanoshima 2015	Major congenital malformations	Sodium valproate	Lamotrigine – epilepsy	7 (OBS)	8,074	-	RR 3.23 (2.59, 4.03)	0% (NR)	✓	
Cardiac malformations										
Weston 2016	Cardiac malformations	Carbamazepine	Unexposed – any	3 (OBS)	832	-	RR 1.41 (0.28, 7.02)	0% (0.78)		
Weston 2016	Cardiac malformations	Carbamazepine	Unexposed – epilepsy (no medication)	7 (OBS)	1,026	-	RR 1.84 (0.32, 10.71)	0% (0.62)	✓	
Weston 2016	Cardiac malformations	Lamotrigine	Unexposed – any	1 (OBS)	355	-	RR 2.57 (0.11, 62.03)	NA		
Weston 2016	Cardiac malformations	Lamotrigine	Unexposed – epilepsy (no medication)	2 (OBS)	542	-	RR 1.40 (0.15, 13.35)	NA	✓	
Weston 2016	Cardiac malformations	Sodium valproate	Unexposed – any	2 (OBS)	502	-	RR 16.40 (3.05, 88.19)	0% (0.57)		
Weston 2016	Cardiac malformations	Sodium valproate	Unexposed – epilepsy (no medication)	6 (OBS)	768	-	RR 4.85 (1.28, 18.47)	0% (0.95)	✓	
Weston 2016	Cardiac malformations	Carbamazepine	Lamotrigine	6 (OBS)	7,509	-	RR 1.57 (0.85, 2.89)	0% (0.85)	✓	
Weston 2016	Cardiac malformations	Carbamazepine	Sodium valproate	16 (OBS)	6,646	-	RR 0.45 (0.31, 0.68)	12% (0.33)	✓	
Weston 2016	Cardiac malformations	Sodium valproate	Lamotrigine	6 (OBS)	6,151	-	RR 4.07 (2.33, 7.09)	0% (0.54)	✓	
Tanoshima 2015	Congenital heart defects	Sodium valproate	Carbamazepine	15 (OBS)	9,998	-	RR 1.82 (1.30, 2.54)	0% (NR)	✓	

²²⁶ Data taken from NICE 2015 Appendix 19, p288. Differs from risk estimate presented in main body of report (OR 1.51; 95% CI 1.38, 1.65 – NICE 2015, p 765).

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity I ² (P value)	Appropriate comparator population?	Adjusted analysis?
Tanoshima 2015	Congenital heart defects	Sodium valproate	Lamotrigine	5 (OBS)	7,651	-	RR 3.75 (2.27, 6.18)	0% (NR)	✓	

Abbreviations: CC, case-control study; CI, confidence interval; OBS, observational studies; OR, odds ratio; RE, risk estimate; RR, relative risk.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. Data shown in grey hatching is either (i) adjusted for potential confounders or (ii) limited/adjusted for psychiatric illness. Data shown in grey shading is (i) adjusted for potential confounders and (ii) limited/adjusted for psychiatric illness. Only shaded data is carried into **Section 4.1.3**.

Table AppD3-14 Anticonvulsant infant harms data extraction from systematic reviews – pregnancy outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Neonatal mortality										
NICE 2015	Still birth/perinatal death	Carbamazepine	Unexposed – any	2 (cohort)	3,202	-	OR 0.79 (0.12, 5.31)	67% (0.08)		
NICE 2015	Still birth/perinatal death	Lamotrigine	Unexposed – any	1 (cohort)	1,973	-	OR 0.49 (0.003, 8.42)	NA		
NICE 2015	Still birth/perinatal death	Sodium valproate	Unexposed – any	2 (cohort)	3,975	-	OR 1.93 (0.79, 4.7)	0% (0.71)		
Preterm birth										
NICE 2015	Preterm birth	Carbamazepine	Unexposed – any	2 (cohort)	3,202	-	OR 1.65 (0.64, 4.22)	67% (0.08)		
NICE 2015	Preterm birth	Lamotrigine	Unexposed – any	1 (cohort)	1,973	-	OR 0.98 (0.47, 2.05)	NA		
NICE 2015	Preterm birth	Sodium valproate	Unexposed – any	2 (cohort)	3,804	-	OR 1.31 (0.94, 1.83)	0% (0.44)		

Abbreviations: CI, confidence interval; OBS, observational studies; OR, odds ratio; RE, risk estimate.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. Data shown in grey hatching is either (i) adjusted for potential confounders or (ii) limited/adjusted for psychiatric illness. Data shown in grey shading is (i) adjusted for potential confounders and (ii) limited/adjusted for psychiatric illness. Only shaded data is carried into **Section 4.1.3**.

Table AppD3-15 Anticonvulsant infant harms data extraction from systematic reviews – neurodevelopmental outcomes

Study ID	Outcome (follow-up)	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI) <i>P value</i>	Heterogeneity <i>P value</i> (<i>I</i> ²)	Appropriate comparator population?	Adjusted analysis?
Autism spectrum disorder										
NICE 2015	ASD (ICD-10) (9 years)	Carbamazepine	Unexposed – any	1 (cohort)	655,539	-	OR 1.25 (0.47, 3.35)	NA		
NICE 2015	ASD (ICD-10) (9 years)	Lamotrigine	Unexposed – any	1 (cohort)	655,394	-	OR 1.5 (0.75, 3.01)	NA		
NICE 2015	ASD (ICD-10) (9 years)	Sodium valproate	Unexposed – any	1 (cohort)	655,495	-	OR 3.82 (2.15, 6.80)	NA		
Autism checklist										
NICE 2015	Autism checklist (78 week)	Carbamazepine	Unexposed – any	1 (cohort)	262	-	OR 0.79 (0.22, 2.8)	NA		
NICE 2015	Autism checklist (78 week)	Lamotrigine	Unexposed – any	1 (cohort)	286	-	OR 1.83 (0.81, 4.13)	NA		
NICE 2015	Autism checklist (78 week)	Sodium valproate	Unexposed – any	1 (cohort)	246	-	OR 0.87 (0.19, 3.98)	NA		
IQ										
NICE 2015	Full scale IQ	Carbamazepine	Unexposed – epilepsy	4 (cohort)	377	-	MD -3.80 (-16.81, 0.80)	87% (<0.001) ²²⁷	✓	
NICE 2015	Full scale IQ	Lamotrigine	Unexposed – any	1 (cohort)	93	-	MD -3.15 (-7.87, -1.57)	NA		
NICE 2015	Full scale IQ	Sodium valproate	Unexposed – epilepsy	4 (cohort)	286	-	MD -5.06 (-8.42, -1.70)	0% (0.51)	✓	
NICE 2015	Verbal IQ	Carbamazepine	Unexposed – epilepsy	3 (cohort)	289	-	MD 1.47 (-2.42, 5.36)	0% (0.85)	✓	
NICE 2015	Verbal IQ	Lamotrigine	Unexposed – any	1 (cohort)	93	-	MD -2.49 (-7.88, 2.90)	NA		
NICE 2015	Verbal IQ	Sodium valproate	Unexposed – epilepsy	4 (cohort)	286	-	MD -6.83 (-10.51, 2.15)	0% (0.83)	✓	
NICE 2015	Performance IQ	Carbamazepine	Unexposed – epilepsy	3 (cohort)	289	-	MD 0.92 (-3.29, 5.13) ²²⁸	16% (0.31)	✓	
NICE 2015	Performance IQ	Lamotrigine	Unexposed – any	1 (cohort)	93	-	MD -3.79 (-8.48, 0.90) ²²⁸	NA		
NICE 2015	Performance IQ	Sodium valproate	Unexposed – epilepsy	4 (cohort)	286	-	MD -3.54 (-10.6, 2.98) ²²⁸	60% (0.06)	✓	

²²⁷ Heterogeneity values relate to meta-analysis of SMD as presented in NICE 2015, Appendix 19.²²⁸ Reported as standardised mean difference in the Guideline document (NICE 2015) and Appendix 19. Recalculated as mean difference for this review.

Study ID	Outcome (follow-up)	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI) <i>P value</i>	Heterogeneity <i>P value</i> (<i>I</i> ²)	Appropriate comparator population?	Adjusted analysis?
Bromley 2014	Full scale IQ	Carbamazepine	Unexposed – any	3 (OBS)	702	-	MD -0.03 (-3.08, 3.01)	0% (0.44)		
Bromley 2014	Full scale IQ	Carbamazepine	Unexposed – any	1 (p-cohort)	260	-	MD -2.0 (-6.46, 2.46)	NA		
Bromley 2014	Full scale IQ	Carbamazepine	Unexposed – any	2 (registry)	442	-	MD 1.68 (-2.49, 5.85)	0% (0.61)		
Bromley 2014	Full scale IQ - <2SD	Carbamazepine	Unexposed – any	1 (OBS)	227	-	RR 0.41 (0.05, 3.61)	NA		
Bromley 2014	Verbal IQ	Carbamazepine	Unexposed – any	2 (p-cohort)	487	-	MD -1.81 (-4.94, 1.33)	74% (0.05)		
Bromley 2014	Performance IQ	Carbamazepine	Unexposed – any	2 (p-cohort)	487	-	MD 1.27 (-1.55, 4.09)	0% (0.65)		
Bromley 2014	Full scale IQ	Carbamazepine	Unexposed – epilepsy (no medication)	4 (OBS)	250	-	MD 1.84 (-2.13, 5.80)	0% (0.81)	✓	
Bromley 2014	Full scale IQ	Carbamazepine	Unexposed – epilepsy (no medication)	2 (p-cohort)	93	-	MD 1.27 (-5.08, 7.63)	0% (0.75)	✓	
Bromley 2014	Full scale IQ	Carbamazepine	Unexposed – epilepsy (no medication)	2 (registry)	157	-	MD 2.20 (-2.87, 7.28)	0% (0.36)	✓	
Bromley 2014	Full scale IQ - <2SD	Carbamazepine	Unexposed – epilepsy (no medication)	1 (registry)	131	-	RR 0.26 (0.02, 2.81)	NA	✓	
Bromley 2014	Verbal IQ	Carbamazepine	Unexposed – epilepsy (no medication)	3 (OBS)	232	-	MD 0.13 (-3.98, 4.23)	0% (0.76)	✓	
Bromley 2014	Verbal IQ	Carbamazepine	Unexposed – epilepsy (no medication)	1 (p-cohort)	75	-	MD -1.0 (-7.28, 5.28)	NA	✓	
Bromley 2014	Verbal IQ	Carbamazepine	Unexposed – epilepsy (no medication)	2 (registry)	157	-	MD 0.97 (-4.47, 6.40)	0% (0.57)	✓	
Bromley 2014	Performance IQ	Carbamazepine	Unexposed – epilepsy (no medication)	3 (OBS)	232	-	MD 3.65 (-0.60, 7.90)	0% (0.81)	✓	
Bromley 2014	Performance IQ	Carbamazepine	Unexposed – epilepsy (no medication)	1 (p-cohort)	75	-	MD 4.0 (-2.72, 10.72)	NA	✓	
Bromley 2014	Performance IQ	Carbamazepine	Unexposed – epilepsy (no medication)	2 (registry)	157	-	MD 3.42 (-2.07, 8.91)	0% (0.52)	✓	
Bromley 2014	Full scale IQ	Carbamazepine	Lamotrigine	2 (p-cohort)	162	-	MD -1.62 (-5.44, 2.21)	0% (0.65)	✓	
Bromley 2014	Full scale IQ - >1SD	Carbamazepine	Lamotrigine	2 (p-cohort)	159	-	RR 2.28 (0.63, 8.22)	0% (0.51)	✓	

Study ID	Outcome (follow-up)	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI) <i>P value</i>	Heterogeneity <i>P value</i> (<i>I</i> ²)	Appropriate comparator population?	Adjusted analysis?
Bromley 2014	Full scale IQ	Carbamazepine	Sodium valproate	5 (OBS)	303	-	MD 8.69 (5.51, 11.87)	43% (0.13)	✓	
Bromley 2014	Full scale IQ	Carbamazepine	Sodium valproate	2 (p-cohort)	152	-	MD 9.19 (5.49, 12.88)	36% (0.21)	✓	
Bromley 2014	Full scale IQ	Carbamazepine	Sodium valproate	3 (registry)	151	-	MD 7.29 (1.06, 13.53)	62% (0.07)	✓	
Bromley 2014	Verbal IQ	Carbamazepine	Sodium valproate	3 (OBS)	226	-	MD 8.44 (4.21, 12.66)	0% (0.43)	✓	
Bromley 2014	Performance IQ	Carbamazepine	Sodium valproate	3 (OBS)	226	-	MD 10.48 (6.02, 14.94)	0% (0.52)	✓	
Bromley 2014	Full scale IQ - >2SD	Carbamazepine	Sodium valproate	4 (OBS)	277	-	RR 0.26 (0.05, 1.19)	0% (0.86)	✓	
Bromley 2014	Full scale IQ - >2SD	Carbamazepine	Sodium valproate	2 (p-cohort)	152	-	RR 0.40 (0.04, 4.30)	NA	✓	
Bromley 2014	Full scale IQ - >2SD	Carbamazepine	Sodium valproate	2 (registry)	125	-	RR 0.18 (0.02, 1.46)	0% (0.89)	✓	
Bromley 2014	Full scale IQ - >1SD	Carbamazepine	Sodium valproate	3 (OBS)	178	-	RR 0.40 (0.19, 0.83)	0% (0.83)	✓	
Bromley 2014	Full scale IQ - >1SD	Carbamazepine	Sodium valproate	2 (p-cohort)	152	-	RR 0.40 (0.17, 0.93)	0% (0.55)	✓	
Bromley 2014	Full scale IQ - >1SD	Carbamazepine	Sodium valproate	1 (registry)	26	-	RR 0.40 (0.09, 1.70)	NA	✓	
Bromley 2014	Full scale IQ	Sodium valproate	Unexposed – any	3 (OBS)	628	-	MD -8.94 (-11.96, -5.92)	88% (<0.001)		
Bromley 2014	Full scale IQ	Sodium valproate	Unexposed – any	1 (p-cohort)	261	-	MD -12.22 (-15.84, -8.60)	NA		
Bromley 2014	Full scale IQ	Sodium valproate	Unexposed – any	2 (registry)	367	-	MD -1.48 (-6.94, 3.98)	83% (0.02)		
Bromley 2014	Full scale IQ - <2SD	Sodium valproate	Unexposed – any	1 (registry)	154	-	RR 2.71 (0.33, 22.51)	NA		
Bromley 2014	Full scale IQ - <1SD	Sodium valproate	Unexposed – any	1 (p-cohort)	236	-	RR 16.88 (6.27, 45.44)	NA		
Bromley 2014	Verbal IQ	Sodium valproate	Unexposed – any	2 (OBS)	415	-	MD -11.39 (-14.68, -8.10)	0% (1.00)		
Bromley 2014	Verbal IQ	Sodium valproate	Unexposed – any	1 (p-cohort)	261	-	MD -11.39 (-15.02, -7.76)	NA		

Study ID	Outcome (follow-up)	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI) <i>P value</i>	Heterogeneity <i>P value</i> (<i>I</i> ²)	Appropriate comparator population?	Adjusted analysis?
Bromley 2014	Verbal IQ	Sodium valproate	Unexposed – any	1 (registry)	154	-	MD -11.40 (-19.21, -3.59)	NA		
Bromley 2014	Performance IQ	Sodium valproate	Unexposed – any	2 (OBS)	456	-	MD -10.48 (-13.94, -7.02)	68% (0.08)		
Bromley 2014	Performance IQ	Sodium valproate	Unexposed – any	1 (p-cohort)	261	-	MD -8.94 (-12.79, -5.09)	NA		
Bromley 2014	Performance IQ	Sodium valproate	Unexposed – any	1 (registry)	195	-	MD -16.80 (-24.61, -8.99)	NA		
Bromley 2014	Full scale IQ	Sodium valproate	Lamotrigine	2 (p-cohort)	158	-	MD -10.80 (-14.42, -7.17)	0% (0.43)	✓	
Bromley 2014	Full scale IQ - >1SD	Sodium valproate	Lamotrigine	2 (p-cohort)	157	-	RR 4.87 (1.50, 15.78)	0% (0.68)	✓	
Bromley 2014	Full scale IQ	Sodium valproate	Unexposed – epilepsy (no medication)	4 (OBS)	176	-	MD -8.17 (-12.80, -3.55)	27% (0.25)	✓	
Bromley 2014	Full scale IQ	Sodium valproate	Unexposed – epilepsy (no medication)	1 (p-cohort)	76	-	MD -9.30 (-15.34, -3.26)	NA	✓	
Bromley 2014	Full scale IQ	Sodium valproate	Unexposed – epilepsy (no medication)	3 (registry)	100	-	MD -6.58 (-13.77, 0.62)	47% (0.15)	✓	
Bromley 2014	Full scale IQ - <2SD	Sodium valproate	Unexposed – epilepsy (no medication)	1 (registry)	58	-	MD 1.73 (0.17, 17.61)	NA	✓	
Bromley 2014	Full scale IQ - <1SD	Sodium valproate	Unexposed – epilepsy (no medication)	2 (OBS)	76	-	RR 10.33 (2.05, 52.01)	0% (0.96)	✓	
Bromley 2014	Full scale IQ - <1SD	Sodium valproate	Unexposed – epilepsy (no medication)	1 (p-cohort)	50	-	RR 10.0 (1.38, 72.39)	NA	✓	
Bromley 2014	Full scale IQ - <1SD	Sodium valproate	Unexposed – epilepsy (no medication)	1 (registry)	26	-	RR 11.0 (0.67, 180.65)	NA	✓	
Bromley 2014	Verbal IQ	Sodium valproate	Unexposed – epilepsy (no medication)	3 (OBS)	160	-	-MD -8.81 (-13.32, -4.30)	0% (0.69)	✓	
Bromley 2014	Verbal IQ	Sodium valproate	Unexposed – epilepsy (no medication)	1 (p-cohort)	76	-	MD -7.45 (-13.02, -1.88)	NA	✓	
Bromley 2014	Verbal IQ	Sodium valproate	Unexposed – epilepsy (no medication)	2 (registry)	84	-	MD -11.42 (-19.13, -3.72)	0% (0.79)	✓	
Bromley 2014	Performance IQ	Sodium valproate	Unexposed – epilepsy (no medication)	3 (OBS)	160	-	MD -7.20 (-12.44, -1.96)	12% (0.32)	✓	
Bromley 2014	Performance IQ	Sodium valproate	Unexposed – epilepsy (no medication)	1 (p-cohort)	76	-	MD -7.30 (-13.71, -0.89)	NA	✓	

Study ID	Outcome (follow-up)	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI) <i>P value</i>	Heterogeneity <i>P value</i> (<i>I</i> ²)	Appropriate comparator population?	Adjusted analysis?
Bromley 2014	Performance IQ	Sodium valproate	Unexposed – epilepsy (no medication)	2 (registry)	84	-	MD -7.01 (-16.13, 2.11)	56% (0.13)	✓	
Bromley 2014	Full scale IQ	Lamotrigine	Unexposed – any	1 (p-cohort)	239	-	MD -4.0 (-8.32, 0.32)	NA		
Bromley 2014	Full scale IQ	Lamotrigine	Unexposed – epilepsy (no medication)	1 (p-cohort)	54	-	MD -1.0 (-7.48, 5.48)	NA	✓	
Banach 2010	Full scale IQ (Weschler)	Sodium valproate	Unexposed – any	NR	NR	-	NR P=0.001	NR		
Banach 2010	Verbal IQ (Weschler)	Sodium valproate	Unexposed – any	NR	NR	-	NR P=0.001	NR		
Banach 2010	Performance IQ (Weschler)	Sodium valproate	Unexposed – any	NR	NR	-	NR P=0.007	NR		
Banach 2010	Full scale IQ (Weschler)	Carbamazepine	Unexposed – any	NR	NR	-	NR P=0.095	NR		
Banach 2010	Verbal IQ (Weschler)	Carbamazepine	Unexposed – any	NR	NR	-	NR P=0.097	NR		
Banach 2010	Performance IQ (Weschler)	Carbamazepine	Unexposed – any	NR	NR	-	NR P<0.002	NR		
Banach 2010	Full scale IQ (Weschler)	Carbamazepine	Unexposed – epilepsy	NR	NR	-	NR P=0.41	NR	✓	
Banach 2010	Verbal IQ (Weschler)	Carbamazepine	Unexposed – epilepsy	NR	NR	-	NR P=0.39	NR	✓	
Banach 2010	Performance IQ (Weschler)	Carbamazepine	Unexposed – epilepsy	NR	NR	-	NR P=0.19	NR	✓	
Banach 2010	Full scale IQ (Bayley/ McCarthy)	Carbamazepine	Unexposed – any	NR	NR	-	NR P=0.3	NR		

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; ICD, International Statistical Classification of Diseases; IQ, intelligence quotient; MD, mean difference; NR, not reported; OBS, observational studies; OR, odds ratio; p, prospective; RE, risk estimate; RR, relative risk; SD, standard deviation.

Note: Risk estimates shown in black bold text denote greater harm for the exposure of interest. Risk estimates shown in grey bold text denote lesser harm for the exposure of interest. Data shown in grey hatching is either (i) adjusted for potential confounders or (ii) limited/adjusted for psychiatric illness. Data shown in grey shading is (i) adjusted for potential confounders and (ii) limited/adjusted for psychiatric illness. Only shaded data is carried into **Section 4.1.3**.

AppD3.1.5 Benzodiazepines and z-drugs

AppD3.1.5.1 Systematic reviews – benzodiazepines and z-drugs

Table AppD3-16 Benzodiazepines and/or z-drug infant harms data extraction from systematic reviews – malformations

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Major malformations										
NICE 2015	Major malformations	Benzodiazepines	Unexposed - any	5 (cohort) ²²⁹	130,429	-	OR 1.01 (0.81, 1.25) ²³⁰	0.88 (0%)	✗	✗
NICE 2015	Major malformations	Benzodiazepines	Unexposed - any	1 (CC) ²³¹	78	-	OR 19.95 (4.17, 95.45) ²³²	NA	✗	✗
Enato 2011	Major malformations	Benzodiazepines	Unexposed - any	9 (OBS)	1,055,020	-	OR 1.07 (0.91, 1.25)	0.95 (0%)	✗	✗
Cardiac malformations										
NICE 2015	Cardiac abnormalities	Benzodiazepines	Unexposed - any	5 (cohort) ²³³	1,007,764	-	OR 1.04 (0.56, 1.90)	0.02 (66%)	✗	✗
Enato 2011	Cardiac malformations	Benzodiazepines	Unexposed - any	3 (OBS)	116,415	-	OR 1.27 (0.69, 2.32)	0.20 (38%)	✗	✗
Septal malformations										
NICE 2015	Septal heart defects	Benzodiazepines	Unexposed - any	1 (cohort) ²³⁴	108,288	-	OR 1.48 (0.21, 10.65)	NA	✗	✗

Abbreviations: CC, case control; CI, confidence interval; OR, odds ratio; RE, risk estimate.

²²⁹ Includes Ban 2014, Laegreid 1992, Oberlander 2008, Ornoy 1998 and Pastuszak 1996.²³⁰ Peto odds ratio.²³¹ Includes Laegreid 1990.²³² Peto odds ratio.²³³ Includes Ban 2014, Leppee 2010, Oberlander 2008, Ornoy 1998 and Wikner 2007.²³⁴ Includes Oberlander 2008.

Table AppD3-17 Benzodiazepines infant harms data extraction from systematic reviews – pregnancy outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Miscarriage										
NICE 2015	Miscarriage	Benzodiazepines	Unexposed - any	3 (cohort) ²³⁵	1,204	-	OR 1.83 (1.19, 2.82)	0.95 (0%)	×	×
Respiratory distress										
NICE 2015	Respiratory disorder	Benzodiazepines	Unexposed - any	2 (cohort) ²³⁶	875,904	-	OR 1.26 (1.04, 1.52)	0.39 (0%)	×	×

Abbreviations: CI, confidence interval; OR, odds ratio; RE, risk estimate.

AppD3.1.5.2 Individual studies – benzodiazepines and z-drugs**Table AppD3-18 Benzodiazepines infant harms data extraction from observational studies – malformations**

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) P value
Major malformations						
Ban 2014b	Major congenital anomalies	Diazepam (first trimester)	Unexposed - depression or anxiety	1 (cohort)	20,352	OR 0.99 (0.61, 1.61)
Ban 2014b	Major congenital anomalies	Temazepam (first trimester)	Unexposed - depression or anxiety	1 (cohort)	19,572	OR 1.04 (0.47, 2.32)
Ban 2014b	Major congenital anomalies	Zopiclone (first trimester)	Unexposed - depression or anxiety	1 (cohort)	19,599	OR 0.93 (0.40, 2.15)
Wikner 2011	Relatively severe malformations ²³⁷	Z-drugs (any time)	Unexposed - any	1 (cohort)	36,321	OR 0.95 (0.69, 1.30)
Wang 2010	Major congenital abnormalities ²³⁸	Zolpidem (any time)	Unexposed - any	1 (cohort)	14,982	OR 0.70 (0.38, 1.28)
Wang 2010	Major congenital abnormalities ²³⁸	Zolpidem (first trimester)	Unexposed - any	1 (cohort)	13,020	Not estimable
Wang 2010	Major congenital abnormalities ²³⁸	Zolpidem (second or third trimester)	Unexposed - any	1 (cohort)	14,447	OR 0.74 (0.38, 1.44)

²³⁵ Includes Laegreid 1992, Ornoy 1998 and Pastuszak 1996.²³⁶ Includes Laegreid 1992 and Wikner 2007.²³⁷ Excludes preauricular appendix, undescended testicle, unstable hip, patent ductus arteriosus in preterm infants, single umbilical artery, tongue tie and nevus.²³⁸ Limited to hydrocephaly, anencephaly, microcephaly, meningomyelocele, encephalocele and spina bifida.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Wang 2010	Major congenital abnormalities ²³⁸	Zolpidem (30-90 days)	Unexposed - any	1 (cohort)	13,946	OR 0.60 (0.26, 1.38)
Wang 2010	Major congenital abnormalities ²³⁸	Zolpidem (90-180 days)	Unexposed - any	1 (cohort)	13,016	Not estimable
Wang 2010	Major congenital abnormalities ²³⁸	Zolpidem (> 180 days)	Unexposed - any	1 (cohort)	12,990	Not estimable
Oberlander 2008a	Major congenital anomalies	Benzodiazepines (first trimester)	Unexposed – adjusted for depression in first trimester	1 (cohort)	108,288	RD -0.0041 (-0.0151, 0.0069)
Wikner 2007	Malformations excluding mild and variable ²³⁹	Benzodiazepines (any time)	Unexposed - any	1 (cohort)	NR	OR 1.37 (1.07, 1.76)
Wikner 2007	Malformations excluding mild and variable ²⁴⁰	Z-drugs (any time)	Unexposed - any	1 (cohort)	NR	OR 1.09 (0.68, 1.75)
Wikner 2007	Malformations excluding mild and variable ²⁴¹	Benzodiazepines and z-drugs ²⁴² –excluding anticonvulsants (any time)	Unexposed - any	1 (cohort)	NR	OR 1.22 (0.97, 1.52)
Diav-Citrin 1999	Major birth defects	Zopiclone (any time)	Unexposed - any	1 (cohort)	68	0% vs. 2.7%; 1.00
Cardiac malformations						
Ban 2014b	Heart anomalies	Diazepam (first trimester)	Unexposed - depression or anxiety	1 (cohort)	20,352	OR 1.29 (0.60, 2.80)
Ban 2014b	Heart anomalies	Diazepam (first trimester)	Unexposed - depression or anxiety	1 (cohort)	19,572	OR 1.31 (0.35, 4.92)
Ban 2014b	Heart anomalies	Zopiclone (first trimester)	Unexposed - depression or anxiety	1 (cohort)	19,599	OR 2.03 (0.69, 6.02)
Wikner 2011	Any cardiovascular defect	Z-drugs (any time)	Unexposed - any	1 (r-cohort)	11,910	RR 0.55 (0.27, 1.09)
Oberlander 2008a	Cardiovascular congenital defects	Benzodiazepines (first trimester)	Unexposed – adjusted for depression in first trimester	1 (r-cohort)	108,288	RD -0.0013 (-0.0055, 0.0029)
Kjær 2007	Cardiovascular congenital abnormalities	Diazepam (any time)	Unexposed - matched	1 (r-cohort)	42,630	OR 1.0 (0.8, 1.4)

²³⁹ Mild and variable malformations include the following diagnoses: preauricular appendix, undescended testicle, hip (sub)luxation, patent ductus arteriosus at preterm birth, tongue tie, single umbilical artery and nevus.

²⁴⁰ Mild and variable malformations include the following diagnoses: preauricular appendix, undescended testicle, hip (sub)luxation, patent ductus arteriosus at preterm birth, tongue tie, single umbilical artery and nevus.

²⁴¹ Mild and variable malformations include the following diagnoses: preauricular appendix, undescended testicle, hip (sub)luxation, patent ductus arteriosus at preterm birth, tongue tie, single umbilical artery and nevus.

²⁴² Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs. Of the 415 infant exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Eros 2002	Cardiovascular congenital abnormalities	Benzodiazepines ²⁴³ (any time)	Unexposed – adjusted for chronic maternal disorders ²⁴⁴	1 (case control)	4,467	OR 1.6 (0.9, 2.8)
Eros 2002	Cardiovascular congenital abnormalities	Benzodiazepines ²⁴³ (Month 1)	Unexposed – adjusted for chronic maternal disorders ²⁴⁴	1 (case control)	4,467	OR 1.6 (0.7, 3.7)
Eros 2002	Cardiovascular congenital abnormalities	Benzodiazepines ²⁴³ (Months 2-3)	Unexposed – adjusted for chronic maternal disorders ²⁴⁴	1 (case control)	4,467	OR 1.0 (0.2, 4.6)
Eros 2002	Cardiovascular congenital abnormalities	Benzodiazepines ²⁴³ (Months 4-9)	Unexposed – adjusted for chronic maternal disorders ²⁴⁴	1 (case control)	4,467	OR 1.9 (0.8, 4.6)
Eros 2002	Cardiovascular congenital abnormalities	Benzodiazepines ²⁴³ (any time)	Unexposed – adjusted for chronic maternal disorders ²⁴⁴	1 (case control)	4,467	OR 1.6 (0.7, 3.6) ²⁴⁵
Eros 2002	Cardiovascular congenital abnormalities	Benzodiazepines ²⁴³ (Months 2-3)	Unexposed – adjusted for chronic maternal disorders ²⁴⁴	1 (case control)	4,467	OR 5.0 (0.2, 104) ²⁴⁵

Abbreviations: CI, confidence interval; OR, odds ratio; RD, risk difference; RE, risk estimate, RR, relative risk.

Table AppD3-19 Benzodiazepines infant harms data extraction from observational studies – malformations

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Miscarriage						
Diav-Citrin 1999	Miscarriage	Zopiclone (any time)	Unexposed - any	1 (cohort)	80	NR 17.5% vs. 7.5%; <i>NR</i>
Preterm birth						
Wang 2010	Preterm birth	Zolpidem (any time)	Unexposed - any	1 (cohort)	14,982	OR 1.49 (1.28, 1.74)
Wang 2010	Preterm birth	Zolpidem (first trimester)	Unexposed - any	1 (cohort)	13,020	OR 1.48 (1.10, 1.98)
Wang 2010	Preterm birth	Zolpidem (second or third trimester)	Unexposed - any	1 (cohort)	14,447	OR 1.49 (1.26, 1.77)
Wang 2010	Preterm birth	Zolpidem (duration 30-90 days)	Unexposed - any	1 (cohort)	13,946	OR 1.46 (1.20, 1.76)

²⁴³ Includes nitrazepam, medazepam, tofisopam, alprazolam and clonazepam.

²⁴⁴ Includes psychiatric disorders.

²⁴⁵ McNemar analysis.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Wang 2010	Preterm birth	Zolpidem (duration 90-180 days)	Unexposed - any	1 (cohort)	13,016	OR 1.35 (1.00, 1.84)
Wang 2010	Preterm birth	Zolpidem (duration > 180 days)	Unexposed - any	1 (cohort)	12,990	OR 1.74 (1.31, 2.32)
Juric 2009	Preterm birth	Zolpidem and other psychotropic drugs (any time)	Unexposed – exposed to other psychotropic drugs	1 (cohort)	90	NR 0.18
Wikner 2007	Preterm birth (< 37 weeks)	Benzodiazepines or z-drugs ²⁴⁶ (early exposure)	Unexposed - any	1 (cohort)	42,875	OR 1.48 (1.26, 1.75)
Wikner 2007	Preterm birth (< 37 weeks)	Benzodiazepines or z-drugs ²⁴⁷ (late exposure)	Unexposed - any	1 (cohort)	42,875	OR 2.57 (1.92, 3.43)
Wikner 2007	Preterm birth (< 37 weeks)	Benzodiazepines or z-drugs ²⁴⁸ - excluding antidepressants (any time)	Unexposed - any	1 (cohort)	NR	OR 1.20 (0.97, 1.50)
Diav-Citrin 1999	Preterm birth (< 37 weeks)	Zopiclone (any time)	Unexposed - any	1 (cohort)	69	NR 21.9% vs. 5.4%; 0.07
Small for gestational age						
Wang 2010	Small for gestational age (< 10 th percentile)	Zolpidem (any time)	Unexposed - any	1 (cohort)	14,982	OR 1.34 (1.20, 1.49)
Wang 2010	Small for gestational age (< 10 th percentile)	Zolpidem (first trimester)	Unexposed - any	1 (cohort)	13,020	OR 1.36 (1.09, 1.69)
Wang 2010	Small for gestational age (< 10 th percentile)	Zolpidem (second or third trimester)	Unexposed - any	1 (cohort)	14,447	OR 1.33 (1.18, 1.50)
Wang 2010	Small for gestational age (< 10 th percentile)	Zolpidem (duration 30-90 days)	Unexposed - any	1 (cohort)	13,946	OR 1.21 (1.05, 1.40)
Wang 2010	Small for gestational age (< 10 th percentile)	Zolpidem (duration 90-180 days)	Unexposed - any	1 (cohort)	13,016	OR 1.57 (1.27, 1.94)
Wang 2010	Small for gestational age (< 10 th percentile)	Zolpidem (duration > 180 days)	Unexposed - any	1 (cohort)	12,990	OR 1.48 (1.19, 1.85)
Wikner 2007	Small for gestational age (< -2 SDs)	Benzodiazepines or z-drugs ²⁴⁹ (early exposure)	Unexposed - any	1 (cohort)	18,260	OR 1.12 (0.87, 1.44)

²⁴⁶ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs.

²⁴⁷ Of the 415 infant exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

²⁴⁸ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs. Of the 415 exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

²⁴⁹ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Wikner 2007	Small for gestational age (< -2 SDs)	Benzodiazepines or z-drugs ²⁵⁰ (late exposure)	Unexposed - any	1 (cohort)	18,260	OR 1.39 (0.80, 2.40)
Diav-Citrin 1999	Small for gestational age (< 3 rd percentile)	Zopiclone (any time)	Unexposed - any	1 (cohort)	68	NR 6.3% vs. 5.6%; NR
Respiratory distress						
Juric 2009	Respiratory difficulty	Zolpidem and other psychotropic drugs (any time)	Unexposed – exposed to other psychotropic drugs	1 (cohort)	90	NR 0.49
Wikner 2007	Respiratory problems	Benzodiazepines or z-drugs ²⁵¹ (early exposure)	Unexposed - any	1 (cohort)	38,638	OR 1.19 (0.98, 1.45)
Wikner 2007	Respiratory problems	Benzodiazepines or z-drugs ²⁵² (late exposure)	Unexposed - any	1 (cohort)	38,638	OR 2.21 (1.62, 3.02)
Wikner 2007	Respiratory difficulty	Benzodiazepines or z-drugs ²⁵³ - excluding antidepressants (any time)	Unexposed - any	1 (cohort)	NR	OR 1.12 (0.88, 1.43)
Neonatal convulsions						
Wikner 2007	Neonatal convulsions	Benzodiazepines or z-drugs ²⁵⁴ (early exposure)	Unexposed - any	1 (cohort)	1386	RR 1.35 (0.44, 3.15)

Abbreviations: CI, confidence interval; NR, not reported; OR, odds ratio; RD, risk difference; RE, risk estimate; RR, relative risk.

²⁵⁰ Of the 415 infant exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

²⁵¹ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs.

²⁵² Of the 415 infant exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

²⁵³ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs. Of the 415 exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

²⁵⁴ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs. Of the 415 exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

Table AppD3-20 Benzodiazepines infant harms data extraction from observational studies – neurodevelopmental outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Language competence						
Odsbu 2015	Lower language competence ²⁵⁵ (3 years)	Benzodiazepines or z-drugs (one period only)	Unexposed – adjusted for depression and anxiety	1 (cohort)	51,411	OR 1.0 (0.7, 1.3)
Odsbu 2015	Lower language competence ²⁵⁵ (3 years)	Benzodiazepines or z-drugs (≥ 2 periods)	Unexposed – adjusted for depression and anxiety	1 (cohort)	51,174	OR 1.3 (0.8, 2.3)

Abbreviations: CI, confidence interval; OR, odds ratio; RE, risk estimate.

²⁵⁵ Validated language grammar rating scale: (i) not yet talking, (2) talking, but unintelligible, (3) talking in one-word utterances, such as “milk” or “down”, (4) talking in 2-3 word phrases, such as “met got ball” or “give doll”, (5) talking in fairly complete sentences, such as “I got a doll” or “can I go outside?” and (6) talking in long and complicated sentences, such as “when I went to the park, I went on the swings” or “I saw a man standing on the corner”. Categories one and two were combined due to low numbers. The interpretation of the odds ratio is the change in the odds of being in a lower category of the language grammar rating scale regardless of how the outcome has been dichotomised.

AppD3.1.6 Lithium

AppD3.1.6.1 Systematic reviews – lithium

Table AppD3-21 Lithium infant harms data extraction from systematic reviews – malformations

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population?	Adjusted analysis?
Congenital malformations										
NICE 2015	Congenital malformations	Lithium	Unexposed – any	4 (cohort) ²⁵⁶	974,914	-	OR 2.10 (1.21, 3.64)	0.65 (0%)	✗	✗
NICE 2015	Congenital malformations	Lithium	Unexposed – psychiatric diagnosis	2 (cohort) ²⁵⁷	782	-	OR 2.12 (0.80, 5.61)	0.36 (0%)	✓	✗
NICE 2015	Congenital malformations	Lithium	Unexposed – any	1 (CC) ²⁵⁸	33,244	-	OR 2.21 (0.67, 7.25)	NA	✗	✗
Cardiac malformations										
NICE 2015	Heart defects	Lithium	Unexposed – any	2 (cohort) ²⁵⁹	973,967	-	OR 1.43 (0.59, 3.46)	0.35 (0%)	✗	✗
NICE 2015	Ebstein's anomaly	Lithium	Unexposed – any	2 (cohort) ²⁶⁰	3,912	-	Estimates unstable because of low number of events		✗	✗

Abbreviations: CC, case control; CI, confidence interval; NA, not applicable; OR, odds ratio; RE, risk estimate; SR, systematic review.

Note: Statistically significant differences are shown in bold.

²⁵⁶ Bodén 2012a; Reis 2008; Kallen 1993; Jacobseon 1992

²⁵⁷ Bodén 2012a; Kallen 1983

²⁵⁸ Czeizel 1990

²⁵⁹ Reis 2008; Kallen 1983

²⁶⁰ Correa-Villasenor 1994; Jacobson 1992

AppD3.1.6.2 Individual studies – lithium

AppD3.1.6.2.1 Malformations – lithium

Table AppD3-22 Lithium infant harms data extraction from observational studies – malformations

Study ID	Outcome	Exposure	Comparator population	Study type	N	RE (95% CI) or n/N (%) <i>P value</i>
Malformations						
Diav-Citrin 2014	Major anomalies	Lithium ²⁶¹	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 140 Unexposed: 711	5.7% vs. 3.4% <i>P=NS</i>
Diav-Citrin 2014	Major anomalies	Lithium ²⁶¹	Unexposed – bipolar disorder	Prospective cohort	Exposed: 140 Unexposed: 61	5.7% vs. 4.9% <i>P=NS</i>
Diav-Citrin 2014	Major anomalies without chromosomal or genetic conditions	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 ²⁶² Unexposed: 711	6.5% vs. 2.7% <i>P=NS</i>
Diav-Citrin 2014 [Australian data ²⁶³]	Major anomalies without chromosomal or genetic conditions	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 16 Unexposed: 65	25% vs. 0% <i>P=0.001</i>
Diav-Citrin 2014 [Canadian data ²⁶³]	Major anomalies without chromosomal or genetic conditions	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 13 Unexposed: 66	7.7% vs. 3.0% <i>P=0.421</i>
Diav-Citrin 2014 [multicentre data ²⁶⁴]	Major anomalies without chromosomal or genetic conditions	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 152 Unexposed: 842	8.6% vs. 2.5% <i>P=0.001</i>
Diav-Citrin 2014	Major anomalies without chromosomal or genetic conditions	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 ²⁶² Unexposed: 61	6.5% vs. 3.3% <i>P=NS</i>
Diav-Citrin 2014	Non-cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 ^{262,265} Unexposed: 711	4.1% vs. 2.1% <i>P=NS</i>
Diav-Citrin 2014 [Australian data ²⁶³]	Non-cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 16 Unexposed: 65	25% vs. 0% <i>P=0.001</i>
Diav-Citrin 2014 [Canadian data ²⁶³]	Non-cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 13 Unexposed: 66	0% vs. 3.0% <i>P=1.000</i>
Diav-Citrin 2014 [multicentre data ²⁶⁴]	Non-cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 152 Unexposed: 842	5.9% vs. 2.0% <i>P=0.011</i>

²⁶¹ The exposure was at least in the first trimester of pregnancy in 90.2% of this lithium-exposed group. The medication was taken throughout pregnancy in 58.5% of these pregnancies. Concurrent psychiatric medications were taken by 66.1% of women in this cohort.

²⁶² Data do not include non-first-trimester lithium exposures.

²⁶³ Includes data from MotherSafe (Australia) or Motherisk Program (Canada) shown in Table 4 of the Diav-Citrin 2014 publication.

²⁶⁴ Multicentre data from ITIS (Israel), MotherSafe (Australia) and Motherisk Program (Canada) to increase the power of the analysis. Data are shown in Table 4 of the Diav-Citrin 2014 publication.

²⁶⁵ Two cases of multiple anomalies in the lithium group and one case in the bipolar group counted twice, both as a cardiovascular and a non-cardiovascular anomaly.

Study ID	Outcome	Exposure	Comparator population	Study type	N	RE (95% CI) or n/N (%) <i>P value</i>
Diav-Citrin 2014	Non-cardiovascular anomalies	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 ^{262,265} Unexposed: 61 ²⁶⁵	4.1% vs. 1.6% <i>P=NS</i>
Källén 2013	Relatively severe malformations	Lithium (early)	Unexposed	Retrospective cohort	Infants exposed: 234 Total: 1,575,847	Adjusted ²⁶⁶ RR 1.09 (0.52, 2.00) ²⁶⁷
Reis 2008	Congenital malformations ²⁶⁸	Lithium (first trimester)	Unexposed (to lithium)	Retrospective cohort	Exposed: 79 Total: 973,767	10.1% vs. 4.5% <i>P value NR</i>
Jacobson 1992	Major congenital malformations (liveborns)	Lithium (first trimester)	Unexposed (to lithium)	Prospective cohort	Exposed: 105 Unexposed: 123	Unadjusted RR 1.2 (0.2, 5.7) 2.9% vs. 2.4%; <i>P=NS</i>
Jacobson 1992	Major congenital malformations (including terminations) ²⁶⁹	Lithium (first trimester)	Unexposed (to lithium)	Prospective cohort	Exposed: NR Unexposed: NR	Unadjusted RR 1.5 (0.4, 6.7)
Czeizel 1990	Major isolated congenital anomalies and unidentified multiple congenital anomalies	Lithium	Unexposed	Retrospective case control	Exposed: 11 Unexposed: 32,233	54.5% vs. 36.3% ²⁷⁰ <i>P value NR</i>
Källén 1983	Relatively severe congenital malformations	Lithium (first trimester) ²⁷¹	Unexposed – manic depression	Retrospective cohort	Exposed: 41 Unexposed: 80	12.2% vs. 3.8% <i>P value NR</i>
Källén 1983	Relatively severe congenital malformations	Lithium ± other psychotropic drug/s (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 59 Unexposed: 80	11.9% vs. 3.8% <i>P value NR</i>
Cardiac malformations						
Diav-Citrin 2014	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Cases in analysis: 822	Adjusted²⁷² OR 4.75 (1.11, 20.36)
Diav-Citrin 2014	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 ^{262,273} Unexposed: 711	Unadjusted RR 7.23 (1.97, 26.53) 4.1% vs. 0.6%; <i>P<0.017</i>
Diav-Citrin 2014 [Australian data ²⁶³]	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 16 Unexposed: 65	0% vs. 0% <i>P=NS</i>
Diav-Citrin 2014 [Canadian data ²⁶³]	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 13 Unexposed: 66	7.7% vs. 0% <i>P=0.165</i>

²⁶⁶ Adjusted for year of birth, maternal age (5-year class), parity (1-4+), smoking in early pregnancy and BMI.

²⁶⁷ As the expected number of events in the exposed group was less than 10, a RR was calculated instead of OR, using the observed over expected number with 95% CI from exact Poisson distributions.

²⁶⁸ In the lithium arm, includes one infant with Down syndrome, one with an unspecified skin malformation, two with unstable hip, and four with cardiac defects (none of which were considered to be major).

²⁶⁹ One pregnancy in the lithium exposure group was terminated due to Ebstein's anomaly.

²⁷⁰ Unexposed population size and percentages taken from NICE 2015 (p198) forest plots.

²⁷¹ Drug use was recorded at the woman's first visit to the maternity health care service, usually in the 10th to 12th week.

²⁷² Regression analysis independent variables included pregnancy order, smoking 10 or more cigarettes a day, bipolar disorder.

²⁷³ Two cases of multiple anomalies in the lithium group and one case in the bipolar group counted twice, both as a cardiovascular and a non-cardiovascular anomaly.

Study ID	Outcome	Exposure	Comparator population	Study type	N	RE (95% CI) or n/N (%) <i>P value</i>
Diav-Citrin 2014 [multicentre data ²⁶⁴]	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 152 Unexposed: 842	3.9% vs. 0.5% <i>P=0.001</i>
Diav-Citrin 2014	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 ^{262,273} Unexposed: 61 ²⁷³	4.1% vs. 3.3% <i>P=NS</i>
Diav-Citrin 2014	Cardiovascular anomalies excluding resolved cases	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 ^{262,273} Unexposed: 711	Unadjusted RR 5.78 (0.82, 40.65) 2.4% vs. 0.3%; <i>P=NS</i>
Diav-Citrin 2014 [Australian data ²⁶³]	Cardiovascular anomalies excluding resolved cases	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 16 Unexposed: 65	0% vs. 0% <i>P=NS</i>
Diav-Citrin 2014 [Canadian data ²⁶³]	Cardiovascular anomalies excluding resolved cases	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 13 Unexposed: 66	7.7% vs. 0% <i>P=0.165</i>
Diav-Citrin 2014 [multicentre data ²⁶⁴]	Cardiovascular anomalies excluding resolved cases	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 152 Unexposed: 842	2.6% vs. 0.2% <i>P=0.006</i>
Diav-Citrin 2014	Cardiovascular anomalies excluding resolved cases	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 ^{262,273} Unexposed: 72 ²⁷³	2.4% vs. 1.6% <i>P=NS</i>
Reis 2008	Relatively severe cardiac defects	Lithium (first trimester)	Unexposed (to lithium)	Retrospective cohort	Exposed: 79 Total: 973,767	5.1% ²⁷⁴ vs. NR <i>P value NR</i>
Jacobson 1992	Cardiac anomalies	Lithium (first trimester)	Unexposed (to lithium)	Prospective cohort	Exposed: NR Unexposed: NR	Unadjusted RR 1.1 (0.1, 16.6)
Källén 1983	Heart defects	Lithium (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 41 Unexposed: 80	7.3% ²⁷⁵ vs. 2.5% <i>P value NR</i>
Källén 1983	Heart defects	Lithium ± other psychotropic drug/s (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 59 Unexposed: 80	6.8% vs. 2.5% <i>P value NR</i>
Septal defects						
Diav-Citrin 2014	Septal defects ²⁷⁶	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 Unexposed: 61	2.4% vs. 1.6% <i>P=NR</i>
Reis 2008	Septal defects ²⁷⁷	Lithium (first trimester)	Unexposed (to lithium)	Retrospective cohort	Exposed: 79 Total: 973,767	2.5% vs. NR <i>P value NR</i>

²⁷⁴ Four cases of cardiac defects included one combined atrium septum defect and tricuspidal and mitral malformations, one mitral insufficiency and also hypospadias, one ventricular septum defect, and one patent ductus arteriosus in a term baby (born after 41 completed weeks). The authors stated that the defects were relatively minor.

²⁷⁵ Among the infants with heart defects after maternal use of lithium, none had Ebstein's anomaly.

²⁷⁶ Collated from Table 5 in Diav-Citrin 2014.

²⁷⁷ The publication text stated that among the four cases of cardiac defects, there was one case with a ventricular septum defect and another with an atrium septum defect combined with tricuspidal and mitral malformations. The authors stated that the cardiac defects were relatively mild.

Study ID	Outcome	Exposure	Comparator population	Study type	N	RE (95% CI) or n/N (%) <i>P value</i>
Ebstein's anomaly						
Diav-Citrin 2014	Ebstein's anomaly	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 Unexposed: 711	0.8% vs. 0% <i>P=NR</i>
Diav-Citrin 2014	Ebstein's anomaly	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 Unexposed: 61	0.8% vs. 0% <i>P=NR</i>
Jacobson 1992	Ebstein's anomaly	Lithium (first trimester)	Unexposed (to lithium)	Prospective cohort	Exposed: NR Unexposed: NR	Unadjusted RR 3.5 (0.1, 84.9) ²⁷⁸
Källén 1983	Ebstein's anomaly	Lithium (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 41 Unexposed: 80	0% ²⁷⁹ vs. NR <i>P value NR</i>

Abbreviations: CI, confidence interval; NR, not reported; NS, not significant; OBS, observational study; OR, odds ratio; RE, risk estimate; RR, relative risk.

Note: Statistically significant differences are shown in bold.

²⁷⁸ One fetus in the lithium group had a severe form of Ebstein's anomaly, which was diagnosed at 16 weeks' gestation, and this pregnancy was terminated.

²⁷⁹ Among the infants born with heart defects after maternal use of lithium, none had Ebstein's anomaly.

AppD3.1.6.2.2 Pregnancy and birth outcomes – lithium

Table AppD3-23 Lithium infant harms data extraction from observational studies – birth outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	Study type	N	RE (95% CI) or n/N (%) <i>P value</i>
Miscarriage						
Diav-Citrin 2014	Miscarriage	Lithium ²⁸⁰	Unexposed – nonteratogenic exposure	Prospective cohort	Cases in analysis: 911	Adjusted²⁸¹ OR 1.94 (1.08, 3.48)
Diav-Citrin 2014	Miscarriage	Lithium ²⁸⁰	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 183 Unexposed: 748	16.4% vs. 5.7% <i>P</i><0.017
Diav-Citrin 2014	Miscarriage	Lithium ²⁸⁰	Unexposed – bipolar disorder	Prospective cohort	Exposed: 183 Unexposed: 72	16.4% vs. 8.3% <i>P</i> =NS
Jacobson 1992	Spontaneous abortion	Lithium (first trimester)	Unexposed	Prospective cohort	Exposed: 148 Unexposed: 148	8.8% vs. 8.1% <i>P</i> =NS
Stillbirth						
Diav-Citrin 2014	Stillbirth	Lithium ²⁸⁰	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 183 Unexposed: 748	1.6% vs. 0.7% <i>P</i> =NS
Diav-Citrin 2014	Stillbirth	Lithium ²⁸⁰	Unexposed – bipolar disorder	Prospective cohort	Exposed: 183 Unexposed: 72	1.6% vs. 0% <i>P</i> =NS
Jacobson 1992	Stillbirth	Lithium (first trimester)	Unexposed	Prospective cohort	Exposed: 138 ²⁸² Unexposed: 148	0.7% vs. 0% <i>P</i> =NS
Neonatal mortality						
Källén 1983	Neonatal deaths ²⁸³	Lithium (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 41 Unexposed: 80	9.8% vs. 0% <i>P value</i> NR
Källén 1983	Neonatal deaths ²⁸³	Lithium ± other psychotropic drug/s (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 59 Unexposed: 80	10.2% vs. 0% <i>P value</i> NR
Preterm birth						
Diav-Citrin 2014	Preterm delivery (<37 weeks)	Lithium ²⁸⁰	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 131 Unexposed: 683	13.7% vs. 6.0% <i>P</i><0.017
Diav-Citrin 2014	Preterm delivery (<37 weeks)	Lithium ²⁸⁰	Unexposed – bipolar disorder	Prospective cohort	Exposed: 131 Unexposed: 59	13.7% vs. 10.2% <i>P</i> =NS

²⁸⁰ The exposure was at least in the first trimester of pregnancy in 90.2% of this lithium-exposed group. The medication was taken throughout pregnancy in 58.5% of these pregnancies.²⁸¹ Regression analysis independent variables included maternal age, previous miscarriage, smoking status, bipolar disorder, gestational age at initial contact with the information centre.²⁸² 10 women were lost to follow-up postnatally²⁸³ Defined by the presence of a date of death in the delivery record.

Study ID	Outcome	Exposure (subgroup)	Comparator population	Study type	N	RE (95% CI) or n/N (%) <i>P value</i>
Troyer 1993	Preterm delivery (<38 weeks)	Lithium (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: ~60 Unexposed: ~290 ²⁸⁴	33% vs. 13% <i>P value NR</i>
Jacobson 1992	Premature (<36 weeks)	Lithium (first trimester)	Unexposed	Prospective cohort	Exposed: 138 ²⁸² Unexposed: 148	4.3% vs. 4.7% <i>P=NS</i>
Large for gestational age						
Troyer 1993	Large for gestational age	Lithium (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: ~60 Unexposed: ~290 ²⁸⁴	5% vs NR <i>P value NR (but no increase due to lithium)</i>

Abbreviations: CI, confidence interval; NR, not reported; NS, not significant; OBS, observational study; OR, odds ratio; RE, risk estimate.

Note: Statistically significant differences are shown in bold.

²⁸⁴ Of 350 women in the manic-depressive cohort, 17% were exposed to lithium (12% to lithium alone and 5% to lithium plus another psychotropic drug).

AppD3.2 COMPLEMENTARY

AppD3.2.1 Omega-3 fatty acids

AppD3.2.1.1 Existing systematic reviews – omega-3 fatty acids

AppD3.2.1.1.1 Pregnancy and birth outcomes – omega-3 fatty acids

Table AppD3-24 Omega-3 fatty acids infant harms data extraction from observational studies – pregnancy and birth outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population	Adjusted analysis?
Preterm birth										
Kar 2016	Early preterm delivery (<34 weeks)	Omega-3 fatty acids	Placebo	6 (RCT)	4,193	RR 0.42 (0.27, 0.66)	-	0.46 (0%)	✓ ²⁸⁵	✓ ²⁸⁶
Kar 2016	Early preterm delivery (<34 weeks) – High risk	Omega-3 fatty acids	Placebo	3 (RCT)	3,670	RR 0.36 (0.18, 0.71)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Kar 2016	Early preterm delivery (<34 weeks) – Any risk	Omega-3 fatty acids	Placebo	3 (RCT)	523	RR 0.50 (0.24, 1.06)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Kar 2016	Any preterm delivery (<37 weeks)	Omega-3 fatty acids	Placebo	9 (RCT)	5,980	RR 0.83 (0.70, 0.98)	-	0.45 (0%)	✓ ²⁸⁵	✓ ²⁸⁶
Kar 2016	Any preterm delivery (<37 weeks) – High risk	Omega-3 fatty acids	Placebo	4 (RCT)	814	RR 0.83 (0.61, 1.11)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Kar 2016	Any preterm delivery (<37 weeks) – Any risk	Omega-3 fatty acids	Placebo	5 (RCT)	5,166	RR 0.83 (0.66, 1.05)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Kar 2016	Any preterm delivery (<37 weeks)	Omega-3 fatty acids - > 400 mg	Placebo	8 (RCT)	5,689	RR 0.83 (0.69, 1.00)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Kar 2016	Any preterm delivery (<37 weeks)	Omega-3 fatty acids - < 400 mg	Placebo	1 (RCT)	291	RR 0.86 (0.44, 1.69)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Kar 2016	Any preterm delivery (<37 weeks)	Omega-3 fatty acids - < 24 weeks	Placebo	7 (RCT)	5,156	RR 0.84 (0.69, 1.03)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Kar 2016	Any preterm delivery (<37 weeks)	Omega-3 fatty acids - > 24 weeks	Placebo	2 (RCT)	824	RR 0.75 (0.45, 1.25)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶

²⁸⁵ Both intervention and comparator populations included pregnant women, not limited to those with a mental health disorder.

²⁸⁶ Data based on RCT evidence so not likely to be selection bias.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population	Adjusted analysis?
Saccone 2016b	Preterm birth (< 37 weeks; women without prior preterm birth)	Omega-3 fatty acids	Placebo	7 (RCT)	3,493	RR 0.90 (0.72, 1.11)	-	0.67 (0%)	✓ ²⁸⁵	✓ ²⁸⁶
Imhoff-Kunsch 2012	Early preterm birth (<34 weeks)	n-3 LCPUFA	Placebo	5 (RCT)	4,343	RR 0.74 (0.58, 0.94)	-	0.42 (0%)	✓ ²⁸⁵	✓ ²⁸⁶
Imhoff-Kunsch 2012	Preterm birth (<37 weeks)	n-3 LCPUFA	Placebo	9 (RCT)	6,505	RR 0.91 (0.82, 1.01)	-	0.66 (0%)	✓ ²⁸⁵	✓ ²⁸⁶
Salvig 2011	Preterm birth (<37 weeks)	Marine n-3 fatty acids	Placebo	3 (RCT)	921	RR 0.61 (0.40, 0.93)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Salvig 2011	Early preterm birth (<34 weeks)	Marine n-3 fatty acids	Placebo	3 (RCT)	921	RR 0.32 (0.09, 0.95)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Small for gestational age										
Kar 2016	SFGA	Omega-3 fatty acids	Placebo	8 (RCT)	5,469	RR 0.82 (0.66, 1.03)	-	NR (41%)	✓ ²⁸⁵	✓ ²⁸⁶
Saccone 2016b	SFGA	Omega-3 fatty acids	Placebo	3 (RCT)	558	RR 1.13 (0.83, 1.54)	-	0.38 (0%)	✓ ²⁸⁵	✓ ²⁸⁶
Imhoff-Kunsch 2012	SFGA or IUGR	n-3 LCPUFA	Placebo	5 (RCT)	3,461	RR 1.06 (0.92, 1.21)	-	0.69 (0%)	✓ ²⁸⁵	✓ ²⁸⁶
Neonatal mortality										
Kar 2016	Neonatal death	Omega-3 fatty acids	Placebo	7 (RCT)	6,751	RR 0.51 (0.26, 1.01)	-	NR	✓ ²⁸⁵	✓ ²⁸⁶
Saccone 2016b	Perinatal death	Omega-3 fatty acids (from ≤ 20 weeks gestation)	Placebo	2 (RCT)	2,462	RR 0.27 (0.09, 0.79)	-	0.85 (0%)	✓ ²⁸⁵	✓ ²⁸⁶
Imhoff-Kunsch 2012	Infant deaths	n-3 LCPUFA	Placebo	6 (RCT)	6,235	RR 0.69 (0.38, 1.23)	-	0.89 (0%)	✓ ²⁸⁵	✓ ²⁸⁶
Imhoff-Kunsch 2012	Stillbirth	n-3 LCPUFA	Placebo	8 (RCT)	7,038	RR 0.80 (0.50, 1.26)	-	0.51 (0%)	✓ ²⁸⁵	✓ ²⁸⁶

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; n-3 LCPUFA, n-3 long-chain polyunsaturated fatty acids; NR, not reported; RCT, randomised controlled trial; RE, risk estimate; RR, relative risk; SFGA, small for gestational age.

AppD3.2.1.1.2 Neurodevelopmental outcomes – omega-3 fatty acids

Table AppD3-25 Omega-3 fatty acids infant harms data extraction from systematic reviews – pregnancy and birth outcomes

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)	Appropriate comparator population	Adjusted analysis?
Cognitive development										
Gould 2013	Cognitive development - < 12 months (BSID-II)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	1 (RCT)	249	MD 1.00 (-0.96, 2.96)	-	NA	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Cognitive development – 12-24 months (BSID-II, BSID-III)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	2 (RCT)	801	MD -0.08 (-1.72, 1.57)	-	0.60 (0%)	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Cognitive development – 2-5 years (GMDS, K-ABC)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	2 (RCT)	156	MD 3.92 (0.77, 7.08)	-	0.90 (0%)	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Cognitive development – 5-12 years (GMDS, K-ABC)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	2 (RCT)	225	MD 0.36 (-2.61, 3.32)	-	0.88 (0%)	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Cognitive development – 12-24 months (BSID-III)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	726	MD 0.06 (-1.66, 1.78)	-	NA	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Cognitive development – 2-5 years (GMDS)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	72	MD 3.70 (-1.02, 8.42)	-	NA	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Cognitive development – 5-12 years (NR)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	82	MD 0.00 (-5.52, 5.52)	-	NA	✓ ²⁸⁷	✓ ²⁸⁸
Motor development										
Gould 2013	Motor development - < 12 months (BSID-II)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	1 (RCT)	249	MD 1.20 (-1.41, 3.81)	-	NA	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Motor development – 12-24 months (BSID-II)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	2 (RCT)	801	MD 1.52 (-2.29, 5.32)	-	0.09 (64%)	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Motor development – 2-5 years (GMDS)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	1 (RCT)	72	MD 4.60 (-1.14, 10.34)	-	NA	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Motor development – 12-24 months (BSID-III)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	726	MD 0.06 (-1.52, 1.64)	-	NA	✓ ²⁸⁷	✓ ²⁸⁸
Language development										
Gould 2013	Language development – 12-24 months (BSID-III)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	726	MD -1.47 (-3.58, 0.64)	-	NA	✓ ²⁸⁷	✓ ²⁸⁸
Gould 2013	Language development – 2-5 years (PPVT)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	70	MD 3.90 (-0.73, 8.53)	-	NA	✓ ²⁸⁷	✓ ²⁸⁸

Abbreviations: BSID, Bayley Scales of Infant Development; CI, confidence interval; GMDS, Griffiths Mental Development Scales; K-ABC, Kaufman Assessment Battery for Children; LCPUFA, long-chain polyunsaturated fatty acids; MD, mean difference; NA, not applicable; NR, not reported; PPVT, Peabody Picture Vocabulary Test; RCT, randomised controlled trial; RE, risk estimate.

²⁸⁷ Both intervention and comparator populations included pregnant women, not limited to those with a mental health disorder.

²⁸⁸ Data based on RCT evidence so not likely to be selection bias.

AppD3.2.2 St John's wort

AppD3.2.2.1 Systematic reviews – St John's wort

No systematic reviews provided quantitative results for the effect of exposure to St John's wort on infant harms.

AppD3.2.2.2 Individual studies – St John's wort

Table AppD3-26 St John's wort infant harms data extraction from observational studies

Study ID	Outcome	Population	Exposure	Comparator	# studies (type)	N	RE (95% CI) % vs. %; p value
Malformations							
Kolding 2015	Malformation	Pregnant women with singleton livebirths	St John's wort	Unexposed/any	1 (cohort)	Exposed: 37 Unexposed: 87,606	NR 8.1% ²⁸⁹ vs. 3.3%; 0.13
Moretti 2009	Major malformations	Pregnant women seeking teratogen information	St John's wort	Unexposed/depression and unexposed/any (no teratogens) Matched ²⁹⁰	1 (cohort)	Exposed: 38 Unexposed: 48	NR 5.3% ²⁹¹ vs. 4.2% ²⁹² vs. 0%; 0.26
Miscarriage							
Kolding 2015	Miscarriage	Pregnant women with singleton livebirths	St John's wort	Unexposed/any	1 (cohort)	Exposed: 38 Unexposed: 88,700	NR 2.6% vs. 1.0%; NR
Moretti 2009	Spontaneous abortion	Pregnant women seeking teratogen information	St John's wort	Unexposed/depression and unexposed/any (no teratogens) Matched ²⁹³	1 (cohort)	Exposed: 54 Unexposed/depression: 56 Unexposed: 56	NR 20.3% vs. 12.5% vs. 8.9%; NR
Preterm birth							
Kolding 2015	Preterm (<37 weeks) ²⁹⁴	Pregnant women with singleton livebirths	St John's wort	Unexposed/any	1 (cohort)	Exposed: 37 Unexposed: 85,978	NR 2.7% vs. 4.5%; 1.00
Moretti 2009	Preterm delivery (not defined)	Pregnant women seeking teratogen information	St John's wort	Unexposed/depression and unexposed/any (no teratogens) Matched ²⁹⁵	1 (cohort)	Exposed: 54 Unexposed/depression: 56 Unexposed: 56	NR 4.7% vs. 20.5% vs. 13.3%; 0.10

Abbreviations: CI, confidence interval; SD, standard deviation.

²⁸⁹ Includes three malformations – bilateral hip dislocation, heart septum defect and hypospadias.

²⁹⁰ Comparator populations matched on gestational age at intake, maternal age and gravidity.

²⁹¹ Offspring malformations are reported in the St. John's wort group as a proportion of first trimester exposures that were liveborn (1 obstructed ureter and 1 hypospadias).

²⁹² Offspring malformations in the disease matched cohort included 1 plagiocephaly and 1 esophageal atresia with tracheoesophageal fistula.

²⁹³ Comparator populations matched on gestational age at intake, maternal age and gravidity.

²⁹⁴ Includes liveborn singleton births only.

²⁹⁵ Comparator populations matched on gestational age at intake, maternal age and gravidity.

AppD3.3 PHYSICAL

AppD3.3.1 Electroconvulsive therapy

AppD3.3.1.1 Systematic reviews – ECT

Table AppD3-27 ECT infant harms data extraction from systematic reviews

Study ID	Outcome	Exposure	Comparator population	# studies (type)	N (events)	Result n (% of events)
Leiknes 2015 ²⁹⁶	Fetal cardiac arrhythmias, bradycardia	ECT	-	14 studies (11 case reports, 3 case series)	35	15 (43)
Leiknes 2015 ²⁹⁶	Stillbirth and neonatal death	ECT	-	7 studies (3 case report, 4 case series)	35	8 (23)
Leiknes 2015 ²⁹⁶	Neonatal respiratory distress	ECT	-	1 study (case report)	35	1 (3)
Leiknes 2015 ²⁹⁶	General mental impairment	ECT	-	2 studies (2 case report)	35	2 (5)
Leiknes 2015 ²⁹⁶	Fetal malformations (teratogenicity)	ECT	-	6 studies (5 case report, 1 case series)	35	7 (20)

Abbreviations: ECT, electro convulsion therapy; NR, not reported.

²⁹⁶ Data from case reports with the same adverse event were pooled together; no comparative evidence reported.

*AppD3.3.1.2 Individual studies – ECT***Table AppD3-28 ECT infant harms data extraction from observational studies**

Study ID	Outcome	Exposure	Comparator population	Study type	N	Result
Babu 2013	Clinical adverse effects	ECT	No ECT	Prospective cohort study	78	None of the infants whose mothers had ECT had clinically observable adverse effects

Abbreviations: ECT, electro convulsion therapy.

AppD3.3.2 Transcranial magnetic stimulation

AppD3.3.2.1 Systematic reviews – TMS

No systematic reviews or meta-analyses were identified which investigated the harms associated with TMS treatment during the antenatal or postnatal period.

AppD3.3.2.2 Individual studies – TMS**Table AppD3-29 TMS or rTMS infant harms data extraction from observational studies**

Study ID	Outcome	Exposure	Comparator population	Study type	N	RE (95% CI), p value
Eryilmaz 2015	Delays in language (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	OR 0.38 (0.09, 1.66), 0.43
Eryilmaz 2015	Delays in social and self-help skills (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	OR 0.75 (0.06, 8.98), 0.67
Eryilmaz 2015	Delays in fine motor (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	OR 1.53 (0.27, 8.63), 0.57
Eryilmaz 2015	Delays in gross motor (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	No events
Eryilmaz 2015	Delays in total development (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	No events

Abbreviations: ADSI, Ankara Developmental Screening Inventory Subscale Scores; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; SD, standard deviation

Appendix D4 ASSESSMENT OF EVIDENCE

AppD4.1 PHARMACOLOGICAL

AppD4.1.1 Antidepressants

AppD4.1.1.1 Included systematic reviews – antidepressants

Thirteen SRs were identified that provided moderate/higher quality evidence relating to the assessment of antidepressant harms; i.e. the SR either analysed adjusted data, included a comparator group with a psychiatric diagnosis, or both. A summary of the characteristics of the identified SRs is presented in **Table AppD4-1**.

Table AppD4-1 Characteristics of the included systematic reviews of antidepressant harms

Study ID	Study characteristics	Population for outcomes assessment	Exposure (subgroups)	Comparator (subgroups)	Outcomes
Jiang 2016	SR including 8 observational studies (6 cohort studies and 2 case-control studies)	Pregnant/ postpartum women	Antidepressants SRI ²⁹⁷ Non-SRI SSRI SNRI	Unexposed	Postpartum haemorrhage
Kaplan 2016	SR/MA 6 case-control studies	Children	SSRIs during pregnancy	No exposure to SSRIs	Autism spectrum disorders
Kobayashi 2016	SR/MA 8 cohort/case-control studies	Children	SSRIs during pregnancy	No exposure to SSRIs	Autism spectrum disorder
Man 2015	6 cohort/case-control studies	Children	SSRIs during pregnancy	No exposure to SSRIs	Autism spectrum disorder
Wang 2015	SR/MA 4 cohort studies	Neonates	SSRIs during the first trimester	No exposure to SSRIs (2 studies)/ADs (2 studies)	Cardiac malformations
McDonagh 2015	SR/some meta-analysed ²⁹⁸ Various	Pregnant women and neonates	Antidepressants/SSRIs during pregnancy	No exposure to antidepressants/SSRIs	Major malformations Neonatal mortality Preterm birth Persistent pulmonary hypertension Respiratory distress Neonatal convulsions Others
Huybrechts 2014b	SR/MA 41 cohort/case-control studies	Neonates	Antidepressants during pregnancy	No exposure to antidepressants	Preterm birth
Grigoriadis 2013a	SR/MA 27 cohort/case-control studies	Neonates	Antidepressants during pregnancy	No exposure to antidepressants	Congenital malformations Major malformations Cardiac malformations Septal malformations
Grigoriadis 2013b	SR/MA 12 cohort/case-control studies	Neonates	Antidepressants during pregnancy	No exposure to antidepressants	PNAS Respiratory distress Tremors
Myles 2013	SR/MA 19 cohort/case-control studies	Neonates	SSRIs during pregnancy	No exposure to SSRIs	Major malformations Minor malformations Cardiac malformations
Ross 2013	SR 23 cohort/case-control studies	Pregnant women and neonates	Antidepressants during pregnancy	No exposure to antidepressants	Spontaneous abortion Preterm birth Gestational age Birth weight Apgar scores
Lopez-Yarto 2012	SR/MA 2 cohort studies	Pregnant women	Antidepressants/SSRIs during pregnancy	No exposure to antidepressants/SSRIs	Maternal metabolic outcomes

²⁹⁷ Includes SSRIs and SNRIs.²⁹⁸ The McDonagh 2015 SR covered a wide range of interventions, comparators and outcomes; however, only those presented quantitatively are included here.

Study ID	Study characteristics	Population for outcomes assessment	Exposure (subgroups)	Comparator (subgroups)	Outcomes
Wurst 2010	SR 15 cohort/5 case control	Neonates	Paroxetine	No SSRI/untreated depression/exposed to nonteratogenic agents/exposed to other antidepressants	Congenital malformations Cardiac malformations

Abbreviations: BA, Bayesian analysis; LBW, low birth weight; MA, meta-analysis; NRD, neonatal respiratory distress; PNAS, poor neonatal adaptation syndrome; SNRI, serotonin and noradrenaline reuptake inhibitor; SR, systematic review; SRI, selective reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

AppD4.1.1.2 Included individual studies – antidepressants

Due to the lack of data from higher quality studies for all outcomes except postpartum haemorrhage, it was necessary to use data from individual studies. Data from individual studies was only eligible for inclusion if it was adjusted for potential confounders and attempted to minimise confounding by indication.

Forty-two studies representing data from 23 cohorts provide evidence of the association between antidepressant use during pregnancy and infant harms. The studies were largely retrospective, with a number being from state- or country-wide population-based cohorts. There were six prospective cohort studies.

Table AppD2-6 presents the characteristics of the 42 identified studies, grouped together by cohort (individual studies from the same cohort are separated in the table by dashed lines).

Table AppD4-2 Characteristics of the included comparative observational studies of antidepressant harms

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Almeida 2016	Retrospective, population-based cohort study Quebec, Canada 1998–2002	Women aged 15 to 45 years with at least one pregnancy (N=41,964)	SSRI monotherapy SNRI monotherapy TCA monotherapy Other monotherapy Polytherapy	Unexposed Unexposed/depression diagnosis Hypothyroid medication	Miscarriage
Bérard 2016	Retrospective, population-based cohort study Quebec, Canada 1998–2009	Full-term singleton infants whose mothers were covered by the RAMQ drug plan for at least 12 months before and during pregnancy (N=145,241)	Citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline SNRI/TCA/MAOI/other ²⁹⁹	Unexposed/adjusted for depression or anxiety and other psychiatric disorders	Autism spectrum disorder
Boukhris 2016	Retrospective, population-based cohort study Quebec, Canada 1998–2009	Full-term singleton infants whose mothers were covered by the RAMQ drug plan for at least 12 months before and during pregnancy (N=145,456)	SSRIs SNRIs MAOIs TCAs Other ADs ³¹ ≥ 2 ADs	Unexposed/adjusted for prior AD use and other psychiatric disorders	Autism spectrum disorder
Bérard 2015	Retrospective, population-based cohort study Quebec, Canada 1998–2010	Pregnancies with a diagnosis of depression and/or anxiety or exposed to antidepressants in the 12 months prior (N=18,493)	Sertraline Non-sertraline SSRIs Non-SSRIs	Unexposed/depression or anxiety	Major congenital malformations (including nervous system, eye/ear/face/neck, circulatory system, respiratory system, digestive system, genital organs, urinary system, musculoskeletal system, cardiac malformations , ventricular/atrial septal defect, omphalocele, craniosyntosis, cleft palate)
Nakhai-Pour 2010	Retrospective nested case-control study Quebec, Canada 1998–2003	Cases: clinically detected spontaneous abortion (N=5,124) Controls: matched on index date and gestational age at spontaneous abortion (N=51,240)	SSRIs Paroxetine Sertraline Fluoxetine Citalopram Fluvoxamine Venlafaxine Polytherapy (SSRIs) TCAs SNRIs Other ADs ³⁰⁰ Polytherapy (classes)	Unexposed/adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy	Spontaneous abortion

²⁹⁹ Includes bupropion, amoxapine, maprotiline, mirtazapine, trazodone and nefazodone.³⁰⁰ Includes serotonin modulators, monoamine oxidase inhibitors, tetracyclic piperazino-azepines, and dopamine and norepinephrine reuptake inhibitors.

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Ramos 2008	Retrospective, case-control study Quebec, Canada 1998–2002	Pregnant women who: (i) received at least one diagnosis of a psychiatric disorder (ICD-9) during pregnancy; (ii) have used antidepressants for at least 30 days in the year prior to pregnancy; and (iii) had a pregnancy ending with a delivery (live or stillbirth)	Any ADs Paroxetine SSRIs TCAs New antidepressants Co-exposure	Unexposed/psychiatric disorder (previous treatment with ADs)	Major congenital malformations
Petersen 2016	Retrospective, primary care-based cohort study THIN ³⁰¹ , UK 1990–2011	Mother-child pairs (live, singleton births) (N=209,135)	SSRIs	Unexposed Unexposed/stopped medication Other ADs	Congenital heart anomalies
Ban 2014a	Retrospective, primary care-based cohort study THIN, UK 1990–2009	Women prescribed antidepressants during early pregnancy, diagnosed with depression without antidepressant prescriptions, no antidepressants/depression during pregnancy (N=349,127)	SSRIs TCAs SSRIs and TCAs Fluoxetine Citalopram Paroxetine Sertraline Escitalopram	Unexposed Unexposed/ depression	Major congenital malformations
Ban 2012	Retrospective, primary care-based cohort study THIN, UK 1990–2009	Singleton pregnancies that ended in live birth, stillbirth, miscarriage or termination (N=512,574)	TCAs SSRIs Benzodiazepines Other classes Multiple classes	Unexposed Unexposed/depression or anxiety	Perinatal death Miscarriage Termination
Furu 2015	Retrospective, population-based cohort study Denmark, Finland, Iceland, Norway and Sweden 1996 to 2010	Women who gave birth to a live singleton infant Data presented here limited to women with at least two children with siblings discordant for both exposure and outcome (N=2288)	SSRIs or venlafaxine	No exposure (sibling cohort)	Congenital malformations Cardiac malformations Non-cardiac malformations
Kieler 2012	Retrospective population-based cohort study Denmark, Finland, Iceland, Norway and Sweden 1996–2007	Infants born after gestational week 33 (N=1,618,255)	SSRIs	Unexposed/subgroup of women with previous psychiatric hospitalisation	Persistent pulmonary hypertension
Grzeskowiak 2015	Retrospective, population-based case-control study Denmark 1996–2002	Singleton, live births (N=80,107)	Any ADs	Unexposed Unexposed/depression	Internalising and externalising problems

³⁰¹ The Health Improvement Network.

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Gidaya 2014	Retrospective, population-based case-control study Denmark 1997–2011	Cases: Children aged 2-15 identified from the DNHR and DPCR with 1 or more ICD-10 code F840, F841, F845, F848 or F849 diagnoses (childhood autism, atypical autism, Asperger's syndrome or pervasive developmental disorder) (N=5,215) Controls: Non-ASD children identified via the DCRS, matched on birth year and month (N=52,150)	SSRIs	Unexposed/adjusted for history of maternal depression	Autism spectrum disorder
Hviid 2013	Retrospective, population-based cohort study Denmark 1996–2009	Singleton, live births (N=626,875)	SSRIs	Unexposed/adjusted for psychiatric diagnoses before delivery	Autism spectrum disorders
Kjaersgaard 2013	Retrospective, population-based cohort study Denmark 1997–2008	Clinically recognised pregnancies (N=1,005,319)	Any ADs	Unexposed Unexposed/diagnosis of depression Unexposed/adjusted for history of severe mental disorder	Spontaneous abortion
Pedersen 2013	Retrospective, population-based cohort study Denmark 1997–2008	Singleton, live births (N=948)	Any ADS	Unexposed Unexposed/depression	Behavioural problems
Sørensen 2013	Retrospective, population-based cohort study Denmark 1996–2006	Live births (N=655,615)	Any ADs SSRIs	Unexposed Unexposed/hospital-diagnosed affective disorder Unexposed/sibling study	Autism spectrum disorder Childhood autism
Malm 2015	Retrospective, population-based cohort study Finland 1996 to 2010	Singleton live births (N= 845,345)	SSRIs	Unexposed Unexposed/psychiatric diagnosis	Preterm birth Small for gestational age Breathing problems
Malm 2016	Retrospective, population-based cohort study Finland 1996–2010	Singleton live births (N=64,754)	SSRIs	Unexposed Unexposed/ psychiatric disorder Unexposed/previous SSRI	Autism spectrum disorder ADHD Depression Anxiety
Brown 2016	Prospective, population-based cohort study Finland 1996-2010	Singleton live births (N=56,340)	SSRIs	Unexposed Unexposed/psychiatric diagnosis	Speech, scholastic and motor disorders

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Huybrechts 2014a	Retrospective insurance-based cohort study Medicaid, 46 States, US 2000–2007	Pregnant women enrolled in Medicaid during the period from 3 months before the last menstrual period through 1 month after delivery of live-born infant/s (N=949,504)	Any ADs SSRI Paroxetine Sertraline Fluoxetine TCAs SNRIs Bupropion Other ADs	Unexposed/depression	Cardiac malformation
Huybrechts 2015	Retrospective insurance-based cohort study Medicaid, 46 States, US 2000 to 2010	Completed pregnancies in women aged 12 to 55 years with live births (N=3,762,559)	SSRI Non-SSRI	Unexposed Unexposed/depression	Persistent pulmonary hypertension
Rai 2013	Retrospective, population-based, nested case-control study Stockholm county, Sweden 2001–2007	Cases: Children aged 0-17 years with ASD (via ICD-9/299 or ICD-10/F84; with or without an intellectual disability) identified via the Stockholm youth cohort (N=4429) Controls: Non-ASD children identified via the Stockholm youth cohort and matched 10:1 by age (year and month) and gender (N=43,277)	Any ADs SSRIs Non-selective MRIs	Unexposed/adjusted for any maternal psychiatric disorder	Autism spectrum disorder
Brandlistuen 2015	Retrospective, population-based sibling-controlled, cohort study Norway 1999-2010	All women in Norway giving birth between late 1999 and 2010 at hospitals and maternity units with more than 100 births annually were eligible for the study. (N=14,435 siblings)	Any ADs	Unexposed/sibling-controlled	Internalising and externalising behaviours
Clements 2015	Retrospective, state-based case-control study Partners HealthCare System, Massachusetts, US 1997–2010	Cases: Children aged 2-19 identified from the Partners HealthCare EHR with 1 or more ICD-9 code 299 (pervasive developmental disorder) diagnoses and were delivered at the MGH, BWH or NWH Controls: Non-ASD children delivered at the MGH, BWH or NWH matched on birth year, hospital, sex, insurance type (as proxy for SES), race/ethnicity and preterm/full-term status	Any ADs	Unexposed/adjusted for history of maternal depression	Autism spectrum disorder ADHD
Cole 2007a	Retrospective, health plan-based cohort study United Health Group, US 1995-2004	Women whose pregnancy resulted in a live birth and who were continuously enrolled in United Health Group for 1-year before delivery	Bupropion	Other ADs	Congenital malformations Cardiovascular malformations

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Cole 2007b	Retrospective, health plan-based cohort study United Health Group, US 1995-2004	Women whose pregnancy resulted in a live birth and who were continuously enrolled in United Health Group for 1-year before delivery	Paroxetine monotherapy Paroxetine mono- or polytherapy	Other AD monotherapy Other AD mono- or polytherapy	Congenital malformations; Cardiovascular malformations
Croen 2011	Retrospective, population-based case-control study KPNC, Northern California, US 1995-2002	<u>Cases</u> Children aged 2-8 identified from the KPNC with a diagnosis of ICD-9 code 299.0 (autism), 299.8 (Asperger syndrome) or 299.8 (pervasive developmental disorder – NOS) (N=298) <u>Controls</u> Non-ASD children identified via the KPNC, matched on sex, birth year and hospital of birth (N=1,507)	SSRIs	Unexposed; unexposed/adjusted for history of depression in year before delivery; unexposed/adjusted for any mental health disorder in year before delivery	Autism spectrum disorder
Djulus 2006	Prospective cohort study Teratogen information services; Canada, US, Israel, Italy, Australia Drug Safety Research Unit, UK 2002-2005	Women contacting a teratogen information service with depression (N=104)	Mirtazapine	Other ADs	Major malformations Spontaneous abortion Preterm birth
El Marroun 2014	Prospective, population-based cohort study Rotterdam, The Netherlands 2002-2006	Children who participated in pre- and postnatal follow-up of the ongoing Generation R Study (N=5,976)	SSRIs	Unexposed unexposed/depression	Pervasive developmental problems Autistic traits Social cognition Social communication Autistic mannerism
Grzeskowiak 2012	Retrospective cohort study South Australia, Australia 2000-2008	Women who gave birth to singleton, live-born infants	SSRIs	Unexposed/psychiatric illness No psychiatric illness	Preterm delivery Low birth weight Small for gestational age Neonate hospital admission Neonate length of hospital stay > 3 d
Harrington 2014	Prospective population-based case-control study California, US 2003-2010	<u>Cases</u> Children aged 2-5 with ASD or DD (confirmed) identified via California-based service providers (N=646) <u>Controls</u> Non-ASD children identified via state birth files and matched by age, gender and regional centre (N=320)	SSRIs	Unexposed; unexposed/history of anxiety/mood disorder	Autism spectrum disorder

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Hayes 2012	Retrospective cohort study Medicaid, Tennessee, US 1995–2007	Singleton pregnancies among women aged 15–44 years enrolled in the Tennessee Medicaid programme (N=228,876)	Any ADs SSRIs Non-SSRIs	Unexposed/adjusted for psychiatric diagnoses	Birth weight Gestational age Early gestational age Early preterm labour Respiratory distress Convulsions
Figueroa 2010	Retrospective, insurance-based cohort study US 1997–2006	Live deliveries (N=38,074 families)	SSRIs Bupropion Other ADs Anticonvulsants Benzodiazepines Other psychotropics	Unexposed/adjusted for maternal and paternal mental health diagnoses, mental health visits and psychotropic drug use	ADHD
Johnson 2016	Prospective cohort study Georgia, US 2010–2012	Women taking part in a study at the Emory Women's Health Program in Atlanta, Georgia with preschool-aged children (N=178)	SSRIs	Unexposed/treated at mental health centre	PDD Expressive language and cognitive functioning
Kieviet 2015	Prospective single-centre cohort study The Netherlands 2007 to 2012	Mothers who used an SSRI, SNRI or NaSSA during at least the third trimester of pregnancy admitted to the maternity ward	SSRI	SNRI	PNAS
Margulis 2013	Retrospective, population-based cohort CPRD, UK 1996–2010	Singleton pregnancies ending in a live birth (N=149,464)	SSRIs	Unexposed/ matched for mental health conditions	Cardiac malformations
Nulman 2015	Prospective cohort study Motherisk, Toronto, Canada NR	Women with depression who contacted the Motherisk service who had two children only, one exposed and one not exposed (N=45 sibling pairs)	SRIs (SSRIs and SNRIs)	Unexposed	IQ Behavioural problems
Oberlander 2006	Retrospective cohort study British Columbia Linked Health Database, Canada 1998–2001	All live births (N=119,547)	SSRIs	Unexposed Unexposed/depression	Caesarean section Birthweight Gestational age Preterm birth Small for gestational age Hospital stay Respiratory distress Feeding problems Jaundice Convulsions
Oberlander 2008a	Retrospective, population-based cohort study British Columbia Linked Health Database, Canada 1998–2001	Women who had registered live births (N=20,188)	SSRIs Benzodiazepines SSRIs + benzodiazepines	Unexposed Adjusted/matched on psychiatric variables	Major congenital anomalies Cardiovascular congenital defects Ventricular septal defects Atrial septal defects

Study ID	Study characteristics Country Period	Population for outcomes assessment (N)	Exposure	Comparator	Outcomes
Oberlander 2008b	Retrospective, population-based cohort study British Columbia Linked Health Database, Canada 1998–2001	Women who had registered live births, matched on pre-pregnancy and prenatal characteristics (N=3,500)	SSRIs/early exposure	SSRIs/late exposure	Birth weight Gestational age Preterm birth Length of hospital stay Small for gestational age Caesarean section Respiratory distress Feeding problems
Simon 2002	Matched cohort study Washington State, US 1986–1998	Women whose pregnancy resulted in a live birth and who were continuously enrolled in Group Health Cooperative (a prepaid health service plan) for 360 days before delivery	SSRIs TCAs	Unexposed/matched on psychiatric variables	Major congenital malformations Minor congenital malformations Specific congenital malformations (genitourinary, cardiac , skeletal, vascular, craniofacial)

Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; BWH, Brigham and Women's Hospital; CPRD, Clinical Practice Research Datalink; DD, developmental delay; DNHR, Danish National Hospital Registry; DPCR, Danish Psychiatric Central Register; HER, electronic health record; ICD, International Statistical Classification of Diseases; IQ, intelligence quotient; KPNC, Kaiser Permanente Medical Care Program; MAOI, monoamine oxidase inhibitor; MGH, Massachusetts General Hospital; MRI, monoamine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NOS, not otherwise specified; NR, not reported; NWH, Newton-Wellesley Hospital; PNAS, poor neonatal adaptation syndrome; RAMQ, Régie de l'assurance maladie du Québec; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; THIN, The Health Improvement Network

AppD4.1.1.3 Major malformations – antidepressants**AppD4.1.1.3.1 Results based on systematic reviews**

The results of the analyses of the association between antidepressants and major malformations presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-4**, grouped by antidepressant type. A number of the analyses based on adjusted data suggested a statistically significant association between antidepressants and major malformations. However, all of these analyses used a comparator population not limited to women with depression or another psychiatric condition, suggesting that there may still be substantial underlying confounding. *As such, these published findings have not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-3 Antidepressants – major malformation outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any ADs								
Grigoriadis 2013a	Major malformations	Any ADs	Unexposed (± ADs) – any	11 ¹²⁵ (OBS)	1,940,124	RR 1.07 (0.99, 1.17)	-	0.86 (0%)
SSRIs								
McDonagh 2014	Major malformations	SSRIs	Unexposed – any	6 (OBS)	2,421,444	OR 1.08 (0.95, 1.22)	-	NR (67%)
McDonagh 2014	Major malformations	SSRIs	Unexposed – prior SSRIs	8 (OBS)	NR	-	OR 1.07 (0.78, 1.47) ³⁰²	0.59 (NE)
McDonagh 2014	Major malformations	SSRIs + psychotherapy	Psychotherapy – condition	1 (cohort)	44	-	OR 0.40 (0.02, 6.93)	NA
Myles 2013	Major malformations	SSRIs	Unexposed – any	27 (OBS)	NR	OR 1.11 (1.04, 1.19)³⁰³	-	0.94 (0%)
Myles 2013	Major malformations	SSRIs	Unexposed – any	32 (OBS)	NR	OR 1.10 (1.04, 1.17)³⁰⁴	-	0.75 (0%)
Myles 2013	Major malformations	SSRIs	Unexposed – any	25 (OBS)	NR	OR 1.12 (1.05, 1.20)³⁰⁵	-	0.62 (0%)
Citalopram/ escitalopram								
McDonagh 2014	Major malformations	Citalopram/ escitalopram	Unexposed – any	8 (OBS)	4,091,225	OR 1.06 (0.97, 1.16)	-	NR (0%)
McDonagh 2014	Major malformations	Citalopram or escitalopram	Fluoxetine or paroxetine – condition	8 (OBS)	NR	-	OR 0.94 (0.82, 1.07)	NR (0%)
Fluoxetine								
McDonagh 2014	Major malformations	Fluoxetine	Unexposed – any	7 (OBS)	3,397,479	OR 1.14 (1.01, 1.30)	-	NR (0%)
Grigoriadis 2013a	Major malformations	Fluoxetine	Unexposed (± ADs) – any	4 ¹²⁵ (OBS)	1,898,925	RR 0.98 (0.98, 1.48)	-	0.38 (4%)
Myles 2013	Major malformations	Fluoxetine	Unexposed – any	5 ³⁰⁶ (OBS)	NR	OR 1.22 (1.01, 1.47)³⁰⁷	-	0.51 (0%)

³⁰² In the McDonagh publication this is included in the table with pooled adjusted analyses. However, in the table for cardiac malformations, this has been shown as being based on unadjusted data. This is assumed here also due to the fact this analysis has a greater number of studies than the overall adjusted analysis.

³⁰³ Includes studies that controlled for tobacco, alcohol or illicit drug use.

³⁰⁴ Includes studies that controlled for maternal age.

³⁰⁵ Includes studies that controlled for maternal parity.

³⁰⁶ Includes higher quality studies only (scored ≥ 4/6 in the quality assessment).

³⁰⁷ Controlled for at least one of the potential confounders of interest: (i) tobacco, alcohol or illicit drug use, (ii) maternal age and (iii) maternal parity.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Paroxetine								
McDonagh 2014	Major malformations	Paroxetine	Unexposed – any	11 (OBS)	4,192,613	OR 1.17 (1.02, 1.35)	-	NR (0%)
Grigoriadis 2013a	Major malformations	Paroxetine	Unexposed (± other ADs) – any	5 ¹²⁵ (OBS)	1,900,864	RR 1.11 (0.88, 1.39)	-	0.32 (14%)
Myles 2013	Major malformations	Paroxetine	Unexposed - any	4 ³⁰⁸ (OBS)	NR	OR 1.40 (1.11, 1.78)³⁰⁹	-	0.38 (3%)
McDonagh 2014	Major malformations	Paroxetine	Fluoxetine – condition	9 (OBS)	NR	-	OR 1.14 (0.95, 1.37)	≥ 0.1 (NR)
Sertraline								
McDonagh 2014	Major malformations	Sertraline	Unexposed - any	7 (OBS)	4,020,791	OR 1.17 (1.02, 1.35)	-	NR (23%)
McDonagh 2014	Major malformations	Sertraline	Fluoxetine or paroxetine – condition	8 (OBS)	NR	-	OR 0.59 (0.38, 0.90)	NR (0%)
Fluvoxamine								
McDonagh 2014	Major malformations	Fluvoxamine	Unexposed – any	2 (OBS)	1,492,881	OR 0.76 (0.38, 1.50)	-	0.68 (NE)
TCAs								
McDonagh 2014	Major malformations	TCAs	Unexposed – any	2 (OBS)	NR	OR 1.31 (1.04, 1.65)	-	NR

Abbreviations: AD, antidepressant; AR, absolute risk; ARD, absolute risk difference; CC, case control; CI, confidence interval; NA, not applicable; ND, no difference; NE, not estimable; NR, not reported; OBS, observational studies (type not specified); OR, odds ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

AppD4.1.1.3.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and major malformations is presented in **Table AppD4-4**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of major malformations in the depressed/unexposed population (2.8% in Ban 2014a), it is assumed that odds ratios (ORs) approximate the relative risks (RRs) and these risk estimates have been pooled together in order to calculate a single relative effect estimate.

Table AppD4-4 Antidepressants – major malformation outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Any ADs						
Ramos 2008 ³¹⁰	Major congenital malformations	Any ADs (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.10 (0.75, 1.62)
Ramos 2008	Major congenital malformations	Any ADs for 1-30 days (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.23 (0.77, 1.98)

³⁰⁸ Includes higher quality studies only (scored ≥ 4/6 in the quality assessment).

³⁰⁹ Controlled for at least one of the potential confounders of interest: (i) tobacco, alcohol or illicit drug use, (ii) maternal age and (iii) maternal parity.

³¹⁰ Major malformations were defined as ICD-9 codes 740–759, excluding the following that were considered to be minor malformations: 743.6, 744.1, 744.2–4, 744.8–9, 747.0, 747.5, 750.0, 752.4, 752.5, 754.6, 755.1, 755.2–6, 757.8–9, 758.4.

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Ramos 2008	Major congenital malformations	Any ADs for 31-60 days (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.03 (0.63, 1.69)
Ramos 2008	Major congenital malformations	Any ADs for ≥ 61 days (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 0.92 (0.50, 1.69)
Ramos 2008	Major congenital malformations	Any ADs (second trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.13 (0.59, 2.17)
Ramos 2008	Major congenital malformations	Any ADs (third trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 0.86 (0.45, 1.65)
SSRIs						
Ban 2014a <i>Moderate</i>	Major congenital anomalies	SSRIs (first trimester)	Unexposed – depression	1 (cohort)	31,516	OR 0.93 (0.78, 1.11)
Bérard 2015 <i>Moderate</i>	Major congenital malformations	Non-sertraline SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,831	RR 1.08 (0.93, 1.25)
Ban 2014a	Major congenital anomalies	SSRIs & TCAs (first trimester)	Unexposed – depression	1 (cohort)	24,123	OR 0.94 (0.46, 1.92)
Oberlander 2008a	Major congenital anomalies	SRIs ³¹¹ (first trimester)	Unexposed – adjusted for depression	1 (cohort)	109,945	RD -0.0061 (-0.0144, 0.0021) ³¹²
Oberlander 2008a	Major congenital abnormalities	SRIs ³¹¹ + benzodiazepines	Unexposed – adjusted for depression	1 (cohort)	107,679	RD 0.0165 (-0.0049, 0.0379)
Ramos 2008 ³¹³	Major congenital malformations	Non-paroxetine SSRIs (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.19 (0.71, 1.97)
Simon 2002 <i>Moderate</i>	Major congenital malformations	SSRIs (any time)	Unexposed – matched population	1 (cohort)	370	OR 1.36 (0.56, 3.30)
Paroxetine						
Ban 2014a <i>Moderate</i>	Major congenital anomalies	Paroxetine (first trimester)	Unexposed – depression	1 (cohort)	25,033	OR 1.01 (0.71, 1.44)
Oberlander 2008a <i>High</i>	Major congenital anomalies	Paroxetine (first trimester)	Unexposed – adjusted for depression	1 (cohort)	108,313	RD -0.0056 (-0.0170, 0.0059) ³¹²
Ramos 2008 <i>Moderate</i>	Major congenital malformations	Paroxetine (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.27 (0.78, 2.06)
Fluoxetine						
Ban 2014a <i>Moderate</i>	Major congenital anomalies	Fluoxetine (first trimester)	Unexposed – depression	1 (cohort)	27,022	OR 0.85 (0.66, 1.09)
Oberlander 2008a <i>High</i>	Major congenital anomalies	Fluoxetine (first trimester)	Unexposed – adjusted for depression	1 (cohort)	107,958	RD -0.0026 (-0.0168, 0.0117) ³¹²
Sertraline						
Bérard 2015 <i>Moderate</i>	Major congenital malformations	Sertraline (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	15,234	RR 1.11 (0.81, 1.52)
Ban 2014 <i>Moderate</i>	Major congenital anomalies	Sertraline (first trimester)	Unexposed – depression	1 (cohort)	24,590	OR 1.17 (0.78, 1.77)
Oberlander 2008a <i>High</i>	Major congenital anomalies	Sertraline	Unexposed – adjusted for depression	1 (cohort)	107,928	RD -0.0041 (-0.0184, 0.0102) ³¹²
Citalopram						
Ban 2014a <i>Moderate</i>	Major congenital anomalies	Citalopram (first trimester)	Unexposed – depression	1 (cohort)	25,779	OR 0.97 (0.71, 1.31)

³¹¹ Includes SSRI or venlafaxine.³¹² Risk differences reported as percentages in Oberlander 2008a. Recalculated as proportions for the purpose of graphing results for this review.³¹³ Excluded from pooled analysis because population overlaps with that included in Bérard 2015.

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Oberlander 2008a	Major congenital anomalies	Citalopram	Unexposed – adjusted for depression	1 (cohort)	107,421	RD 0.0040 (-0.0313, 0.0393) ³¹²
Escitalopram						
Ban 2014a <i>Moderate</i>	Major congenital anomalies	Escitalopram (first trimester)	Unexposed – depression	1 (cohort)	24,166	OR 0.77 (0.36, 1.66)
Fluvoxamine						
Oberlander 2008a <i>Moderate</i>	Major congenital anomalies	Fluvoxamine (first trimester)	Unexposed – adjusted for depression	1 (cohort)	107,439	RD -0.0152 (-0.0402, 0.0098) ³¹²
Venlafaxine						
Oberlander 2008a <i>Moderate</i>	Major congenital anomalies	Venlafaxine	Unexposed – adjusted for depression	1 (cohort)	107,570	RD -0.0118 (-0.0320, 0.0084) ³¹²
Mirtazapine						
Djulus 2006 <i>Moderate</i>	Major malformations	Mirtazapine	Other ADs	1 (cohort)	208	P=0.50
New antidepressants³¹⁴						
Ramos 2008	Major congenital malformations	New antidepressant (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 0.94 (0.51, 1.75)
Non-SSRIs						
Bérard 2015	Major congenital malformations	Non-SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,164	RR 1.12 (0.94, 1.33)
Co-exposures³¹⁵						
Ramos 2008	Major congenital malformations	Co-exposure (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 1.03 (0.44, 2.41)
TCAs						
Ban 2014a <i>Moderate</i>	Major congenital anomalies	TCAs (first trimester)	Unexposed – depression	1 (cohort)	26,261	OR 1.02 (0.79, 1.32)
Ramos 2008 <i>Moderate</i>	Major congenital malformations	TCAs (first trimester)	Unexposed – previous ADs	1 (case control)	2,329	OR 0.78 (0.30, 2.02)
Simon 2002 <i>Moderate</i>	Major congenital malformations	TCAs (any time)	Unexposed – matched	1 (cohort)	418	OR 0.82 (0.35, 1.95)

Abbreviations: AD, antidepressant; CI, confidence interval; OR, odds ratio; RD, risk difference; RE, risk estimate; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Figure AppD4-1 summarises the findings of the association between SSRI use and major malformations. Two studies examined first-trimester exposure with SSRI and found that, overall, there was no significant association (RR 1.01; 95% CI 0.87, 1.17). It should be noted that one of the two studies excluded one commonly used SSRI from their analysis, sertraline (Bérard 2015). The inclusion of an additional study that did not limit exposure to the first trimester did not change the finding (RR 1.02; 95% CI 0.91, 1.14).

In addition to these findings, Ramos 2008 showed no significant association between non-paroxetine SSRIs and major malformations in a population that overlapped with Bérard 2015 (OR 1.19; 95% CI 0.71, 1.97), while Oberlander 2008a examined the *absolute risk* of major malformations following first-trimester SSRI or venlafaxine use and found no significantly increased risk (RD -0.0061; 95% CI -0.0144, 0.0021).

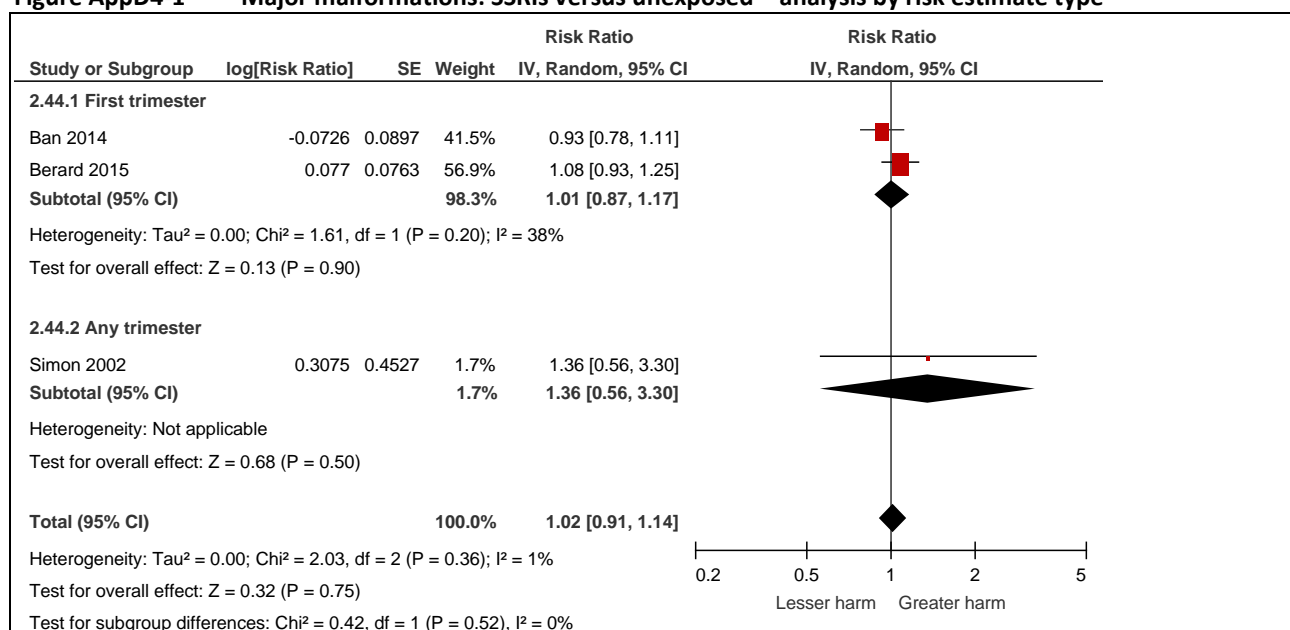
Ban 2014a and Oberlander 2008a also examined the association between SSRIs plus another treatment. Ban 2014a looked at SSRIs plus TCAs in the first trimester and major malformations. While the result

³¹⁴ Includes bupropion, mirtazapine, moclobemide, nefazodone, trazodone and venlafaxine.

³¹⁵ Two or more drug classes.

suggested no increased risk (OR 0.94; 95% CI 0.46, 1.92), it is also subject to imprecision because the 95% CI crosses both the line of no effect and a measure of appreciable benefit or harm. Oberlander 2008a looked at SRIs (SSRIs or venlafaxine) plus benzodiazepines and found no increased risk (RD 0.0165; 95% CI -0.0049, 0.0379).

Figure AppD4-1 Major malformations: SSRIs versus unexposed – analysis by risk estimate type

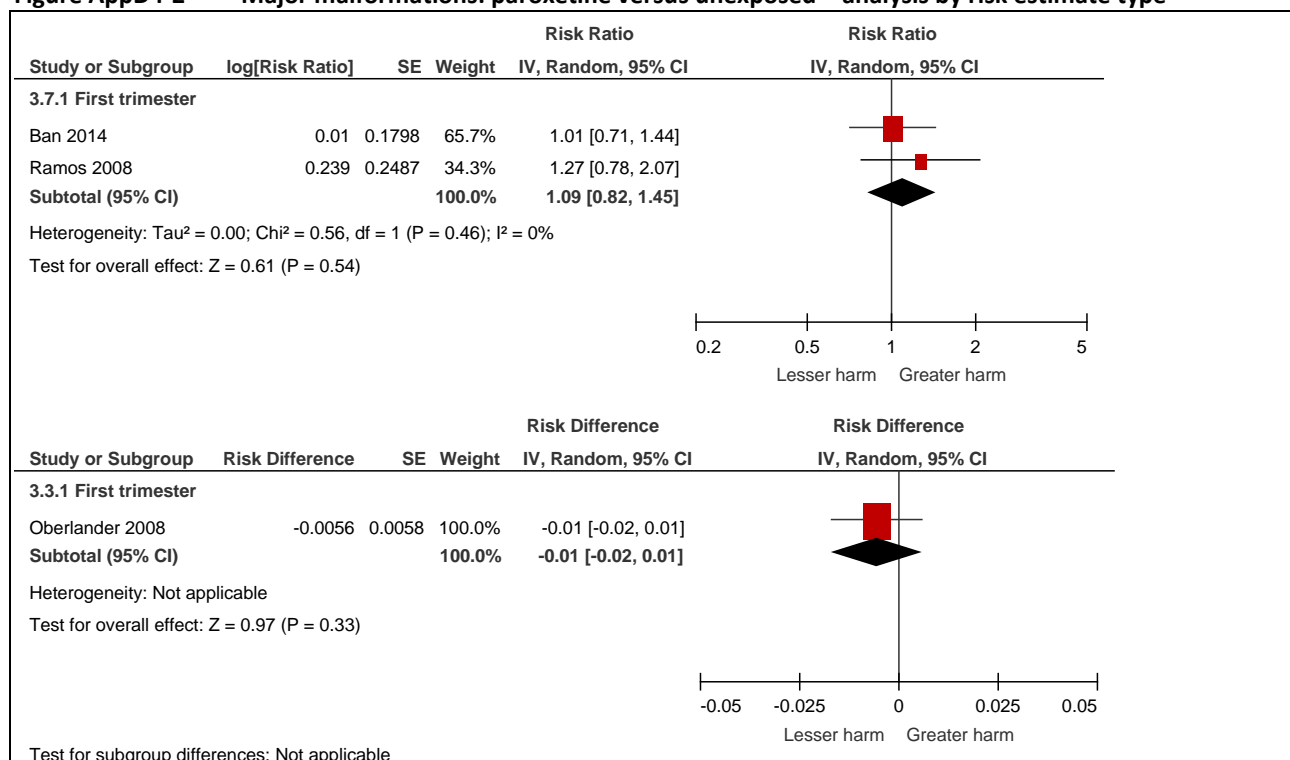


Abbreviations: Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: Bérard 2015 includes non-sertraline SSRIs only. The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-2 summarises the findings of the association between paroxetine use and major malformations. Two studies contributed to the analysis and showed no significant association between first-trimester paroxetine use and major malformation (RR 1.09; 0.82, 1.45); however, this finding is subject to imprecision because the 95% CI crosses both the line of no effect and a measure of appreciable benefit or harm.³¹⁶ Oberlander 2008a examined the *absolute* risk of major malformations following the use of paroxetine in the first trimester and found no increase in risk (RD -0.0056; 95% CI -0.0170, 0.0059).

³¹⁶ Because the prevalence of major malformation is low (~2.7% in the Ban 2014 study), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

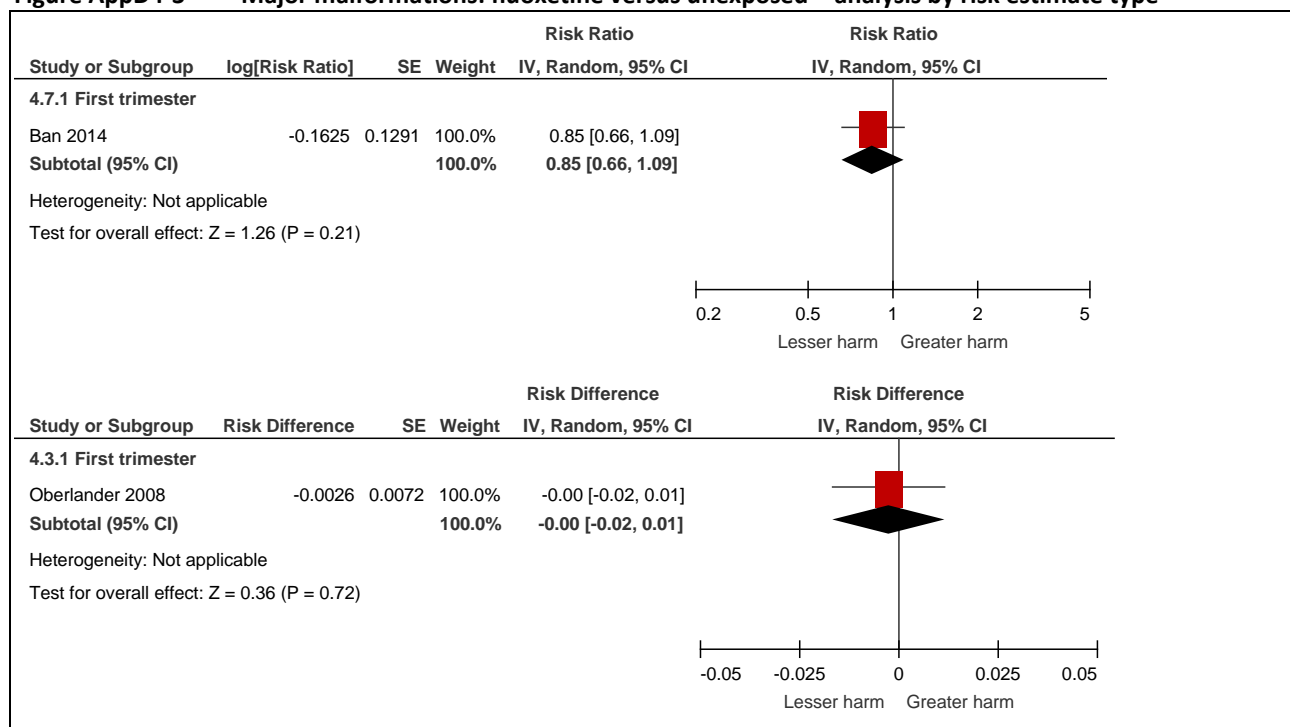
Figure AppD4-2 Major malformations: paroxetine versus unexposed – analysis by risk estimate type

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Ban 2014a examined the association between first-trimester exposure to fluoxetine and major malformations and found no significant association (RR 0.85; 95% CI 0.66, 1.09; **Figure AppD4-3**). This finding is imprecise because the 95% CI includes a measure of appreciable benefit or harm.³¹⁷ Oberlander 2008a examined the absolute risk of major malformations following first-trimester exposure to fluoxetine and also found no significant increase in risk (RD -0.0026; 95% CI -0.0168, 0.0117).

³¹⁷ Because the prevalence of major malformation is low (~2.7% in the Ban 2014 study), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

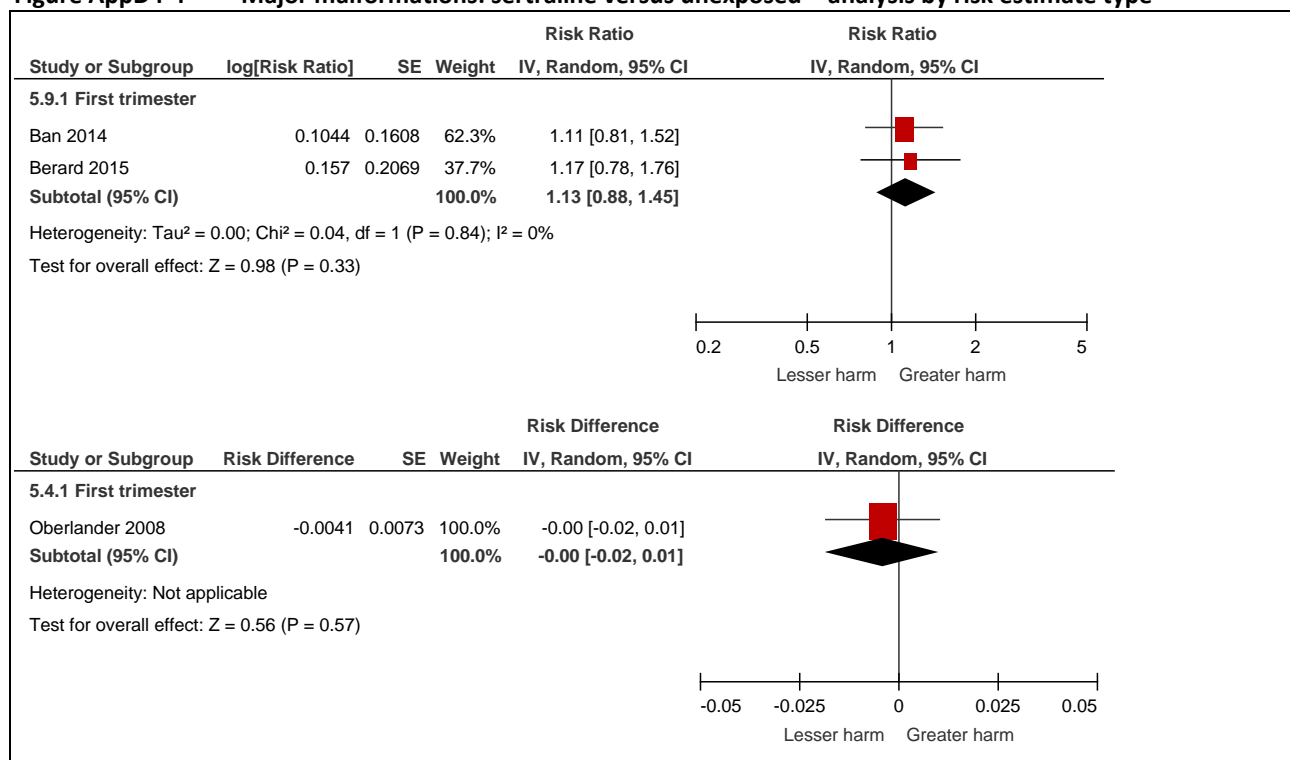
Figure AppD4-3 Major malformations: fluoxetine versus unexposed – analysis by risk estimate type

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-4 summarises the findings of the association between sertraline use and major malformations: there was no statistically significant association (RR 1.13; 95% CI 0.88, 1.45); however, the finding is subject to imprecision as the 95% CI crosses the predefined measure of appreciable benefit or harm.³¹⁸ Oberlander 2008a also examined the association between first-trimester sertraline and major malformations, finding no significant difference in *absolute risk* (RD -0.0041; 95% CI -0.0184, 0.0102).

³¹⁸ Because the prevalence of major malformation is low (~2.7% in the Ban 2014 study), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

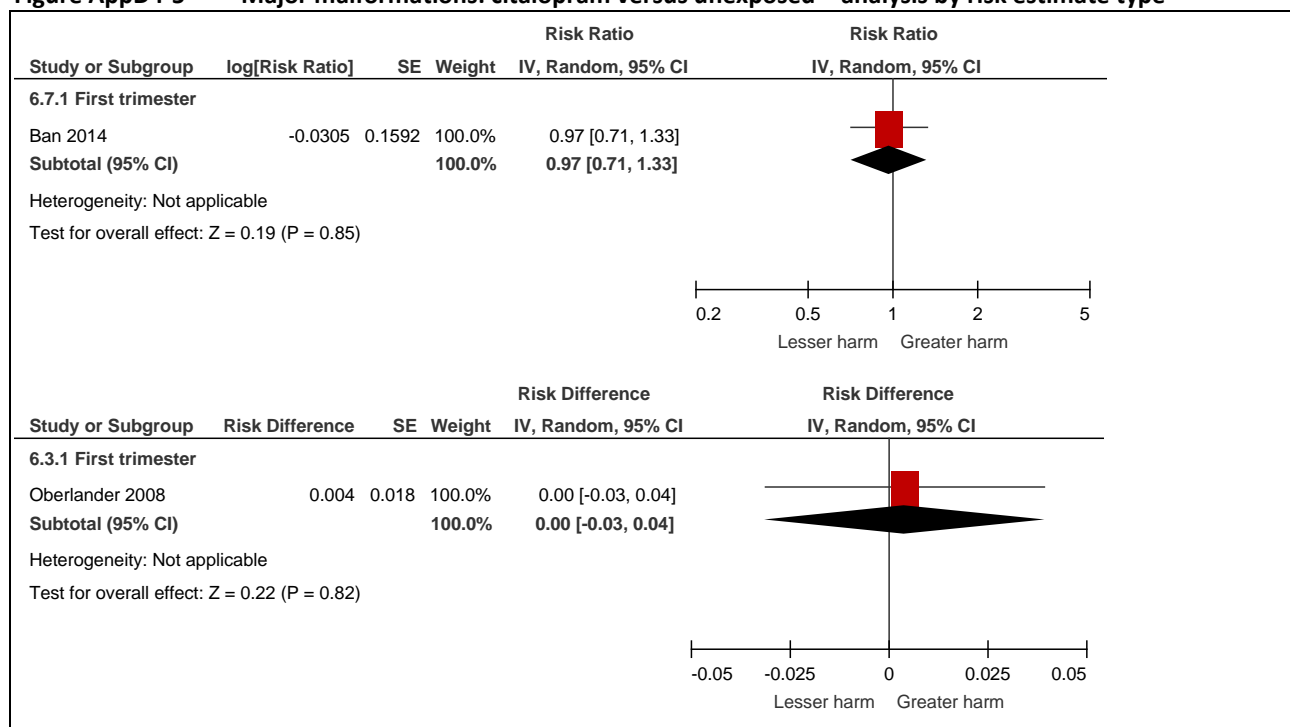
Figure AppD4-4 Major malformations: sertraline versus unexposed – analysis by risk estimate type

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Ban 2014a examined the association between first-trimester exposure to citalopram and major malformations and found significant association (RR 0.97; 95% CI 0.71, 1.31; **Figure AppD4-5**). This finding is imprecise because the 95% CI includes a measure of appreciable benefit or harm.³¹⁹ Oberlander 2008a examined the absolute risk of major malformations following first-trimester exposure to citalopram and also found no significant increase in risk (RD 0.0040; 95% CI -0.0313, 0.0393).

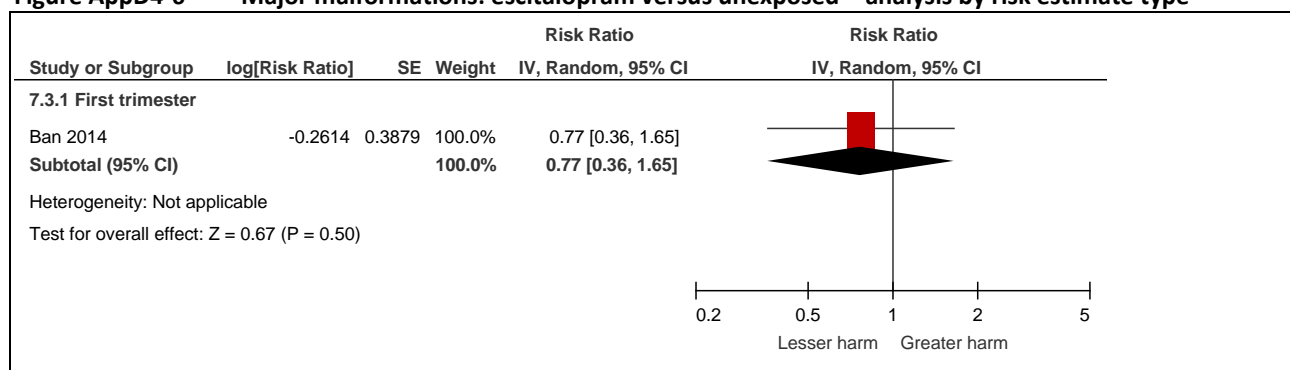
³¹⁹ Because the prevalence of major malformation is low (~2.7% in the Ban 2014 study), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-5 Major malformations: citalopram versus unexposed – analysis by risk estimate type

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Ban 2014a examined the association between first-trimester exposure to escitalopram and major malformations and found no significant association (RR 0.77; 95% CI 0.36, 1.66; **Figure AppD4-6**). This finding is imprecise because the 95% CI includes a measure of appreciable benefit or harm.³²⁰

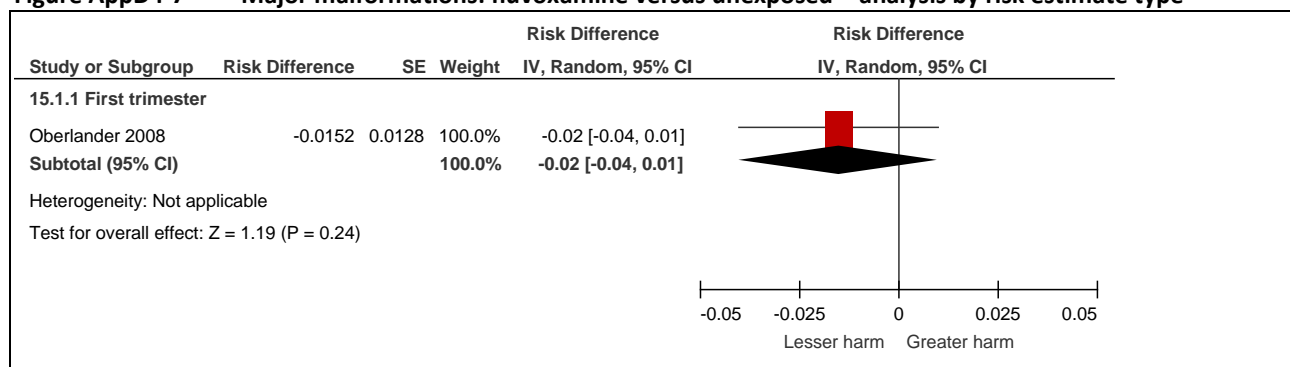
Figure AppD4-6 Major malformations: escitalopram versus unexposed – analysis by risk estimate type

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

As shown in **Figure AppD4-7**, Oberlander 2008a examined the absolute risk associated with the use of first-trimester fluvoxamine on major malformations and found no increased risk (RD -0.0152; 95% CI -0.0402, 0.0098).

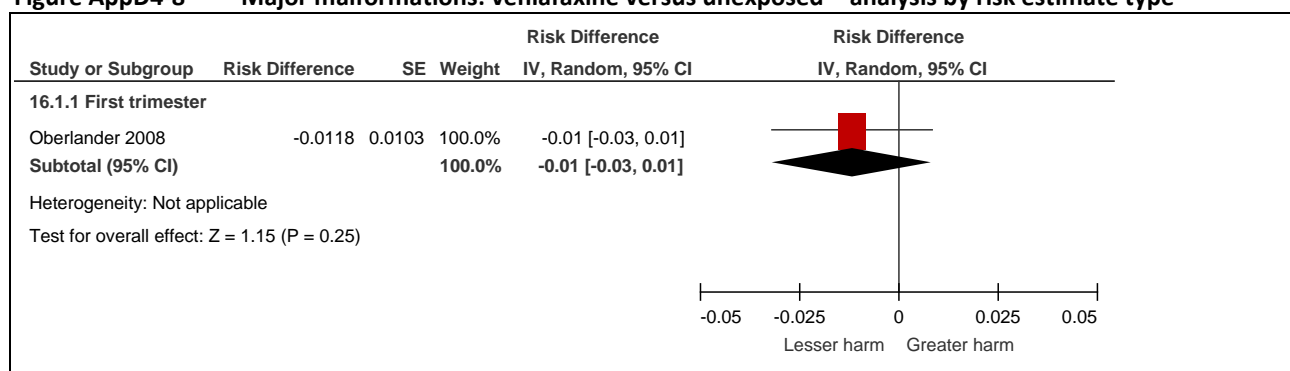
³²⁰ Because the prevalence of major malformation is low (~2.7% in the Ban 2014 study), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-7 Major malformations: fluvoxamine versus unexposed – analysis by risk estimate type

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

As shown in **Figure AppD4-8**, Oberlander 2008a examined the association between first-trimester exposure to venlafaxine and major malformations and found no significantly increased absolute risk (RD -0.0118; 95% CI -0.0320, 0.0084).

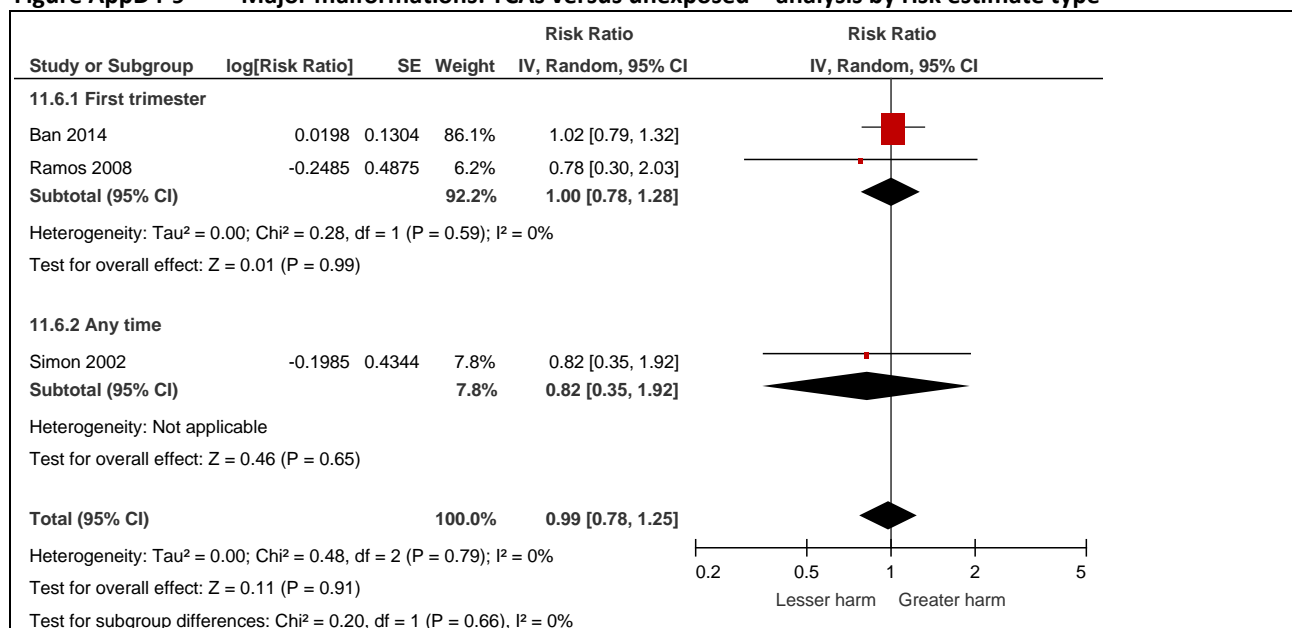
Figure AppD4-8 Major malformations: venlafaxine versus unexposed – analysis by risk estimate type

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Djulus 2006 assessed the association between mirtazapine use and major malformations and found no significant association (p=0.50; unable to graph).

Three studies contributed to the analysis of the association between TCAs and major malformation, as shown in **Figure AppD4-9**. When limited to first-trimester exposure, there was no significant association (RR 1.00; 95% CI 0.78, 1.28). This finding held when a study examining TCA use in any trimester was included (OR 0.99; 95% CI 0.78, 1.25).

Figure AppD4-9 Major malformations: TCAs versus unexposed – analysis by risk estimate type**AppD4.1.1.4 Cardiac malformations – antidepressants****AppD4.1.1.4.1 Results based on systematic reviews**

The results of the analyses of the association between antidepressants and cardiac malformations presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population (see **Table AppD4-5**), grouped by antidepressant type. A number of the analyses based on adjusted data suggested a statistically significant association between antidepressants and cardiac malformations. However, as for major malformations, these analyses used a comparator population not limited to women with depression or another psychiatric condition, suggesting that there may still be substantial underlying confounding. *As such, these findings have not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-5 Antidepressants – cardiac malformation outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I^2)
Any ADs								
Grigoriadis 2013a	Cardiac malformations	Any ADs	Unexposed (\pm ADs) – any	10 ¹⁴⁰ (OBS)	1,450,406	RR 1.35 (1.07, 1.70)	-	0.18 (29%)
SSRIs								
Wang 2015	Cardiac malformations	SSRIs	Unexposed – any	4 (cohort)	2,010,180	OR 1.06 (0.94, 1.18)	-	0.24 (28%)
McDonagh 2014	Cardiac malformations	SSRIs	Unexposed – any	5 (OBS)	NR	OR 1.29 (0.96, 1.72)	-	NR (84%)
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	24 (OBS)	NR	OR 1.17 (1.01, 1.35)³²¹	-	0.05 (34%)
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	20 (OBS)	NR	OR 1.15 (0.98, 1.34) ³²²	-	0.04 (38%)

³²¹ Includes studies that controlled for maternal age.³²² Includes studies that controlled for maternal parity.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
McDonagh 2014	Cardiac malformations	SSRIs	Unexposed – prior SSRIs	NR	NR	-	OR 1.07 (0.94, 1.20)	NR (0%)
Paroxetine								
Wang 2015	Cardiac malformations	Paroxetine	Unexposed – any	3 (cohort)	NR	OR 0.97 (0.75, 1.19)	-	0.50 (0%)
McDonagh 2014	Cardiac malformations	Paroxetine	Unexposed – any	6 (OBS)	NR	OR 1.49 (1.20, 1.85)	-	NR (0%)
Grigoriadis 2013a	Cardiac malformations	Paroxetine	Unexposed (± ADs) – any	6 ⁴⁰ (OBS)	1,635,544	RR 1.46 (1.09, 1.94)	-	0.86 (0%)
Myles 2013	Cardiac malformations	Paroxetine	Unexposed – any	5 ²³ (OBS)	NR	OR 1.41 (1.06, 1.87)³²⁴	-	0.65 (0%)
Wurst 2010	Cardiac malformations	Paroxetine	Unexposed – any	11 (OBS)	NR	OR 1.48 (1.17, 1.86)³²⁵	-	1.00 (NR)
Wurst 2010	Cardiac malformations	Paroxetine	Untreated or treated with other antidepressants/ depression	2 (OBS)	NR	-	OR 1.44 (0.81, 2.54) ³²⁶	0.9 (NR)
McDonagh 2014	Cardiac malformations	Paroxetine	Fluoxetine – condition	8 (OBS)	NR	-	OR 1.10 (0.85, 1.43)	≥ 0.1 (NR)
Sertraline								
Wang 2015	Cardiac malformations	Sertraline	Unexposed – any	3 (cohort)	NR	OR 1.00 (0.81, 1.20)	-	0.17 (43%)
McDonagh 2014	Cardiac malformations	Sertraline	Unexposed – any	7 (OBS)	NR	OR 1.08 (0.70, 1.65)	-	NR (68%)
McDonagh 2014	Cardiac malformations	Sertraline	Fluoxetine or paroxetine – condition	8 (OBS)	NR	-	OR 0.59 (0.38, 0.93)	NR (42%)
Fluoxetine								
Wang 2015	Cardiac malformations	Fluoxetine	Unexposed – any	3 (cohort)	NR	OR 1.11 (0.87, 1.35)	-	0.76 (0%)
McDonagh 2014	Cardiac malformations	Fluoxetine	Unexposed – any	8 (OBS)	NR	OR 1.31 (1.08, 1.58)	-	NR (0%)
Grigoriadis 2013a	Cardiac malformations	Fluoxetine	Unexposed (± ADs) – any	4 ⁴⁰ (OBS)	1,583,857	RR 1.17 (0.89, 1.55)	-	0.42 (0%)
Citalopram								
Wang 2015	Cardiac malformations	Citalopram	Unexposed – any	3 (cohort)	NR	OR 0.86 (0.56, 1.16)	-	0.44 (0%)
McDonagh 2014	Cardiac malformations	Citalopram/ escitalopram	Unexposed – any	6 (OBS)	NR	OR 1.05 (0.84, 1.39)	-	NR (5%)
McDonagh 2014	Cardiac malformations	Citalopram/ escitalopram	Fluoxetine or paroxetine – condition	8 (OBS)	NR	-	OR 0.94 (0.60, 1.47)	NR (49%)
TCAs								
McDonagh 2014	Cardiac malformations	TCAs	Unexposed – any	2 (OBS)	NR	OR 1.58 (1.10, 2.29)	-	NR

³²³ Includes higher quality studies only (scored ≥ 4/6 in the quality assessment).

³²⁴ Controlled for at least one of the potential confounders of interest: (i) tobacco, alcohol or illicit drug use, (ii) maternal age and (iii) maternal parity.

³²⁵ Adjusted for at least one of the nine potential confounders identified a priori as being important: parity, maternal age, use of tobacco and/or alcohol, pregnancy outcome history, other diagnoses, family history of defects, body mass index, vitamin use and use of other medications.

³²⁶ May include some adjusted results.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Bupropion								
McDonagh 2014	Cardiac malformations	Bupropion	Unexposed – any	1 (CC)	12,749	OR 1.4 (0.8, 2.5)	-	NA
McDonagh 2014	Cardiac malformations	Bupropion	Other ADs – any	1 (CC)	7,005	OR 0.95 (0.62, 1.45)	-	NA
Myles 2013	Cardiac malformations	SSRIs	Unexposed – any	25 (OBS)	NR	OR 1.17 (1.01, 1.34) ³²⁷	-	0.07 (31%)

Abbreviations: AD, antidepressant; AR, absolute risk; CC, case control; CI, confidence interval; NA, not applicable; ND, no difference; NR, not reported; OR, odds ratio; RE, risk estimate; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

AppD4.1.1.4.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and major malformations is presented in **Table AppD4-6**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of cardiac malformations in the depressed/unexposed population (0.6% based on weighted pooled estimates from Petersen 2016, Ban 2014a, Huybrechts 2014a and Margulis 2013), it is assumed that ORs closely approximate the RRs, and these risk estimates have been pooled together to calculate a single relative effect estimate.

Table AppD4-6 Antidepressants – cardiac malformations outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Any ADs						
Huybrechts 2014a	Cardiac malformation	Any AD (first trimester)	Unexposed – depression	1 (cohort)	NR	OR 1.02 (0.90, 1.15)
SSRIs						
Petersen 2016 ³²⁸	Congenital heart anomalies	SSRIs (first trimester)	Unexposed – halted treatment	1 (cohort)	7,930	OR 0.82 (0.48, 1.38)
Furu 2015 <i>Moderate</i>	Cardiac birth defects	SSRIs/venlafaxine (first trimester)	Unexposed – sibling-controlled	1 (cohort)	991	OR 0.92 (0.72, 1.17)
Bérard 2015 <i>Moderate</i>	Cardiac malformations	Non-sertraline SSRIs (first trimester)	Unexposed – depression/anxiety	1 (cohort)	16,831	RR 1.10 (0.82, 1.48)
Ban 2014a <i>Moderate</i>	Cardiac anomalies	SSRIs (first trimester)	Unexposed – depression	1 (cohort)	31,516	OR 1.04 (0.76, 1.41)
Ban 2014a	Cardiac anomalies	SSRIs & TCAs (first trimester)	Unexposed – depression	1 (cohort)	24,123	OR 0.78 (0.19, 3.27)
Huybrechts 2014a <i>Moderate</i>	Cardiac malformation	SSRIs (first trimester)	Unexposed – depression	1 (cohort)	217,342	OR 1.06 (0.93, 1.22)

³²⁷ Includes studies that controlled for tobacco, alcohol or illicit drug use.

³²⁸ Population overlaps with that of Ban 2014. Will be included separately.

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Margulis 2013 <i>Moderate</i>	Cardiac malformations (all patent ductus arteriosus included) ³²⁹	SSRIs (first trimester)	Unexposed – matched for mental health conditions	1 (cohort)	12,037	OR 1.00 (0.50, 2.00)
Margulis 2013	Cardiac malformations (surgical patent ductus arteriosus included only)	SSRIs (first trimester)	Unexposed – matched for mental health conditions	1 (cohort)	12,037	OR 0.86 (0.40, 1.85)
Oberlander 2008a <i>High</i>	Cardiovascular congenital defects	SRI ³³⁰ (first trimester)	Unexposed – adjusted for depression	1 (cohort)	109,945	RD 0.0021 (–0.0014, 0.0056) ³³¹
Oberlander 2008a <i>High</i>	Cardiovascular congenital defects	SRI ³³⁰ + benzodiazepines (first trimester)	Unexposed – adjusted for depression	1 (cohort)	109,945	RD 0.0118 (0.0018, 0.0218)
Petersen 2016 <i>Moderate</i>	Congenital heart anomalies	SSRIs (first trimester)	Non-SSRI ADs	1 (cohort)	3,768	OR 1.48 (0.58, 3.73)
Paroxetine						
Ban 2014a <i>Moderate</i>	Cardiac anomalies	Paroxetine (first trimester)	Unexposed – depression	1 (cohort)	25,033	OR 1.67 (1.00, 2.80)
Huybrechts 2014a <i>Moderate</i>	Cardiac malformation	Paroxetine (first trimester)	Unexposed – depression	1 (cohort)	189,312	OR 0.94 (0.73, 1.21)
Oberlander 2008a <i>High</i>	Cardiovascular congenital defects	Paroxetine	Unexposed – adjusted for depression	1 (cohort)	108,313	RD 0.0012 (–0.0038, 0.0062) ³³¹
Cole 2007b <i>Moderate</i>	Cardiovascular malformations	Paroxetine monotherapy (first trimester)	Other ADs monotherapy (first trimester)	1 (cohort)	5,013	OR 1.46 (0.74, 2.88)
Cole 2007b <i>Moderate</i>	Cardiovascular malformations	Paroxetine mono- or polytherapy	Other ADs mono- or polytherapy	1 (cohort)	5,956	OR 1.68 (0.95, 2.97)
Fluoxetine						
Ban 2014a <i>Moderate</i>	Cardiac anomalies	Fluoxetine (first trimester)	Unexposed – depression	1 (cohort)	27,022	OR 0.79 (0.49, 1.26)
Huybrechts 2014a <i>Moderate</i>	Cardiac malformation	Fluoxetine (first trimester)	Unexposed – depression	1 (cohort)	189,227	OR 1.14 (0.90, 1.44)
Oberlander 2008a <i>Moderate</i>	Cardiovascular congenital defects	Fluoxetine	Unexposed – adjusted for depression	1 (cohort)	107,958	RD 0.0008 (–0.0054, 0.0070) ³³¹
Sertraline						
Bérard 2015 <i>Moderate</i>	Cardiac malformations	Sertraline (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	15,234	RR 1.16 (0.62, 2.19)
Ban 2014a <i>Moderate</i>	Cardiac anomalies	Sertraline (first trimester)	Unexposed – depression	1 (cohort)	24,590	OR 1.39 (0.70, 2.74)
Huybrechts 2014a <i>Moderate</i>	Cardiac malformation	Sertraline (first trimester)	Unexposed – depression	1 (cohort)	191,620	OR 1.09 (0.88, 1.34)
Oberlander 2008a <i>Moderate</i>	Cardiovascular congenital defects	Sertraline	Unexposed – adjusted for depression	1 (cohort)	107,928	RD –0.0009 (–0.0065, 0.0047) ³³¹
Citalopram						
Ban 2014a <i>Moderate</i>	Cardiac anomalies	Citalopram (first trimester)	Unexposed – depression	1 (cohort)	25,779	OR 1.02 (0.61, 1.70)

³²⁹ Primary definition.³³⁰ Includes SSRIs or venlafaxine.³³¹ Risk differences reported as percentages in Oberlander 2008. Recalculated as proportions for the purpose of graphing results for this review.

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Oberlander 2008a	Cardiovascular congenital defects	Citalopram	Unexposed – adjusted for depression	1 (cohort)	107,421	RD 0.0228 (0.0019, 0.0436) ³³¹
Escitalopram						
Ban 2014a <i>Moderate</i>	Cardiac anomalies	Escitalopram (first trimester)	Unexposed – depression	1 (cohort)	24,166	OR 1.09 (0.34, 3.50)
Fluvoxamine						
Oberlander 2008a <i>Moderate</i>	Cardiovascular congenital defects	Fluvoxamine	Unexposed – adjusted for depression	1 (cohort)	107,439	RD -0.0055 (-0.0145, 0.0036) ³³¹
Non-SSRIs						
Bérard 2015	Cardiac malformations	Non-SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,164	RR 0.91 (0.62, 1.34)
SNRIs						
Huybrechts 2014a <i>Moderate</i>	Cardiac malformation	SNRIs (first trimester)	Unexposed – depression	1 (cohort)	186,574	OR 1.20 (0.91, 1.57)
Venlafaxine						
Oberlander 2008a <i>Moderate</i>	Cardiovascular congenital defects	Venlafaxine	Unexposed – adjusted for depression	1 (cohort)	107,570	RD 0.0001 (-0.0077, 0.0079) ³³¹
TCAs						
Ban 2014a <i>Moderate</i>	Cardiac anomalies	TCAs (first trimester)	Unexposed – depression	1 (cohort)	26,261	OR 0.90 (0.54, 1.50)
Huybrechts 2014a <i>Moderate</i>	Cardiac malformation	TCAs (first trimester)	Unexposed – depression	1 (cohort)	183,876	OR 0.77 (0.52, 1.14)
Simon 2002 <i>Moderate</i>	Major congenital malformations	TCAs (any time)	Unexposed – matched	1 (cohort)	418	OR 0.50 (0.05, 5.53)
Bupropion						
Huybrechts 2014a <i>Moderate</i>	Cardiac malformation	Bupropion (first trimester)	Unexposed – depression	1 (cohort)	187,254	OR 0.92 (0.69, 1.22)
Cole 2007a <i>Moderate</i>	Cardiovascular malformations	Other ADs monotherapy (first trimester)	Bupropion monotherapy (first trimester)	1 (cohort)	5,381	OR 0.54 (0.19, 1.51) ³³²
Other ADs³³³						
Huybrechts 2014a	Cardiac malformation	Other ADs (first trimester)	Unexposed – depression	1 (cohort)	186,585	OR 1.21 (0.91, 1.60)

Abbreviations: AD, antidepressant; CI, confidence interval; OR, odds ratio; RD, risk difference; RE, risk estimate; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Figure AppD4-10 summarises the findings of the association between SSRI use and cardiac malformations. Based on the results of five cohort studies, there was no significant association with cardiac malformation (RR 1.04; 95% CI 0.94, 1.15). One of the included studies (Furu 2015) included both SSRIs and venlafaxine.

Margulis 2013, used two different definitions of cardiac malformations: one that included all codes for patent ductus arteriosus (included in the meta-analysis), and one that included only surgical codes for patent ductus arteriosus. Exclusion of non-surgical codes for patent ductus arteriosus did not appreciably change the findings of the study, although the result is imprecise (OR 0.86; 95% CI 0.40, 1.85).

Petersen 2016 included a population that overlapped with those included in the study by Ban 2014a, and hence was not included in the meta-analysis. Limiting the comparator population to those who halted SSRI

³³² In the analysis, bupropion is used as the reference group.

³³³ Includes mirtazapine, nefazodone, selegiline and trazodone.

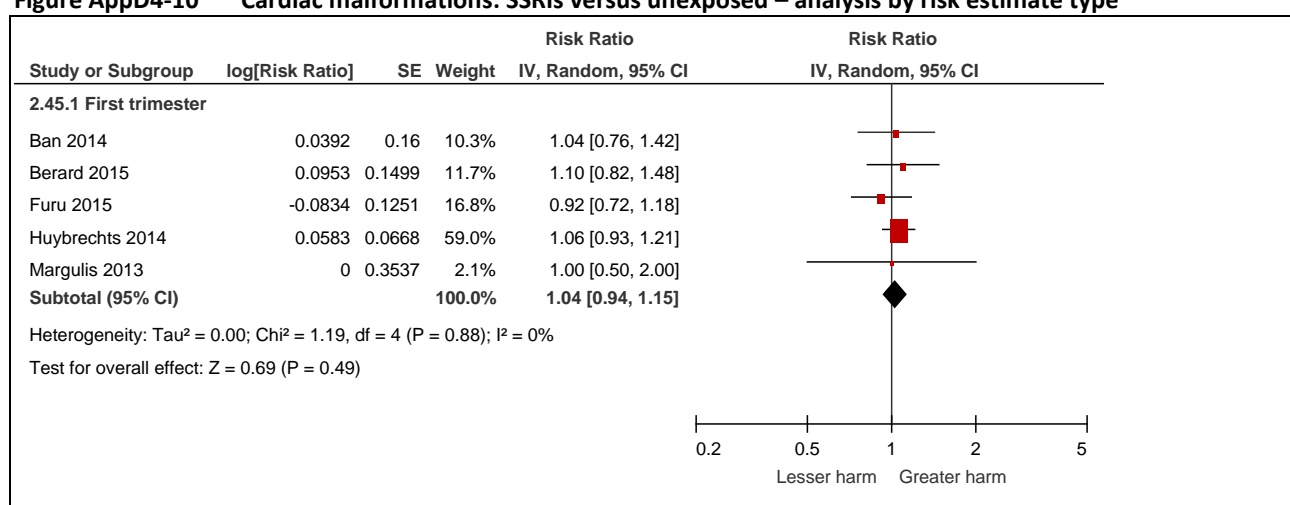
treatment during pregnancy also showed no significant association between first-trimester SSRIs and cardiac malformations (OR 0.82; 95% CI 0.48, 1.38).

Oberlander examined the *absolute risk* of cardiac malformation associated with first-trimester exposure to SRIs (SSRIs or venlafaxine) and also showed no significantly increased risk (RD 0.0012; 95% CI -0.0038, 0.0062). However, when they considered SRIs and benzodiazepines (i.e. dual exposure) there was a significant, but small, increased risk (RD 0.0118; 95% CI 0.0018, 0.0218).

Ban 2014a also examined the association between first-trimester SSRI and TCA use and risk of cardiac malformation and showed no significantly increased risk (OR 0.78; 95% CI 0.19, 3.27), although this finding was also considered imprecise.

Finally, Petersen 2016 compared the risk of exposure to first-trimester SSRIs with exposure to non-SSRI antidepressants and showed no significant association (OR 1.48; 95% CI 0.58, 3.73); this analysis was also considered imprecise.

Figure AppD4-10 Cardiac malformations: SSRIs versus unexposed – analysis by risk estimate type



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: Furu 2015 includes SSRIs and venlafaxine and Bérard 2015 includes non-sertraline SSRIs only. The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

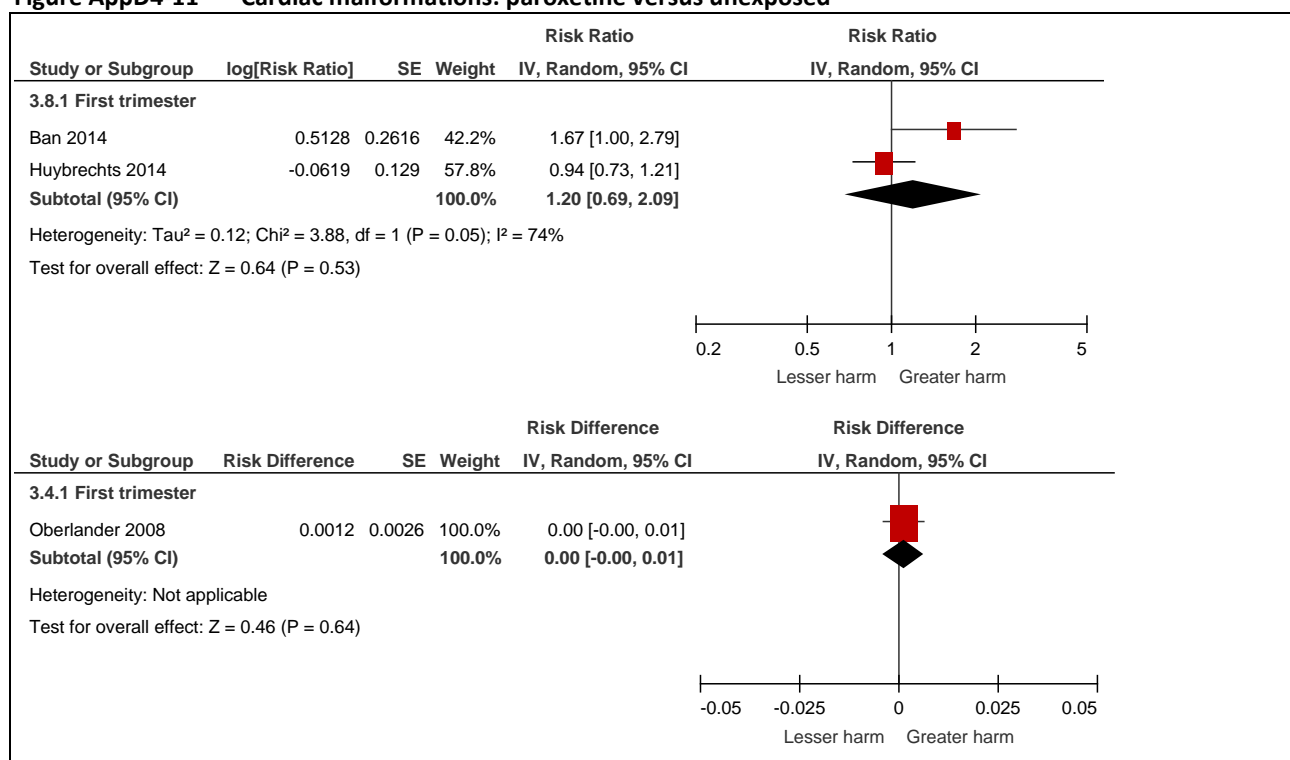
Figure AppD4-11 summarises the findings of the association between paroxetine use and cardiac malformations. Based on the results of two cohort studies there was no association between use in first trimester and cardiac malformation (OR 1.20; 95% CI 0.69, 2.09); however, this analysis was subject to substantial heterogeneity and was considered imprecise due to the 95% CI including the measures of appreciable benefit and harm.³³⁴

Oberlander 2008a examined the *absolute risk* of cardiac malformation following first-trimester exposure to paroxetine and showed no significantly increased risk (RD 0.0012; 95% CI -0.0038, 0.0062).

Cole 2007b assessed the risk of cardiac malformation following paroxetine monotherapy, or paroxetine mono/polytherapy, compared with other antidepressant monotherapy, or other antidepressant mono/polytherapy, respectively, and found no significant increased risks associated with paroxetine use (OR 1.46; 95% CI 0.74, 2.88; OR 1.68; 95% CI 0.95, 2.97). However, both results are considered imprecise because the 95% CI includes a measure of appreciable benefit or harm.³³⁵

³³⁴ Because the prevalence of cardiac malformation is low (<1% in the Petersen 2016, Ban 2014a and Huybrechts 2014a studies, and < 2% in the Furu 2015 study), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

³³⁵ Because the prevalence of cardiac malformation is low (0.6%), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-11 Cardiac malformations: paroxetine versus unexposed

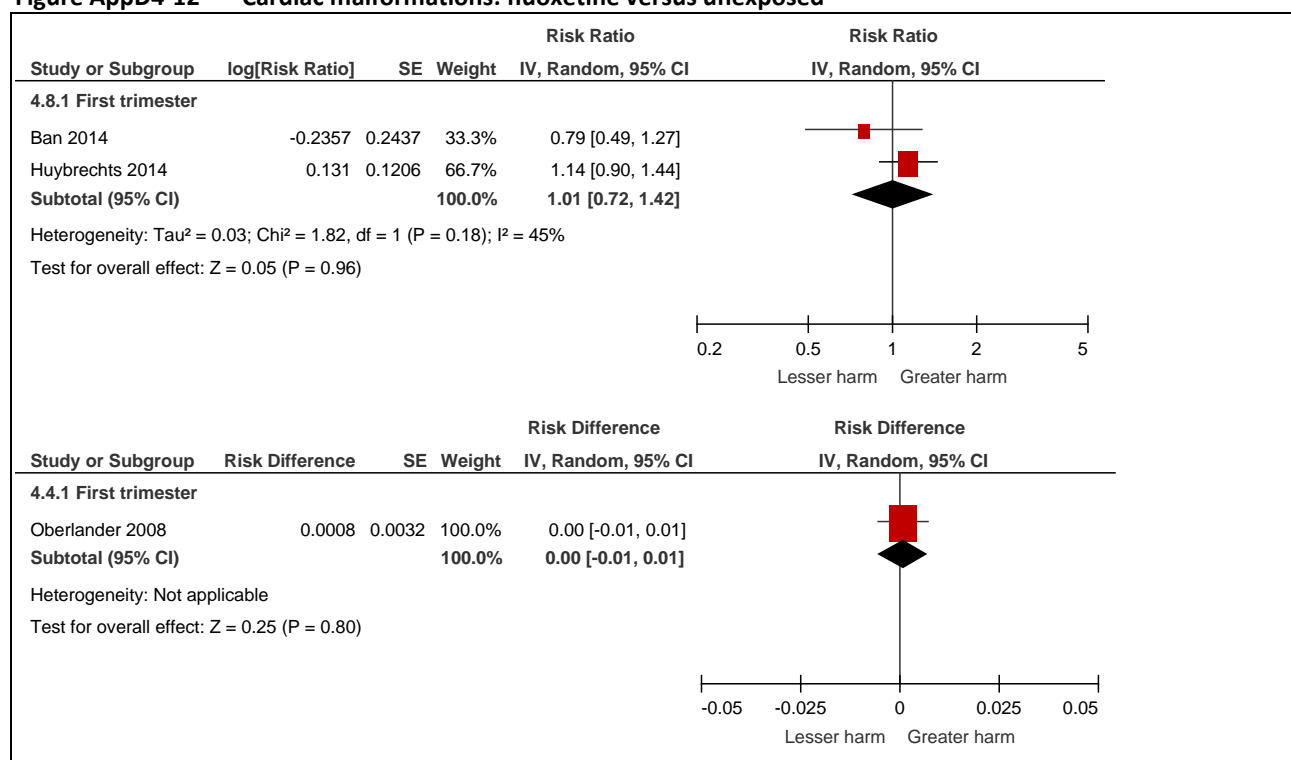
Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-12 summarises the findings of the association between fluoxetine use and cardiac malformations. Based on the results of two cohort studies there was no increased risk associated with fluoxetine use in first trimester and cardiac malformation (RR 1.01; 95% CI 0.72, 1.42); however, this analysis was subject to moderate heterogeneity and is considered imprecise because the 95% CI included measures of appreciable benefit and risk.³³⁶

Oberlander 2008a assessed the absolute risk of cardiac malformation following first-trimester exposure to fluoxetine and also showed no significantly increased risk (RD 0.0008; 95% CI -0.0054, 0.0070).

³³⁶ Because the prevalence of cardiac malformation is low (0.6%), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-12 Cardiac malformations: fluoxetine versus unexposed

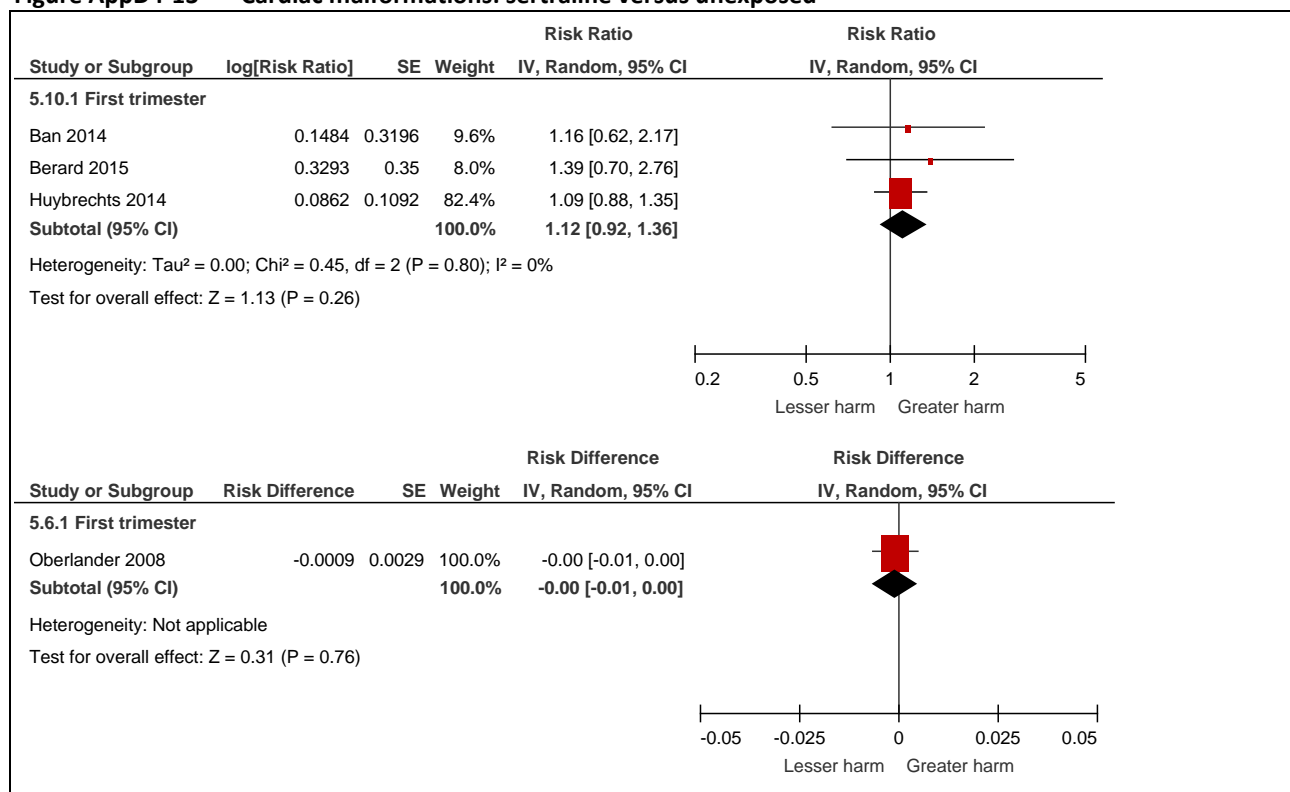
Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-13 summarises the findings of the association between sertraline use and cardiac malformations. Based on the pooled results of three cohort studies there was no significant association with cardiac malformations of first-trimester use of sertraline (OR 1.12; 95% CI 0.92, 1.36). However, this finding is considered imprecise given the 95% CI includes measures of both appreciable benefit and harm.³³⁷

Oberlander 2008a assessed the *absolute risk* of cardiac malformation associated with the first-trimester use of sertraline and found no significantly increased risk (RD -0.0009; 95% CI -0.0065, 0.0047).

³³⁷ Because the prevalence of cardiac malformation is low (<1% in the Petersen 2016, Ban 2014a and Huybrechts 2014a studies, and < 2% in the Furu 2015 study), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-13 Cardiac malformations: sertraline versus unexposed

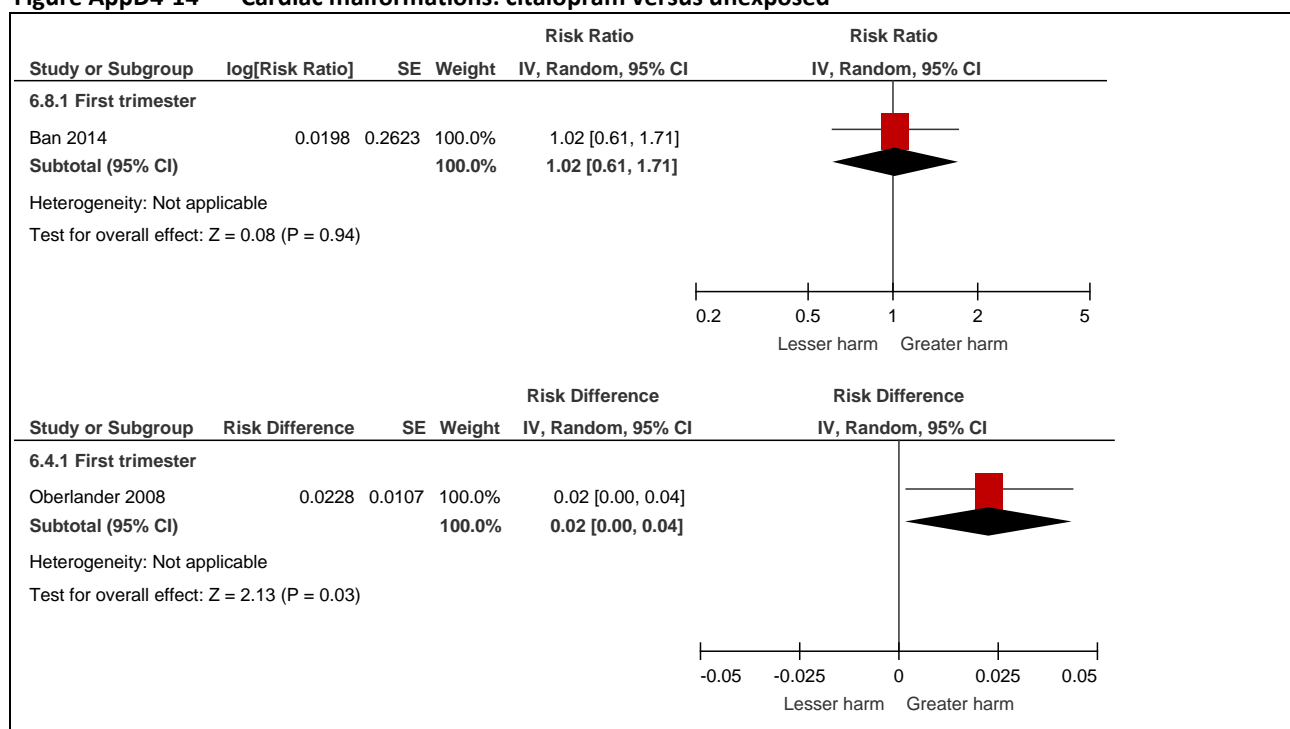
Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Ban 2014a examined the association between citalopram use and cardiac malformations. Based on the result of this cohort study there was significant association (RR 1.02; 0.61, 1.71; **Figure AppD4-14**). This finding is considered imprecise because the 95% CI includes a measure of appreciable benefit and harm.³³⁸

Oberlander 2008a found a statistically significant increase in absolute risk of cardiac malformations following first-trimester exposure to citalopram (RD 0.0228; 95% CI 0.0019, 0.0436).

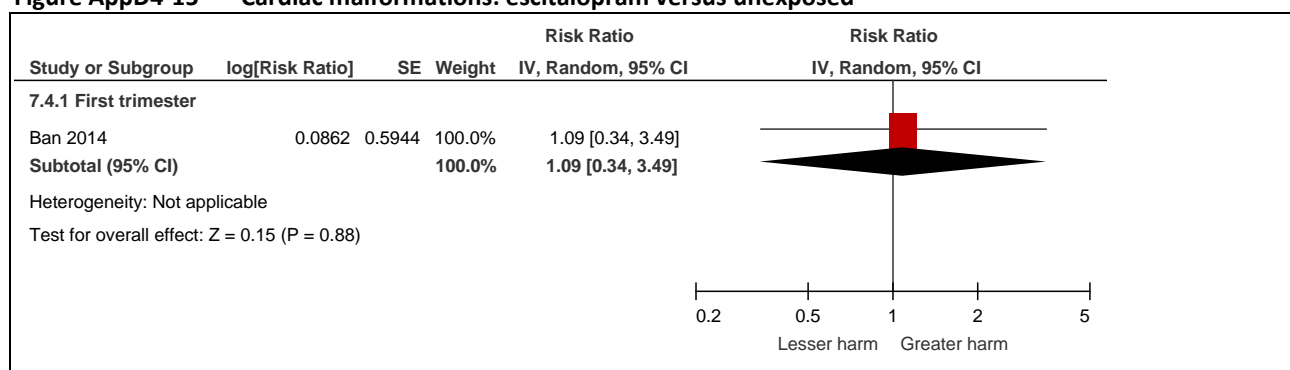
³³⁸ Because the prevalence of cardiac malformation is low (0.6%), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-14 Cardiac malformations: citalopram versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Ban 2014a also examined the association between escitalopram use and cardiac malformations. Based on the result of this cohort study there was no significant association (RR 1.09; 95% CI 0.34, 3.50; **Figure AppD4-15**); however, this finding is considered imprecise because the 95% CI includes measures of both appreciable benefit and harm.³³⁹

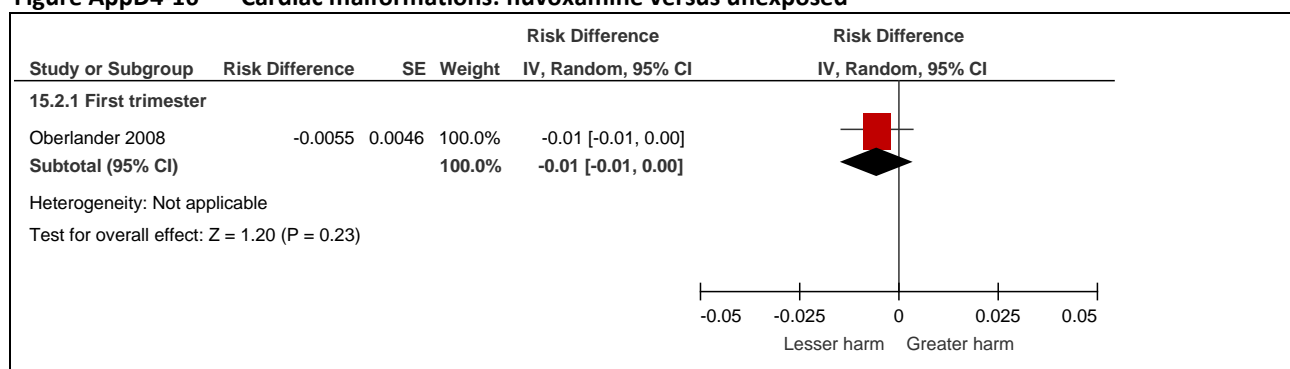
Figure AppD4-15 Cardiac malformations: escitalopram versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Oberlander 2008a examined the association between the *absolute risk* of first-trimester exposure to fluvoxamine and cardiac malformations and found no significantly increased absolute risk (RD -0.0055; 95% CI -0.0145, 0.0036), as shown in **Figure AppD4-16**.

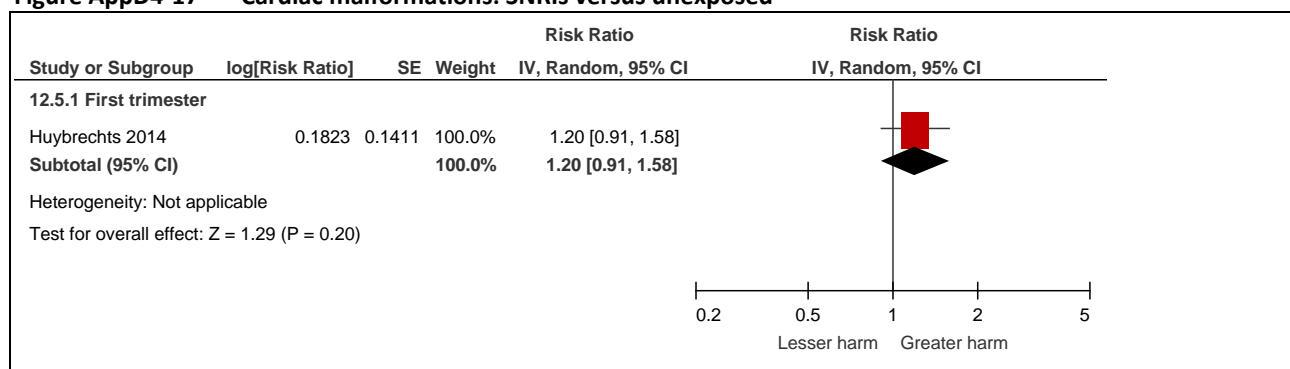
³³⁹ Because the prevalence of cardiac malformation is low (0.6%), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-16 Cardiac malformations: fluvoxamine versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

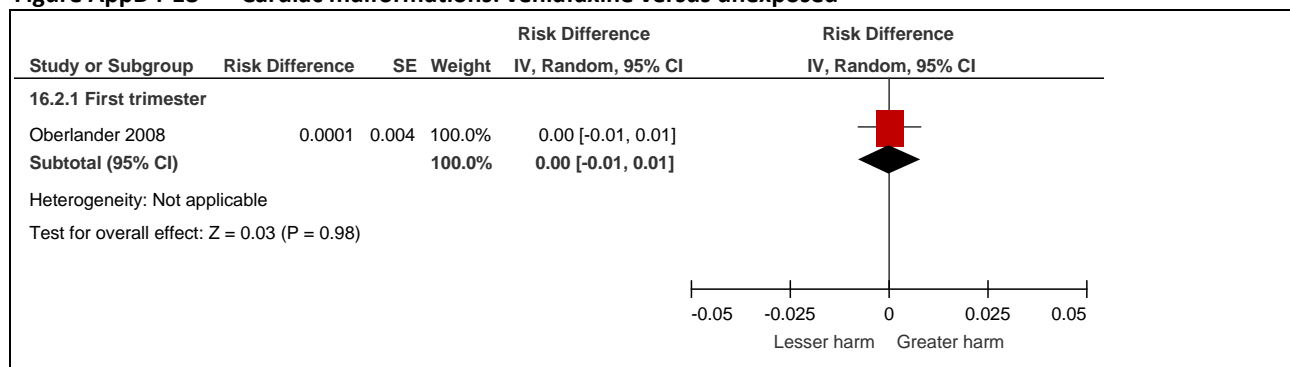
Huybrechts 2014a examined the association between SNRIs and cardiac malformations. Based on the result of this cohort study there was no significant association between use in first trimester and cardiac malformation (OR 1.20; 95% CI 0.91, 1.58; **Figure AppD4-17**); however, this finding is considered imprecise because the 95% CI includes measures of both appreciable benefit and harm.³⁴⁰

Figure AppD4-17 Cardiac malformations: SNRIs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

The absolute risk of cardiac malformation associated with first-trimester exposure to venlafaxine was examined by Oberlander 2008a, who found no increase in risk (RD 0.0001; 95% CI -0.0077, 0.0079; **Figure AppD4-18**).

Figure AppD4-18 Cardiac malformations: venlafaxine versus unexposed

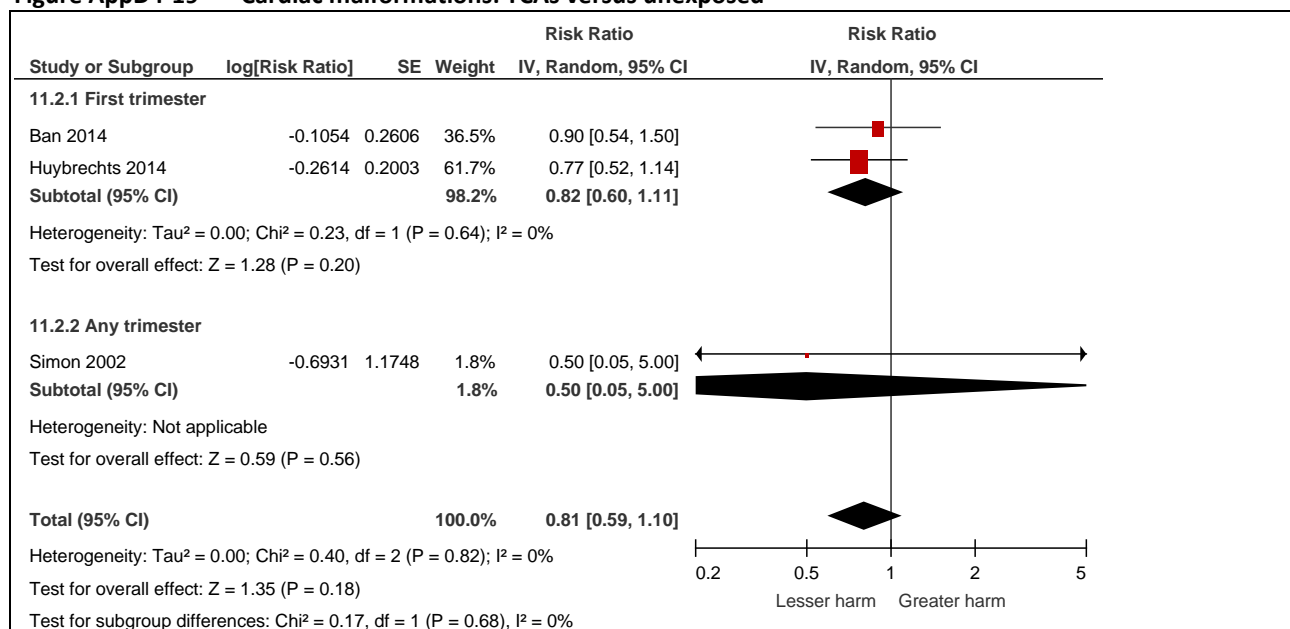
Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

³⁴⁰ Because the prevalence of cardiac malformation is low (0.6%), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-19 summarises the findings of the association between TCAs and cardiac malformations. Based on the pooled results of two cohort studies there was no association between use in first trimester and cardiac malformation (RR 0.82; 95% CI 0.60, 1.11). Expanding this pooled analysis to include a study that examined TCA use in any trimester did not change the result (RR 0.81; 95% 0.59, 1.10). This finding is considered imprecise because the 95% CI includes a measure of appreciable benefit or harm.³⁴¹

Figure AppD4-19 Cardiac malformations: TCAs versus unexposed

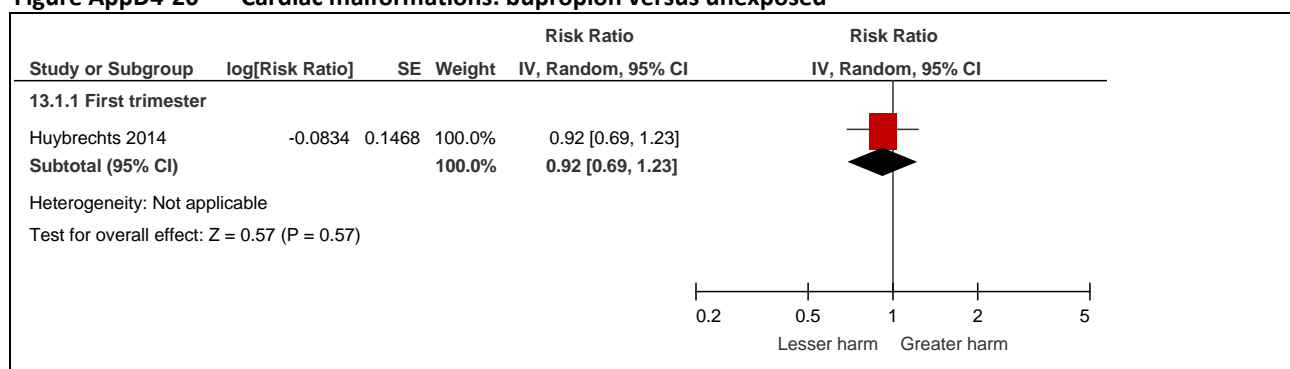


As shown in **Figure AppD4-20**, Huybrechts 2014a examined the association between bupropion and cardiac malformations. Based on the result of this cohort study there was no significant risk associated with first-trimester exposure to bupropion and cardiac malformation (RR 0.92; 95% CI 0.69, 1.22). This finding is considered imprecise because the 95% CI includes a measure of appreciable benefit or harm.³⁴²

Cole 2007a assessed the risk of cardiac malformation following other antidepressants compared with use of bupropion in first trimester and found no significant increased risks associated with bupropion use (OR 0.54; 95% CI 0.19, 1.51). However, this finding is also considered imprecise because the 95% CI includes a measure of appreciable benefit and harm.

³⁴¹ Because the prevalence of cardiac malformation is low (0.6%), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

³⁴² Because the prevalence of cardiac malformation is low (0.6%), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-20 Cardiac malformations: bupropion versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; TCA, tricyclic antidepressant.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.1.5 Septal malformations – antidepressants

AppD4.1.1.5.1 Results based on systematic reviews

The results of the analyses of the association between antidepressants and septal cardiac malformations presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-7**, grouped by antidepressant type. Only one study provided data for this outcome, and one analysis based on adjusted data suggested a statistically significant association between any antidepressants and cardiac septal malformations. However, as for the previous malformation outcomes, this analysis used a comparator population not limited to women with depression or another psychiatric condition, suggesting that there may still be substantial underlying confounding. *As such, these findings have not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-7 Antidepressants – septal cardiac malformation outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any ADs								
Grigoriadis 2013a	Septal malformations	Any ADs	Unexposed (± ADs) – any	7 ³⁴³ (OBS)	1,608,759	RR 1.35 (1.08, 1.68)	-	0.11 (43%)
Paroxetine								
Grigoriadis 2013a	Septal malformations	Paroxetine	Unexposed (± ADs) – any	3 ³⁴³ (OBS)	226,272	RR 0.97 (0.47, 2.03)	-	0.67 (0%)
Fluoxetine								
Grigoriadis 2013a	Septal malformations	Fluoxetine	Unexposed (± ADs) – any	2 ³⁴³ (OBS)	224,937	RR 1.18 (0.65, 2.14)	-	0.46 (0%)

Abbreviations: AD, antidepressant; CI, confidence interval; OBS, observational studies (type not specified); RE, risk estimate; RR, relative risk.

AppD4.1.1.5.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and septal malformations is presented in **Table AppD4-8**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

³⁴³ Includes studies above quality threshold only.

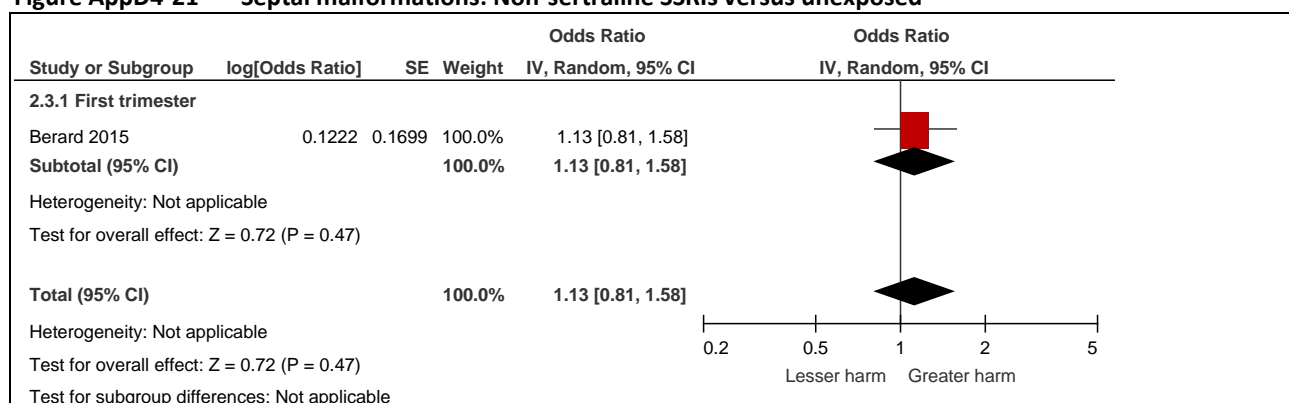
Table AppD4-8 Antidepressants – septal malformations outcomes from observational studies

Study ID	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Non-sertraline SSRIs						
Bérard 2015 <i>Moderate</i>	Ventricular/atrial septal defects	Non-sertraline SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,831	RR 1.13 (0.81, 1.58)
Sertraline						
Bérard 2015 <i>Moderate</i>	Ventricular/atrial septal defects	Sertraline (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	15,234	RR 1.34 (1.02, 1.76)
Non-SSRIs						
Bérard 2015 <i>Moderate</i>	Ventricular/atrial septal defects	Non-SSRIs (first trimester)	Unexposed – depression/ anxiety	1 (cohort)	16,164	RR 0.91 (0.59, 1.42)

Abbreviations: CI, confidence interval; RE, risk estimate; RR, relative risk; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

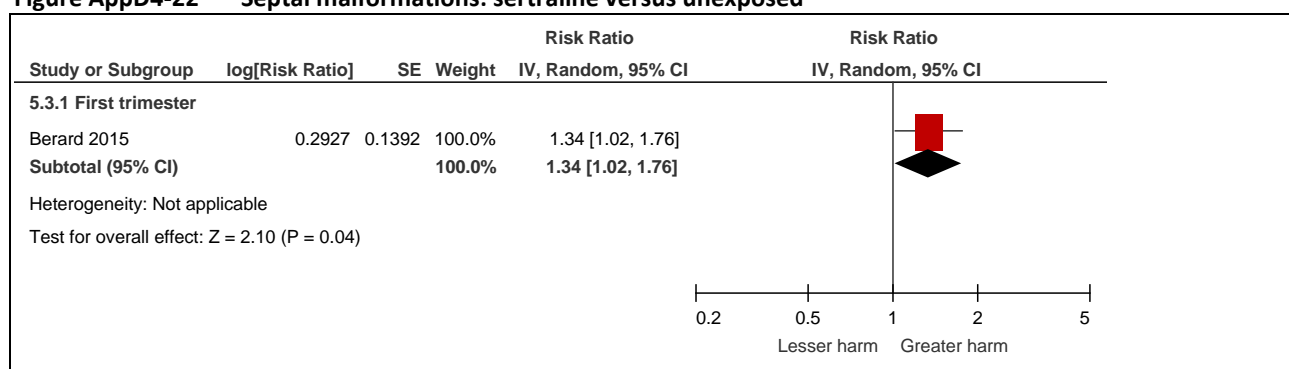
As shown in **Figure AppD4-21**, Bérard 2015 examined the association between non-sertraline SSRIs and septal malformations. Based on the result of this cohort study there was increased risk of septal malformations associated with first-trimester exposure to non-sertraline SSRIs (RR 1.13; 95% CI 0.81, 1.58). This finding is imprecise because the 95% CI includes a measure of appreciable benefit or harm (RR 0.75/1.25).

Figure AppD4-21 Septal malformations: Non-sertraline SSRIs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; TCA, tricyclic antidepressant.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Bérard 2015 examined the association between sertraline use and septal malformations and found there was a significantly significant risk of septal malformations following first-trimester exposure to sertraline (RR 1.34; 95% CI 1.02, 1.76; **Figure AppD4-22**).

Figure AppD4-22 Septal malformations: sertraline versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; TCA, tricyclic antidepressant.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.1.6 Neonatal mortality – antidepressants**AppD4.1.1.6.1 Results based on systematic reviews**

The results of the analyses of the association between antidepressants and neonatal mortality presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-9**. Only one SR reporting on one cohort study provided data for this outcome, and one analysis based on adjusted data suggested no statistically significant association between either early or late exposure to SNRIs. As for previous outcomes, this analysis used a comparator population not limited to women with depression or another psychiatric condition, so there may be substantial underlying confounding. *As such, these findings have not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-9 Antidepressants – neonatal mortality outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
SNRIs								
McDonagh 2014	neonatal mortality (early exposure) ³⁴⁴	SNRIs	Unexposed - any	1 (cohort)	NR	RR 1.3 (0.5, 2.8)	-	NA
McDonagh 2014	Neonatal mortality (late exposure) ³⁴⁵	SNRIs	Unexposed – any	1 (cohort)	NR	RR 0.00 (0.0, 4.4)	-	NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RE, risk estimate; SNRI, serotonin and noradrenaline reuptake inhibitor.

AppD4.1.1.6.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and neonatal mortality is presented in **Table AppD4-10**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Only results for antidepressants as a group, or other groupings of antidepressants, are presented in the table. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-10 Antidepressants – neonatal mortality outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
SSRIs						
Ban 2012 <i>High</i>	Perinatal death ³⁴⁶	SSRIs (first trimester)	Unexposed – unmedicated depression/anxiety	1 (cohort)	NR	RR 1.2 (0.6, 2.3)
TCAs						
Ban 2012 <i>High</i>	Perinatal death ³⁴⁶	TCAs (first trimester)	Unexposed – unmedicated depression/anxiety	1 (cohort)	NR	RR 1.2 (0.5, 2.7)
Stillbirth						
Djulus 2006	Stillbirth	Mirtazapine (any time)	Other ADs	1 (cohort)	208	P=0.50

Abbreviations: CI, confidence interval; NR, not reported; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

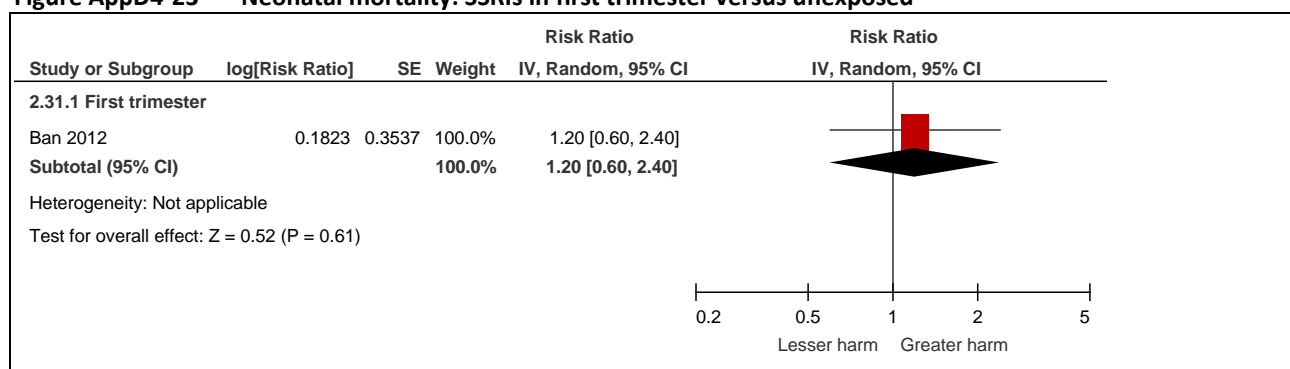
³⁴⁴ Maternal use of drug before first visit to the antenatal care.

³⁴⁵ Prescription of drug during later pregnancy.

³⁴⁶ Includes stillbirth and neonatal death up to 28 days.

Ban 2012 examined the association between first-trimester exposure to SSRIs and perinatal death and found no increased risk when the comparator population was limited to women with unmedicated depression/anxiety (RR 1.2; 95% CI 0.60, 2.3). This finding is considered imprecise because the 95% CI includes measures of appreciable benefit and harm (RR 0.75/1.25).

Figure AppD4-23 Neonatal mortality: SSRIs in first trimester versus unexposed

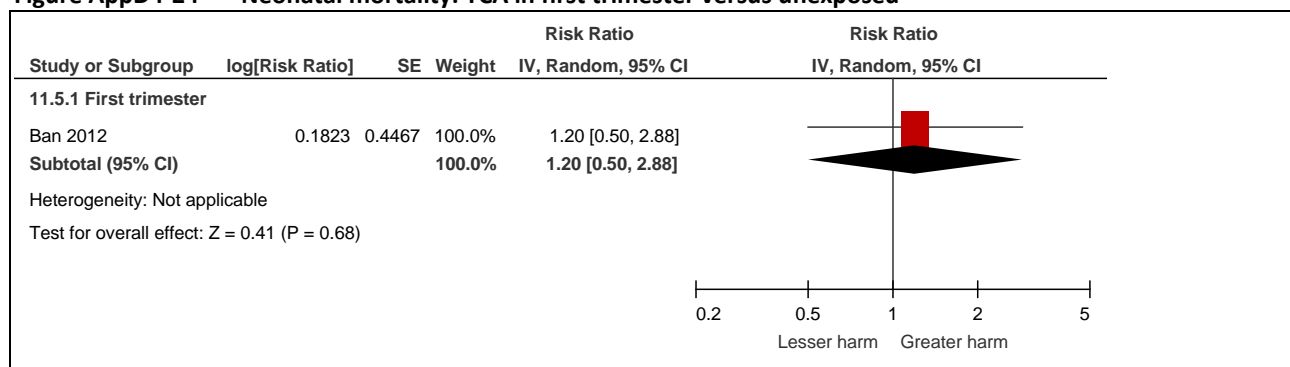


Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Ban 2012 also examined the association between first-trimester exposure to TCAs and perinatal death and found no increased risk when the comparator population was limited to women with unmedicated depression/anxiety (RR 1.2; 95% CI 0.50, 2.7). This finding is also considered imprecise because the 95% CI includes measures of appreciable benefit and harm (RR 0.75/1.25).

Figure AppD4-24 Neonatal mortality: TCA in first trimester versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; TCA, tricyclic antidepressant.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Djulus 2006 examined the risk of stillbirth following exposure to mirtazapine compared with other antidepressants and found no difference (P=0.50).

AppD4.1.1.7 Miscarriage – antidepressants

AppD4.1.1.7.1 Results based on systematic reviews

The results of the analyses of the association between antidepressants and miscarriage presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-11**. Only one SR (reporting two observational studies) provided data for this outcome, and suggested no association between any antidepressants and miscarriage. As for previous outcomes, this analysis used a comparator population not limited to women with depression or another psychiatric condition, so there may still be substantial underlying confounding. *As such, this finding has not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-11 Antidepressants – miscarriage outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any ADs								
Ross 2013	Miscarriage/ spontaneous abortion	Any ADs	Unexposed – any	2 ¹⁶¹ (OBS)	NR	OR 1.49 (0.71, 3.13)	-	0.16 (50%)

Abbreviations: AD, antidepressant; CI, confidence interval; NR, not reported; OBS, observational studies (type not specified); OR, odds ratio; RE, risk estimate.

AppD4.1.1.7.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and miscarriage is presented in **Table AppD4-12**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Based on the findings of the unexposed population in two of the included studies (Almeida 2016 and Ban 2012) the prevalence of miscarriage in the depressed population is estimated to be 8.1%. For this reason, ORs are not be assumed to approximate RRs and the results for studies that report ORs are presented separately.

Table AppD4-12 Antidepressants – miscarriage outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Any ADs						
Kjaersgaard 2013	Spontaneous abortion	Any ADs (any time)	Unexposed - depression	1 (cohort)	315	RR 1.00 (0.80, 1.24)
Kjaersgaard 2013	Spontaneous abortion	Any ADs (any time)	Unexposed – adjusted for history of severe mental disorder	1 (cohort)	113,119	RR 1.14 (1.10, 1.18)
Almeida 2016	Miscarriage	Any ADs (first trimester)	Unexposed - depression	1 (cohort)	10,376	RR 1.2 (1.0, 1.4)
SSRIs						
Almeida 2016 <i>Low</i>	Miscarriage	SSRI monotherapy (first trimester)	Unexposed - depression	1 (cohort)	9,815	RR 1.2 (0.94, 1.5)
Ban 2012 <i>Moderate</i>	Miscarriage	SSRIs (first trimester)	Unexposed – unmedicated depression/anxiety	1 (cohort)	NR	RR 1.4 (1.2, 1.7)
Nakhai-Pour 2010 ³⁴⁷ <i>Low</i>	Spontaneous abortion	SSRIs (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	5,001	OR 1.61 (1.28, 2.04)
Nakhai-Pour 2010	Spontaneous abortion	≥ 2 SSRIs (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,876	OR 2.47 (0.62, 9.83)
Paroxetine						
Nakhai-Pour 2010 <i>Low</i>	Spontaneous abortion	Paroxetine (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,924	OR 1.75 (1.31, 2.34)

³⁴⁷ Population overlaps with Almeida 2016.

³⁴⁸ Depression, anxiety and bipolar disorder, visits to psychiatrists, duration of exposure to antidepressants and other medications in the year before pregnancy

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Sertraline						
Nakhai-Pour 2010 <i>Low</i>	Spontaneous abortion	Sertraline (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,868	OR 1.33 (0.85, 2.08)
Fluoxetine						
Nakhai-Pour 2010 <i>Low</i>	Spontaneous abortion	Fluoxetine (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,862	OR 1.44 (0.86, 2.43)
Citalopram						
Nakhai-Pour 2010 <i>Low</i>	Spontaneous abortion	Citalopram (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,859	OR 1.55 (0.89, 2.68)
Fluvoxamine						
Nakhai-Pour 2010 <i>Low</i>	Spontaneous abortion	Fluvoxamine (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,845	OR 2.19 (0.79, 6.08)
SNRIs						
Almeida 2016 <i>Moderate</i>	Miscarriage	SNRI monotherapy (first trimester)	Unexposed - depression	1 (cohort)	9,014	RR 1.7 (1.2, 2.6)
Nakhai-Pour 2010 <i>Low</i> ³⁴⁹	Spontaneous abortion	SNRIs (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,873	OR 2.11 (1.34, 3.30)
Venlafaxine						
Nakhai-Pour 2010 <i>Low</i>	Spontaneous abortion	Venlafaxine (any time)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,873	OR 2.11 (1.34, 3.30)
Mirtazapine						
Djulus 2006 <i>Moderate</i>	Spontaneous abortion	Mirtazapine	Other ADs - condition	1 (cohort)	208	P=0.86
TCAs						
Almeida 2016 <i>Low</i>	Miscarriage	TCA monotherapy (first trimester)	Unexposed - depression	1 (cohort)	9,024	RR 1.5 (0.96, 2.2)
Ban 2012 <i>Moderate</i>	Miscarriage	TCAs (first trimester)	Unexposed – unmedicated depression/anxiety	1 (cohort)	NR	RR 1.3 (1.1, 1.5)
Nakhai-Pour 2010 ³⁵⁰ <i>Low</i>	Spontaneous abortion	TCAs (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,876	OR 1.27 (0.85, 1.91)
Other ADs³⁵¹						
Almeida 2016	Miscarriage	Other monotherapy (first trimester)	Unexposed - depression	1 (cohort)	8,966	RR 1.0 (0.53, 2.0)
Nakhai-Pour 2010	Spontaneous abortion	Other ADs ³⁵² (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,858	OR 1.53 (0.86, 2.72)
Polytherapy						
Almeida 2016	Miscarriage	Polytherapy	Unexposed - depression	1 (cohort)	9,065	RR 1.5 (0.99, 2.1)

³⁴⁹ Population overlaps with Almeida 2016.³⁵⁰ Population overlaps with Almeida 2016.³⁵¹ Included antidepressants not stated.³⁵² Includes serotonin modulators, monoamine oxidase inhibitors, tetracyclic piperazino-azepines, and dopamine and norepinephrine reuptake inhibitors.

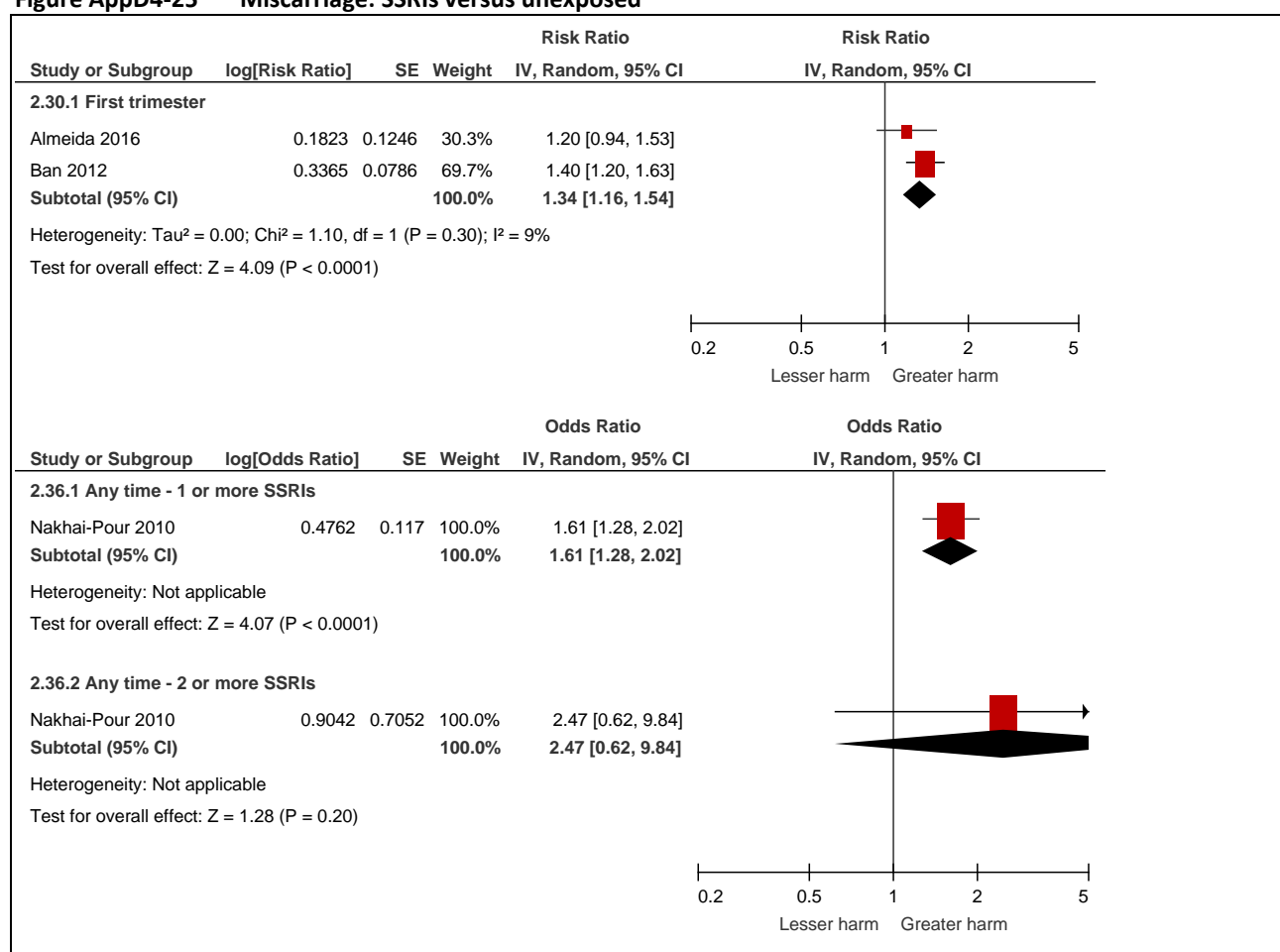
Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Nakhai-Pour 2010	Spontaneous abortion	≥ 2 AD classes (up to 20 weeks)	Unexposed – adjusted for multiple depression-related variables ³⁴⁸	1 (case control)	4,876	OR 3.51 (2.20, 5.61)

Abbreviations: AD, antidepressant; CI, confidence interval; RE, risk estimate; RR, relative risk; SNRI, serotonin-noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

As shown in **Figure AppD4-25**, three studies examined the association between SSRIs and miscarriage/spontaneous abortion. Two studies examined the association between first-trimester exposure to SSRIs and miscarriage in a population with depression/anxiety and found that exposure to SSRIs significantly increased the risk of miscarriage (RR 1.34; 95% CI 1.16, 1.54;). Nakhai-Pour 2010 examined the association between use of SSRIs at any time during pregnancy and spontaneous abortion in a general population adjusted for multiple depression-related variables and found a statistically significant association with use of one or more SSRIs, and no association with the use of two or more SSRIs, although this analysis was likely substantially underpowered.

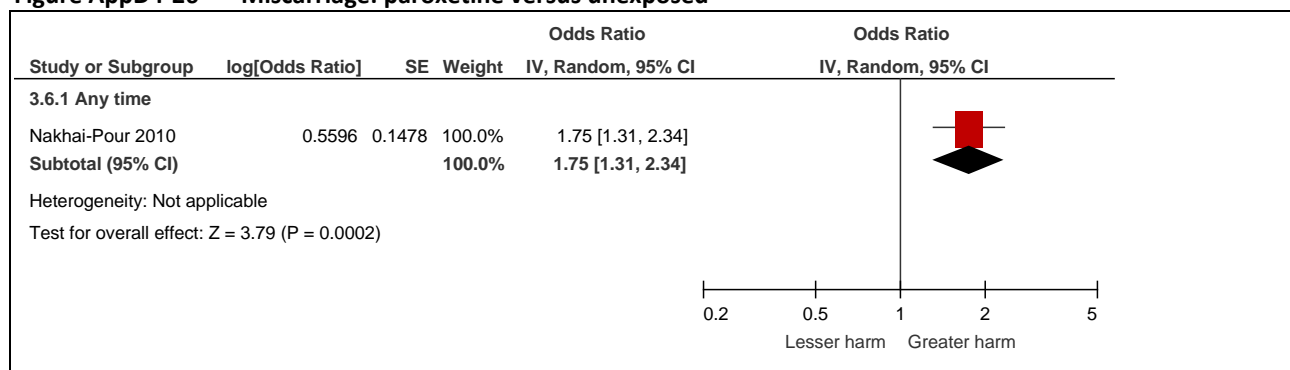
Figure AppD4-25 Miscarriage: SSRIs versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

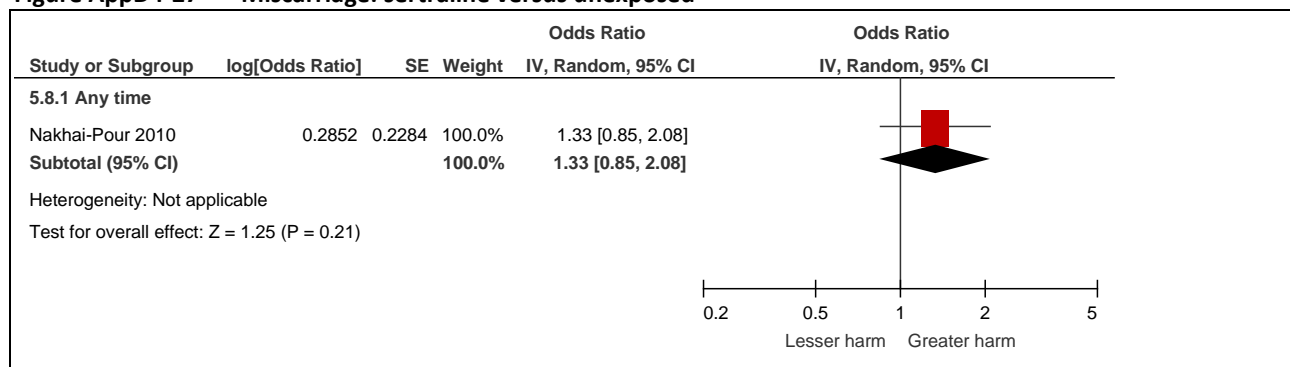
Nakhai-Pour 2010 examined the association between paroxetine at any time during pregnancy and miscarriage and found that exposure to paroxetine significantly increased the risk of miscarriage (OR 1.75; 95% CI 1.31, 2.34). The population in this study was not limited to those with depression, but instead adjusted for a number of depression variables.

Figure AppD4-26 Miscarriage: paroxetine versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

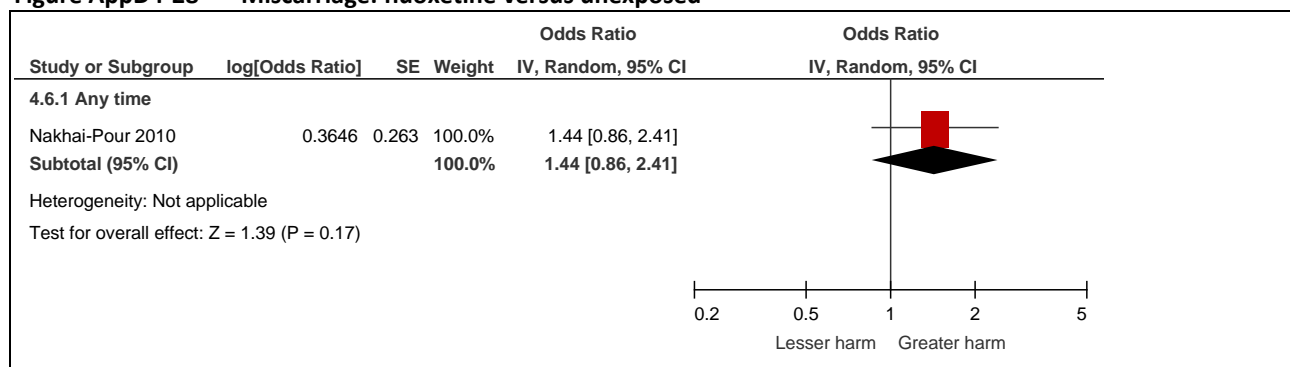
Nakhai-Pour 2010 examined the association between sertraline at any time during pregnancy and spontaneous abortion and found that exposure to sertraline was not significantly associated with miscarriage (OR 1.33; 95% CI 0.85, 2.08). The population in this study was not limited to those with depression, but instead adjusted for a number of depression variables.

Figure AppD4-27 Miscarriage: sertraline versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Nakhai-Pour 2010 examined the association between fluoxetine at any time during pregnancy and spontaneous abortion and found that exposure to fluoxetine was not significantly associated with miscarriage (OR 1.44; 95% CI 0.86, 2.43). The population in this study was not limited to those with depression, but instead adjusted for a number of depression variables.

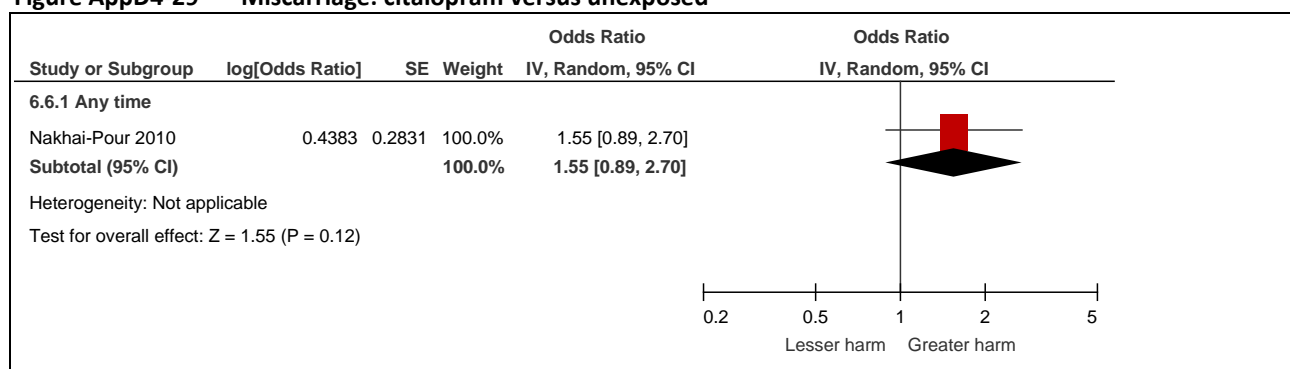
Figure AppD4-28 Miscarriage: fluoxetine versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Nakhai-Pour 2010 examined the association between citalopram at any time during pregnancy and spontaneous abortion and found that exposure to citalopram was not significantly associated with miscarriage (OR 1.55; 95% CI 0.89, 2.69). The population in this study was not limited to those with depression, but instead adjusted for a number of depression variables.

Figure AppD4-29 Miscarriage: citalopram versus unexposed

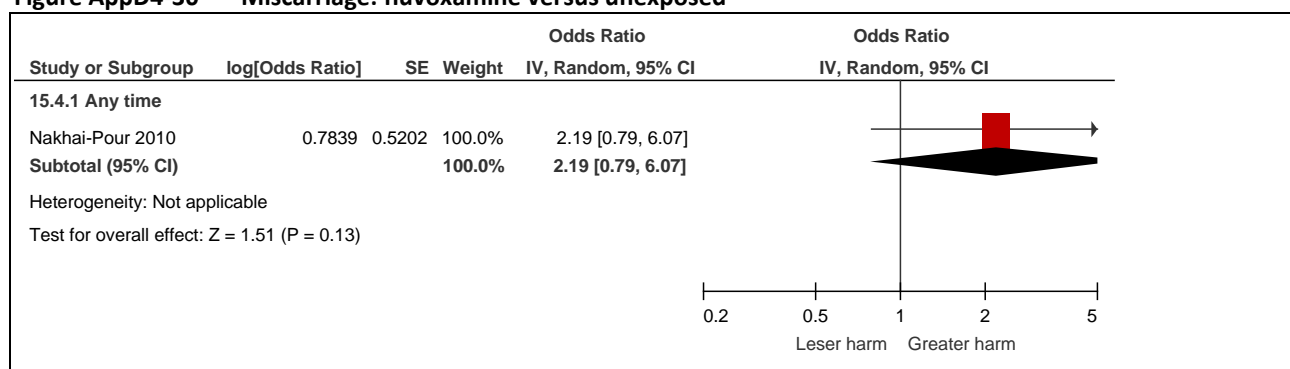


Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Nakhai-Pour 2010 examined the association between fluvoxamine at any time during pregnancy and spontaneous abortion and found that exposure to fluvoxamine was not significantly associated with miscarriage (OR 2.19; 95% CI 0.79, 6.08). The population in this study was not limited to those with depression, but instead adjusted for a number of depression variables.

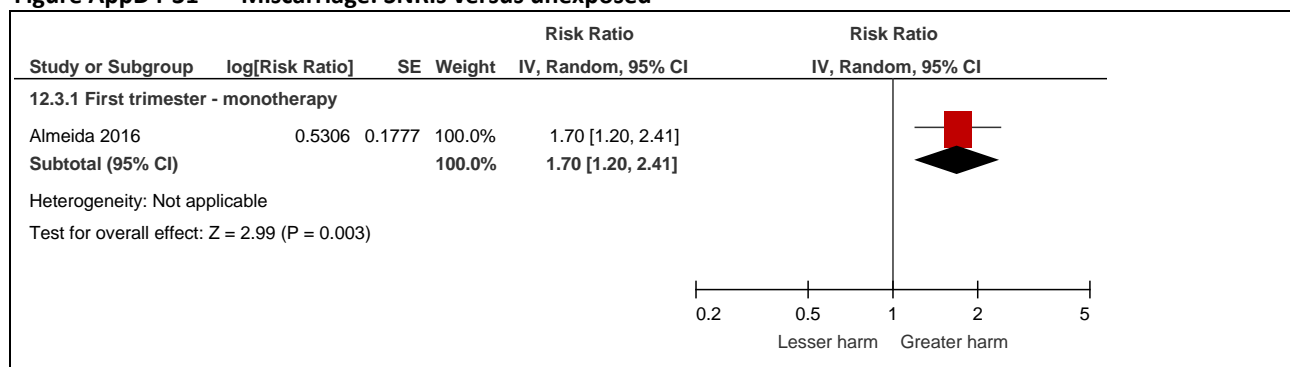
Figure AppD4-30 Miscarriage: fluvoxamine versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

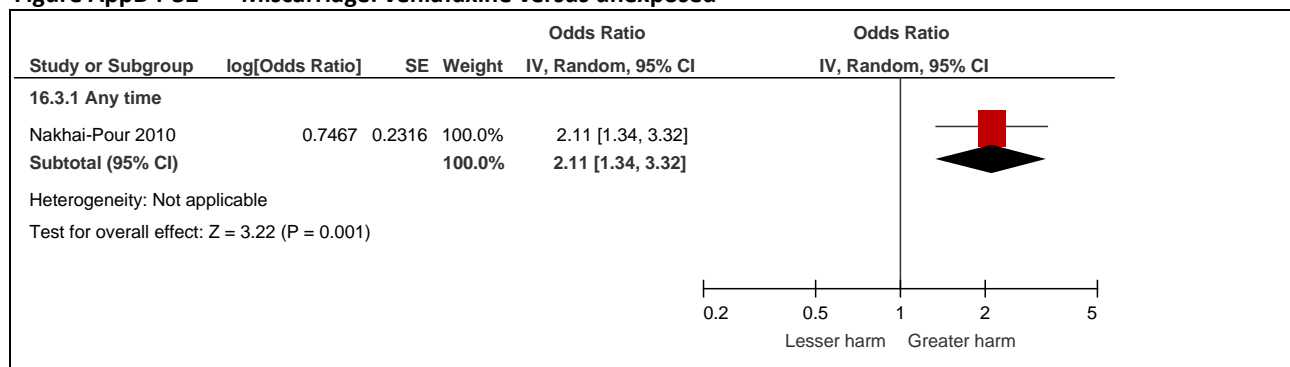
As shown in **Figure AppD4-31**, Almeida 2016 examined the association between first-trimester exposure to SNRI monotherapy and miscarriage in a population with depression and found that exposure to SNRIs significantly increased the risk of miscarriage (RR 1.7; 95% CI 1.2, 2.6).

Figure AppD4-31 Miscarriage: SNRIs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Nakhai-Pour 2010 examined the association between venlafaxine at any time during pregnancy and spontaneous abortion and found that exposure to venlafaxine was significantly associated with miscarriage (OR 2.11; 95% CI 1.34, 3.30). The population in this study was not limited to those with depression, but instead adjusted for a number of depression variables.

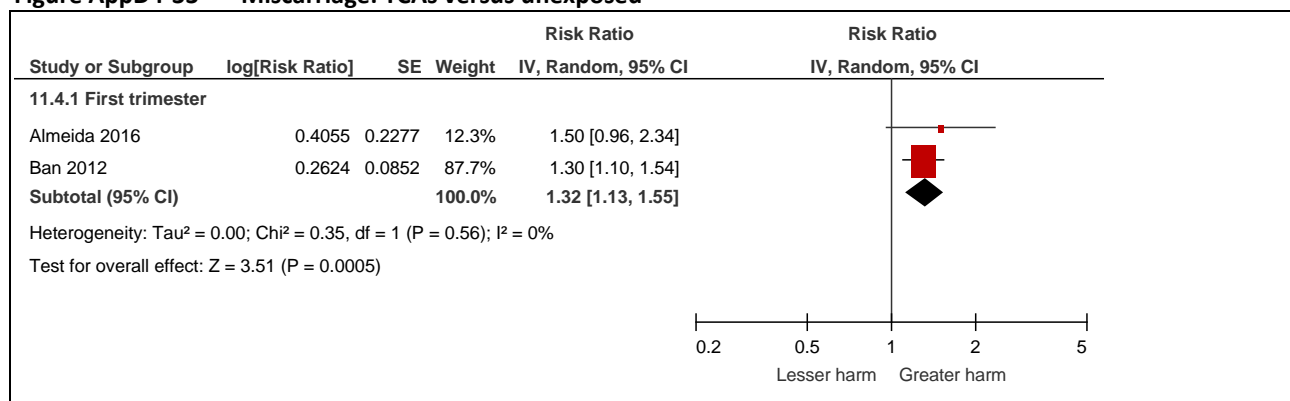
Figure AppD4-32 Miscarriage: venlafaxine versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Djulus 2006 examined the risk of spontaneous abortion following exposure to mirtazapine compared with exposure to other antidepressants and found no difference in risk ($P=0.86$).

As shown in **Figure AppD4-33**, three studies examined the association between TCAs and miscarriage. Two studies examined the association between first-trimester exposure to TCAs and miscarriage in a population with depression/anxiety and found that exposure to SSRIs was associated with miscarriage (RR 1.32; 95% CI 1.13, 1.55). Nakhai-Pour 2010 examined the association between TCAs at any time during pregnancy and spontaneous abortion and found that exposure to TCAs was not significantly associated with miscarriage (OR 1.27; 95% CI 0.85, 1.91). The population in this study was not limited to those with depression, but instead adjusted for a number of depression variables.

Figure AppD4-33 Miscarriage: TCAs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; TCA, tricyclic antidepressant.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.1.8 Preterm birth – antidepressants

AppD4.1.1.8.1 Results based on systematic reviews

The results of the analyses of the association between antidepressants and preterm birth presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-13**. Most results based on either adjusted data or the appropriate comparator population showed a significant association between any antidepressants and preterm birth. One SR (reporting two observational studies; Ross 2013) provided data for this outcome that was both based on unadjusted data and used the appropriate comparator population (shown in shading) and suggested no association between any antidepressants and preterm birth, however the risk estimate is large (OR 1.79) and the confidence interval are wide, suggesting it may have been underpowered; there was also substantial heterogeneity between the two study results. *As such, this finding has not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-13 Antidepressants – preterm birth outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I^2)
Any ADs								
Huybrechts 2014b	Preterm birth	Any ADs (early)	Unexposed – any	4/8 (OBS)	NR	OR 1.16 (0.92, 1.45)	-	<0.001 (85%)
Huybrechts 2014b	Preterm birth	Any ADs (late)	Unexposed – any	8/12 (OBS)	NR	OR 1.96 (1.62, 2.38)	-	<0.001 (84%)
Huybrechts 2014b	Preterm birth	Any ADs (any time)	Unexposed – any	11/17 (OBS)	NR	OR 1.53 (1.40, 1.66)	-	0.23 (19%)
Ross 2013	Preterm birth	Any ADs	Unexposed – any	9 ¹⁶¹ (OBS)	NR	OR 1.70 (1.35, 2.14)	-	0.21 (25%)
Huang 2014	Preterm birth	Any ADs	Unexposed – depressed	4 (OBS)	NR	-	RR 2.85 (2.00, 4.07)	0.57 (0%)
Huang 2014	Preterm birth	Any ADs	Unexposed – controlled for depression severity	6 (OBS)	NR	-	RR 1.90 (1.07, 3.38)	0.07 (50%)
Huybrechts 2014b	Preterm birth	Any ADs	Unexposed – psychiatric illness	10/12 (OBS)	NR	-	OR 1.61 (1.26, 2.05)	0.04 (46%)
Huybrechts 2014b	Preterm birth	Any ADs	Unexposed – no psychiatric illness	10/12 (OBS)	NR	-	OR 1.88 (1.48, 2.40)	0.28 (20%)

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Ross 2013	Preterm birth	Any ADs	Unexposed – disease	5 ¹⁶¹ (OBS)	NR	-	OR 1.58 (0.97, 2.56)	0.001 (75%)
Ross 2013	Preterm birth	Any ADs	Unexposed – disease	2 ¹⁶¹ (OBS)	NR	OR 1.79 (0.77, 4.14)	-	0.007 (80%)

Abbreviations: AD, antidepressant; CI, confidence interval; NR, not reported; OBS, observational studies (type not specified); OR, odds ratio; RE, risk estimate; RR, relative risk.

AppD4.1.1.8.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and preterm birth is presented in **Table AppD4-14**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of preterm birth in the depressed or psychiatric diagnosis/unexposed population (1% for < 32 weeks and 5% for 32-36 weeks),³⁵³ it is assumed that the odds ratio (OR) approximates the relative risk (RR) and ORs and RRs for this outcome have been pooled to generate single relative effect estimates.

Table AppD4-14 Antidepressants – preterm birth outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
SSRIs						
Malm 2015 <i>High</i>	Preterm birth (32–36 weeks)	SSRIs (any time)	Unexposed – psychiatric diagnosis	1 (cohort)	25,381	OR 0.84 (0.74, 0.96)
Malm 2015 <i>High</i>	Preterm birth (<32 weeks)	SSRIs (any time)	Unexposed – psychiatric diagnosis	1 (cohort)	25,381	OR 0.52 (0.37, 0.74)
Grzeskowiak 2012 <i>Low</i>	Preterm delivery (< 37 weeks)	SSRI (late gestation)	Unexposed – psychiatric illness	1 (cohort)	1,787	OR 2.68 (1.83, 3.93)
Oberlander 2006 <i>Low</i>	Preterm birth (<37 weeks)	SSRIs (any time)	Unexposed - depression	1 (cohort)	1,622	RD 0.007 (-0.018, 0.034)
Oberlander 2008b	Gestational age < 37 weeks	SSRI (early exposure) ³⁵⁴	SSRI (late exposure) ³⁵⁵	1 (cohort)	858	10.3% vs 9.1%; p≥0.05
Mirtazapine						
Djulus 2006 <i>Moderate</i>	Preterm birth (< 37 weeks)	Mirtazapine	Other ADs	1 (cohort)	208	P=0.61

Abbreviations: CI, confidence interval; RE, risk estimate; OR, odds ratio; RD, risk difference; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

As shown in **Figure AppD4-34**, three studies examined the association between exposure to SSRIs and preterm birth; however, because the studies used different definitions of preterm birth, or used different risk estimates, it was considered inappropriate to meta-analyse the results.

Grzeskowiak 2012 found that exposure to SSRIs during late gestation (not defined) significantly increased the risk of preterm birth (OR 2.68; 95% CI 1.83, 3.93). Oberlander found no significant difference in absolute risk of preterm birth following exposure to SSRIs (RD 0.007; 95% CI -0.0018, 0.034).

³⁵³ Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

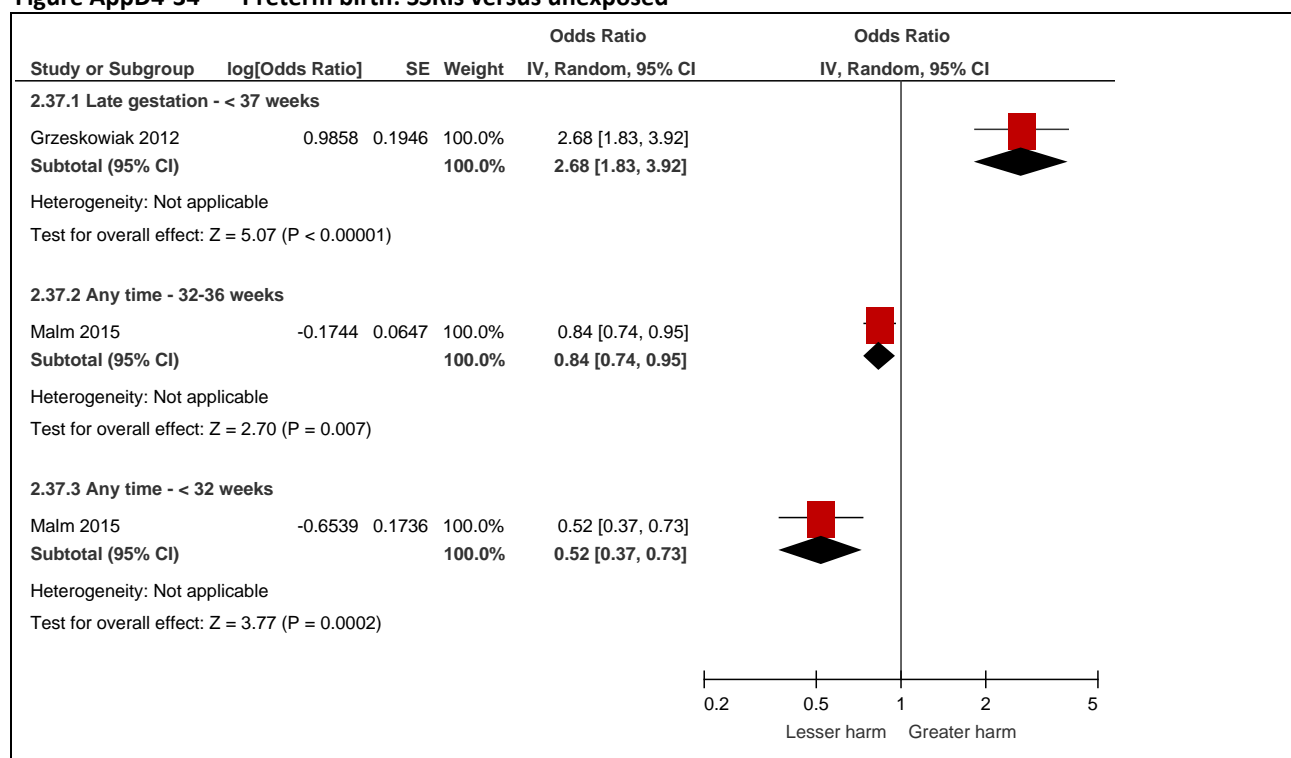
³⁵⁴ Discontinued use in first or second trimester.

³⁵⁵ Continued use into third trimester.

Oberlander 2008b compared the risk of preterm birth (< 37 weeks) in neonates following early versus late exposure to SSRIs and found no difference between the two groups (10.3% versus 9.1%; $p \geq 0.05$).

Malm 2015 found a significantly *decreased* risk of preterm (32-36 weeks) and very early preterm (< 32 weeks) birth. However, the Malm 2015 study uses data from a Finnish cohort in which the comparison between SSRI-exposed women and unexposed women with a psychiatric diagnosis is likely to be subject to selection bias (see **Section AppD4.1.1.16.2** for a detailed description of the methodological issues regarding this study). For this reason, the results from this study have not been included in the Summary of Findings table.

Figure AppD4-34 Preterm birth: SSRIs versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; TCA, tricyclic antidepressant.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Djulus 2006 examined the risk of preterm birth following exposure to mirtazapine compared with exposure to other antidepressants and found no difference in risk ($P=0.61$).

AppD4.1.1.9 Small for gestational age – antidepressants

AppD4.1.1.9.1 Results based on systematic reviews

No SRs were identified that provided analyses of the association between antidepressants and neonates being small for gestational age based on either data adjusted for potential confounding or used the appropriate comparator population. *As such, an examination of the results of individual studies has been undertaken for this outcome.*

AppD4.1.1.9.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and small for gestational age is presented in **Table AppD4-15**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

The prevalence of being small for gestational age in the psychiatric diagnosis/unexposed population differed substantially between the two main studies (2.5% versus 13.0% for Malm 2015 and Grzeskowiak 2012, respectively). As such, the assumption that the OR approximates the RR is uncertain and the ORs and RRs have not been pooled.

Table AppD4-15 Antidepressants – small for gestational age outcomes from observational studies

Study ID Risk of bias	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
SSRIs						
Malm 2015 <i>Moderate</i>	Small for gestational age	SSRI (any time)	Unexposed – psychiatric diagnosis	1 (cohort)	25,381	OR 0.92 (0.77, 1.10)
Grzeskowiak 2012 <i>Low</i>	Small for gestational age	SSRI (late gestation)	Unexposed – psychiatric illness	1 (cohort)	1,787	OR 1.13 (0.65, 1.94)
Oberlander 2006 <i>Low</i>	Birthweight < 10 th percentile for gestational age	SSRI (any time)	Unexposed – depression	1 (cohort)	1,622	RD 0.033 (0.007, 0.059)
Oberlander 2008b	Birth weight < 10 th percentile for gestational age	SSRI (early exposure) ³⁵⁶	SSRI (late exposure) ³⁵⁷	1 (cohort)	858	7.0% vs 7.9%; p≥0.05

Abbreviations: CI, confidence interval; RE, risk estimate; OR, odds ratio; RD, risk difference; SSRI, selective serotonin reuptake.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Three studies examined the association between exposure to SSRIs and being small for gestational age. Two studies were similar and could be meta-analysed. **Figure AppD4-35** summarises the findings of the association between exposure to SSRIs during pregnancy and being small for gestational age. There was no significantly increased risk of the neonate being small for gestational age following exposure to SSRIs in either late gestation, or at any time during pregnancy based on OR analyses; the pooled result also showed no significant risk (OR 0.94; 95% CI 0.79, 1.11).

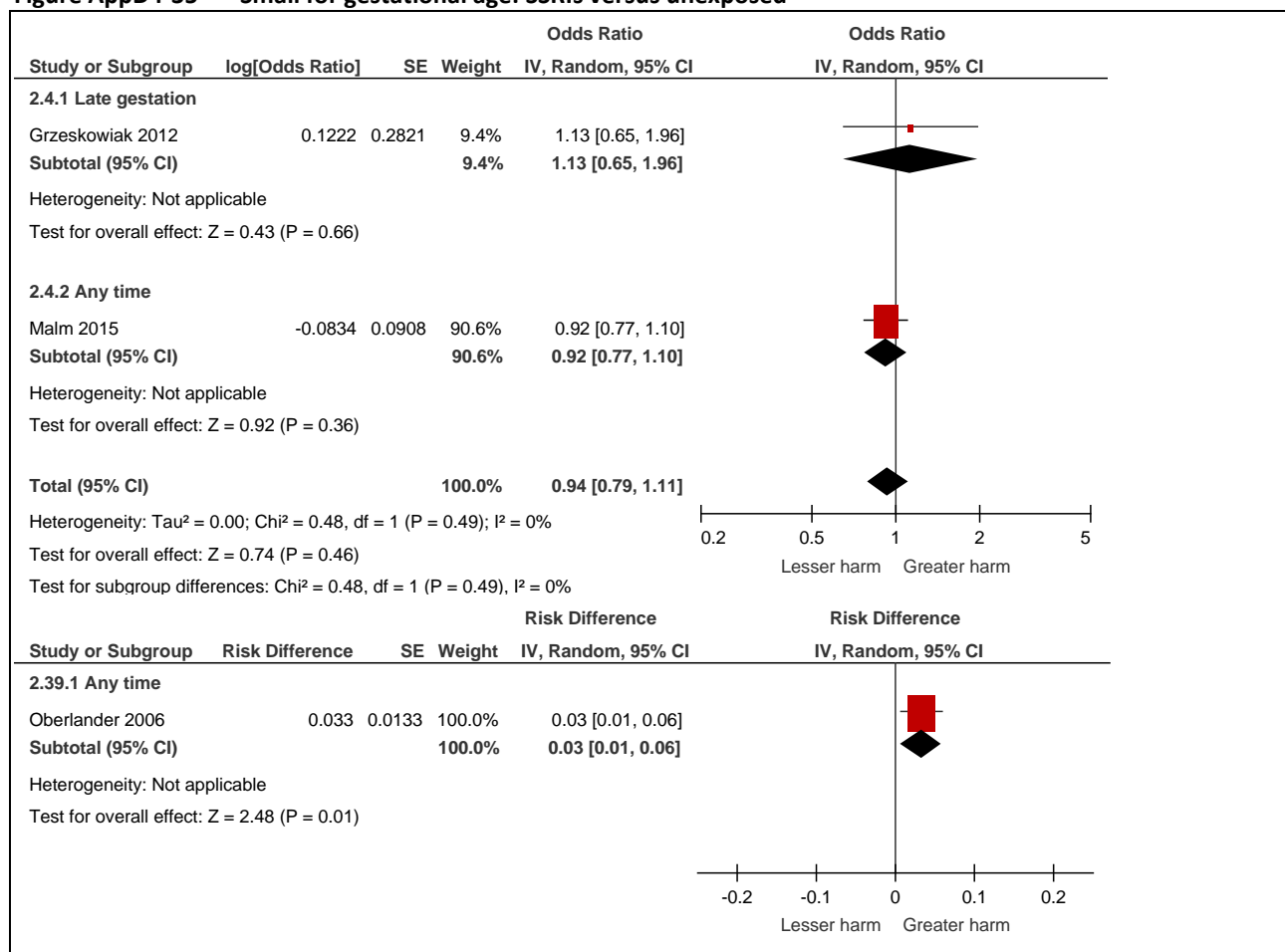
Oberlander 2006, however, found a statistically significant increased absolute risk of the neonate's birthweight being in the < 10th percentile for gestational age, following exposure to SSRIs at any time during pregnancy (RD 0.033; 95% CI 0.07, 0.059).

The Malm 2015 study uses data from a Finnish cohort in which the comparison between SSRI-exposed women and unexposed women with a psychiatric diagnosis is likely to be subject to selection bias (see **Section AppD4.1.1.16.2** for a detailed description of the methodological issues regarding this study). For this reason, the results from this study have not been included in the Summary of Findings table.

Oberlander 2008b compared the risk of small for gestational age in neonates following early versus late exposure to SSRIs and found no difference between the two groups (7.0% versus 7.9%; p≥0.05).

³⁵⁶ Discontinued use in first or second trimester.

³⁵⁷ Continued use into third trimester.

Figure AppD4-35 Small for gestational age: SSRIs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.1.10 Poor neonatal adaptation syndrome – antidepressants

AppD4.1.1.10.1 Results based on systematic reviews

The results of the analyses of the association between antidepressants and PNAS presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-16**. Only one SR (reporting two observational studies) provided data for this outcome, and suggested a strong association between any antidepressants and PNAS. As for previous outcomes, this analysis used a comparator population not limited to women with depression or another psychiatric condition, so there may still be substantial underlying confounding. *As such, an examination of the results of individual studies has been undertaken.*

Table AppD4-16 Antidepressants – PNAS outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I^2)
Any ADs								
Grigoriadis 2013b	PNAS	Any ADs	Unexposed – any	2 (OBS)	312	OR 4.74 (2.14, 10.5)	-	0.17 (48%)

Abbreviations: AD, antidepressant; CI, confidence interval; OBS, observational studies (type not specified); OR, odds ratio; PNAS, poor neonatal adaptation syndrome; RE, risk estimate.

AppD4.1.1.10.2 Results based on individual studies

No studies assessed the association between exposure to antidepressants and PNAS, although one study did compare the risk of PNAS for neonates exposed to SSRIs compared with SNRIs. A summary of the results of this study is presented in **Table AppD4-17**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-17 Antidepressants – PNAS outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
SSRIs						
Kievet 2015 <i>Moderate</i>	Poor neonatal adaptation (≥ 1 Finnegan score ≥ 4 during admission)	SSRIs	SNRIs	1 (cohort)	247	OR 2.75 (1.13, 6.71)
Kievet 2015 <i>Moderate</i>	Poor neonatal adaptation (≥ 1 Finnegan score ≥ 4 during admission) – admitted to maternity ward	SSRIs	SNRIs	1 (cohort)	194	OR 4.12 (1.32, 12.8)

Abbreviations: CI, confidence interval; RE, risk estimate; OR, odds ratio; RD, risk difference; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Kievet 2015 compared the risk of PNAS in infants exposed to SSRIs compared with SNRIs and found that SSRIs significantly increased the risk of PNAS in the overall population (OR 2.75; 95% CI 1.13, 6.71) and in the subgroup admitted to the maternity ward (OR 4.12; 95% CI 0.32, 12.8).

AppD4.1.1.11 Persistent pulmonary hypertension – antidepressants

AppD4.1.1.11.1 Results based on systematic reviews

The results of the analyses of the association between antidepressants and persistent pulmonary hypertension (PPHN) presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-18**. Only one SR (reporting up to 4 observational studies) provided data for this outcome, and suggested a strong association between exposure to SSRIs in late pregnancy and PPHN. As for previous outcomes, this analysis used a comparator population not limited to women with depression or another psychiatric condition, so there may still be substantial underlying confounding. *As such, this finding has not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-18 Antidepressants – persistent pulmonary hypertension outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
SSRIs								
McDonagh 2014	Pulmonary hypertension	SSRIs	Unexposed – any	4 (OBS)	NR	OR 2.41 (1.35, 3.95)	-	NR (14%)
McDonagh 2014	Pulmonary hypertension	SSRIs in early pregnancy ³⁵⁸	Unexposed – any	4 (OBS)	NR	OR 1.45 (0.84, 2.49)	-	NR (69%)
McDonagh 2014	Pulmonary hypertension	SSRIs in late pregnancy ³⁵⁹	Unexposed – any	3 (OBS)	NR	OR 2.72 (1.63, 4.54)	-	NR (48%)
Fluoxetine								
McDonagh 2014	Persistent pulmonary hypertension	Fluoxetine in early pregnancy – ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	1.3 (0.6, 2.8)	-	NA
McDonagh 2014	Persistent pulmonary hypertension	Fluoxetine in late pregnancy – ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 2.0 (1.0, 3.8)	-	NA
Citalopram								
McDonagh 2014	Persistent pulmonary hypertension	Citalopram in early pregnancy – ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	1.8 (1.1, 3.0)	-	NA
McDonagh 2014	Persistent pulmonary hypertension	Citalopram in late pregnancy – ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 2.3 (1.2, 4.1)	-	NA
Paroxetine								
McDonagh 2014	Persistent pulmonary hypertension	Paroxetine in early pregnancy – ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	1.3 (0.5, 3.5)	-	NA
McDonagh 2014	Persistent pulmonary hypertension	Paroxetine in late pregnancy – ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 2.8 (1.2, 6.7)	-	NA
Sertraline								
McDonagh 2014	Persistent pulmonary hypertension	Sertraline in early pregnancy – ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	1.9 (1.0, 3.6)	-	NA
McDonagh 2014	Persistent pulmonary hypertension	Sertraline in late pregnancy – ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 2.3 (1.3, 4.4)	-	NA
Escitalopram								
McDonagh 2014	Persistent pulmonary hypertension	Escitalopram in early pregnancy – ≤ 8 weeks	Unexposed – any	1 (OBS)	1,618,255	0.3 (0, 2.2)	-	NA
McDonagh 2014	Persistent pulmonary hypertension	Escitalopram in late pregnancy – ≥20 weeks	Unexposed – any	1 (OBS)	1,618,255	OR 1.3 (0.2, 9.5)	-	NA

Abbreviations: CI, confidence interval; NR, not reported; OBS, observational studies (type not specified); OR, odds ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor.

AppD4.1.1.11.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and PPHN is presented in **Table AppD4-19**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included

³⁵⁸ Not defined

³⁵⁹ Mostly > 20 weeks

in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of PPHN in the depressed/unexposed population (0.25% in Huybrechts 2015), it is assumed that the odds ratio (OR) approximates the relative risk (RR) and where possible, these risk estimates have been pooled together in order to calculate a single relative effect estimate.

It should be noted that a number of specific factors are thought to be potential confounders of the association between maternal antidepressant treatment and the risk of persistent pulmonary hypertension in the offspring. These include caesarian delivery, maternal obesity and maternal smoking. Consideration of the presence or absence of these potential confounders in the analyses of the included studies is noted.

Table AppD4-19 Antidepressants – persistent pulmonary hypertension outcomes from observational studies

Study ID Risk of bias	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
SSRIs						
Huybrechts 2015	Persistent pulmonary hypertension	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	722,830	OR 1.12 (0.95, 1.31) ³⁶⁰
Huybrechts 2015 Low	Persistent pulmonary hypertension	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	722,831	OR 1.10 (0.94, 1.29) ³⁶¹
Huybrechts 2015	Persistent pulmonary hypertension (full-term deliveries)	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	621,398	OR 1.32 (1.04, 1.68)³⁶⁰
Huybrechts 2015 Low	Persistent pulmonary hypertension (full-term deliveries)	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	621,399	OR 1.27 (1.00, 1.61)³⁶¹
Huybrechts 2015	Persistent pulmonary hypertension without cardiac malformation or lung hypoplasia	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	722,830	OR 1.12 (0.95, 1.32) ³⁶⁰
Huybrechts 2015 Low	Persistent pulmonary hypertension without cardiac malformation or lung hypoplasia	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	722,830	OR 1.08 (0.92, 1.27) ³⁶¹
Huybrechts 2015	Primary persistent pulmonary hypertension (without cardiac malformation or lung hypoplasia in full-term deliveries)	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	621,398	OR 1.33 (1.04, 1.70)³⁶⁰
Huybrechts 2015 Low	Primary persistent pulmonary hypertension (without cardiac malformation or lung hypoplasia in full-term deliveries)	SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	621,399	OR 1.28 (1.01, 1.64)³⁶¹
Kieler 2012 Low	Persistent pulmonary hypertension	SSRIs (early pregnancy) ³⁶²	Unexposed – previous psychiatric hospital admission	1 (cohort)	63,615	OR 1.3 (1.0, 1.6)
Kieler 2012 Low	Persistent pulmonary hypertension and no meconium aspiration	SSRIs (early pregnancy) ³⁶³	Unexposed – previous psychiatric hospital admission	1 (cohort)	NR	OR 1.3 (1.1, 1.7)
Kieler 2012 Low	Persistent pulmonary hypertension	SSRIs (late pregnancy) ³⁶⁴	Unexposed – previous psychiatric hospital admission	1 (cohort)	63,615	OR 3.1 (1.9, 4.9)

³⁶⁰ Propensity score stratified

³⁶¹ High-dimensional propensity score stratified

³⁶² Filled a prescription three months before the start of pregnancy to day 55.

³⁶³ Filled a prescription three months before the start of pregnancy to day 55.

³⁶⁴ Filled a prescription from 140 days after the start of pregnancy to birth.

Study ID Risk of bias	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Non-SSRIs						
Huybrechts 2015	Persistent pulmonary hypertension	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	673,789	OR 1.01 (0.76, 1.35) ¹⁷⁹
Huybrechts 2015	Persistent pulmonary hypertension	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	673,789	OR 1.02 (0.77, 1.35) ¹⁸⁰
Huybrechts 2015	Persistent pulmonary hypertension (full-term deliveries)	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	580,466	OR 1.25 (0.82, 1.90) ¹⁷⁹
Huybrechts 2015	Persistent pulmonary hypertension (full-term deliveries)	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	580,471	OR 1.19 (0.79, 1.79) ¹⁸⁰
Huybrechts 2015	Persistent pulmonary hypertension without cardiac malformation or lung hypoplasia	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	673,789	OR 0.95 (0.70, 1.30) ¹⁷⁹
Huybrechts 2015	Persistent pulmonary hypertension without cardiac malformation or lung hypoplasia	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	673,789	OR 0.96 (0.71, 1.30) ¹⁸⁰
Huybrechts 2015	Primary persistent pulmonary hypertension (without cardiac malformation or lung hypoplasia in full-term deliveries)	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	580,466	OR 1.21 (0.78, 1.86) ¹⁷⁹
Huybrechts 2015	Primary persistent pulmonary hypertension (without cardiac malformation or lung hypoplasia in full-term deliveries)	Non-SSRIs (90 days prior to delivery)	Unexposed – depression	1 (cohort)	580,471	OR 1.14 (0.74, 1.74) ¹⁸⁰

Abbreviations: CI, confidence interval; OR, odds ratio; NR, not reported; NS, not statistically significant; RE, risk estimate; SSRI, selective serotonin reuptake.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

As shown in **Figure AppD4-36**, two studies examined the association between exposure to SSRIs and persistent pulmonary hypertension: Huybrechts 2015 and Kieler 2012. While Kieler 2012 found a borderline increased risk associated with early exposure to SSRIs (OR 1.30; 95% CI 1.00, 1.69), the two studies examining late exposure had differing results, with Huybrechts 2015 showing no significant increased risk (OR 1.10, 0.94, 1.29) and Kieler 2012 showing a highly significant increased risk (OR 3.10; 95% CI 1.90, 5.06). The pooled result was highly heterogenous. A notable difference between the two studies was the populations they included: Huybrechts included an analysis of women with depression and Kieler 2012 included a subgroup analysis in women who had had a previous psychiatric hospital admission. Therefore, it is possible that differences in the underlying conditions of the study populations may explain the differences between the study results.

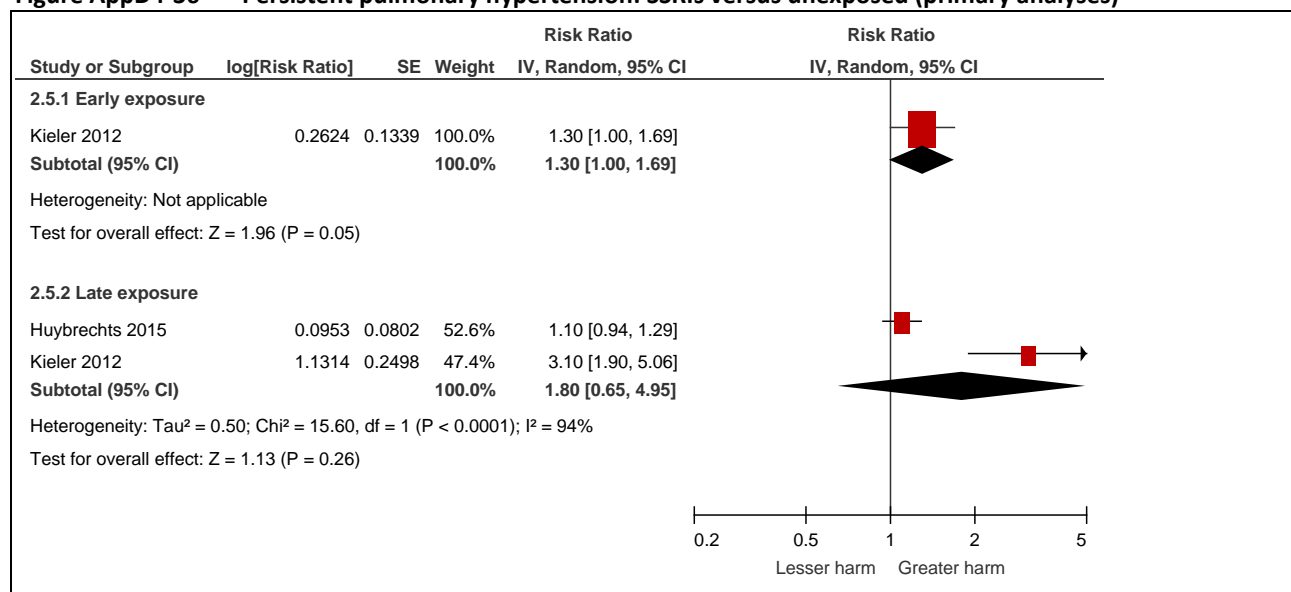
Huybrechts 2015 also found no increased risk when infants with cardiac malformation or lung hypoplasia were excluded from the analysis (OR 1.08; 95% CI 0.92, 1.27). However, when only full-term deliveries were included there was a borderline significantly increased risk (OR 1.27; 95% CI 1.00, 1.61). An increased risk was also found when the population was limited to those without cardiac malformations or lung hypoplasia who went to full-term (OR 1.28; 1.01, 1.64). These results are presented in **Figure AppD4-37**.

Kieler 2012 repeated their analysis for those with no meconium aspiration and this strengthened the finding of increased risk (OR 1.3; 95% CI 1.1, 1.7).

Both studies considered adjustment for smoking, obesity or body mass index (BMI), and caesarean delivery in their analyses. Huybrechts 2015 included adjustment for smoking and obesity in their analysis. The authors note that caesarean delivery was specifically not adjusted for “because it has been shown that conditioning on such an intermediate perinatal factor is susceptible to overadjustment bias.” However, in

response to a comment on their study regarding the lack of adjustment for potential confounding due to caesarean delivery, Huybrechts and colleagues re-ran their base case and primary PPHN definition analyses including adjustment for caesarean delivery. The addition of caesarean delivery to the analysis had little impact on the magnitude or precision of the results.³⁶⁵ Kieler 2012 carried out a subset analysis on the general population (i.e. not limited to those with depression/ psychiatric diagnosis) and found that smoking and BMI did not confound the analysis; thus, these variables were not included in their subsequent analyses. Caesarean delivery was included in their analysis within the general population, but was not found to modify the risk. It is unclear whether these variables were considered in the subgroup analysis of those with a previous admission for a psychiatric disorder, which is the data from Kieler 2012 that has been included in this Evidence Review.

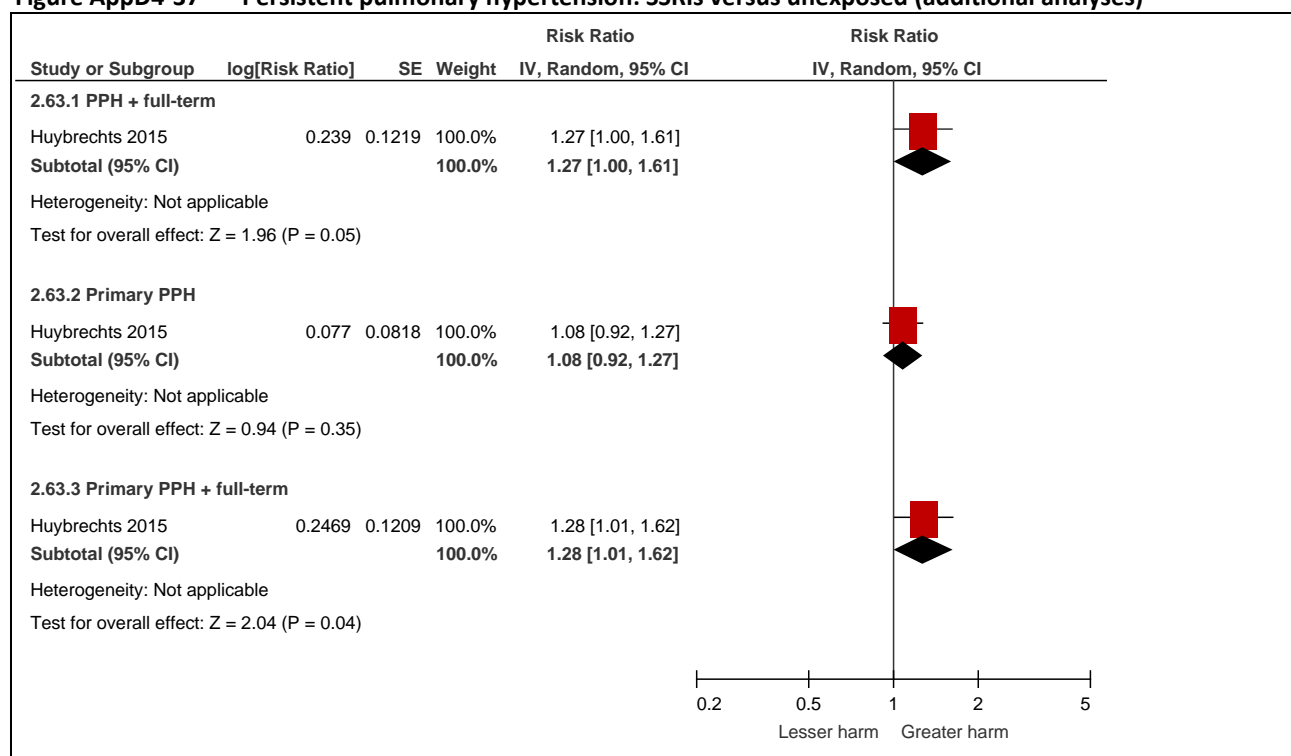
Figure AppD4-36 Persistent pulmonary hypertension: SSRIs versus unexposed (primary analyses)



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

³⁶⁵ Huybrechts, K. F., et al. (2015). "Maternal Antidepressant Use and Persistent Pulmonary Hypertension of the Newborn--Reply." JAMA 314(12): 1294.

Figure AppD4-37 Persistent pulmonary hypertension: SSRIs versus unexposed (additional analyses)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

AppD4.1.1.12 Respiratory distress – antidepressants

AppD4.1.1.12.1 Results based on systematic reviews

The results of the analyses of the association between antidepressants and respiratory distress presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-20**. All four analyses suggested a strong association between exposure to antidepressants and respiratory distress. As for previous outcomes, the majority of these analyses used a comparator population not limited to women with depression or another psychiatric condition, so there may still be substantial underlying confounding. In addition, the remaining analysis based on the correct comparator population did not use adjusted results. *As such, this finding has not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-20 Antidepressants – respiratory distress outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any ADs								
Grigoriadis 2013b	Respiratory distress	Any ADs	Unexposed – any	2 (OBS)	583,939	OR 2.24 (1.75, 2.86)	-	0.77 (0%)
SSRIs								
McDonagh 2014	Respiratory distress	SSRIs	Unexposed – any	4 (OBS)	748,658	OR 1.79 (1.64, 1.97)	-	NR (0%)
McDonagh 2014	Respiratory distress	SSRIs	Unexposed – disease	3 (cohort)	15,793		OR 1.91 (1.63, 2.24)	NR (0%)
TCAs								
McDonagh 2014	Respiratory distress	TCAs	Unexposed – any	2 (OBS)	NR	OR 2.11 (1.57, 2.83)	-	0.78 (NR)

Abbreviations: AD, antidepressant; CI, confidence interval; NR, not reported; OBS, observational studies (type not specified); OR, odds ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

AppD4.1.1.12.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and respiratory distress is presented in **Table AppD4-21**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of respiratory distress in the depressed/unexposed population (3.2% in Malm 2015), it is assumed that the OR approximates the RR.

Table AppD4-21 Antidepressants – respiratory distress outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Any ADs						
Hayes 2012	Respiratory distress	Any ADs – 1 prescription (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Respiratory distress	Any ADs – 2 prescriptions (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Respiratory distress	Any ADs – ≥ 3 prescriptions (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Respiratory distress	Any ADs – 1 prescription (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 1.1 (0.9, 1.3)
Hayes 2012	Respiratory distress	Any ADs – 2 prescriptions (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 1.4 (1.1, 1.8)
Hayes 2012	Respiratory distress	Any ADs – ≥ 3 prescriptions (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 1.6 (1.2, 2.0)
Hayes 2012	Respiratory distress	Any ADs – 1 prescription (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 0.9 (0.7, 1.1)

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Hayes 2012	Respiratory distress	Any ADs – 2 prescriptions (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 0.8 (0.6, 1.0)
Hayes 2012	Respiratory distress	Any ADs – ≥ 3 prescriptions (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 0.6 (0.5, 0.8)
SSRIs						
Malm 2015 <i>Moderate</i>	Breathing problems	SSRI (any time)	Unexposed – psychiatric diagnosis	1 (cohort)	25,381	OR 1.40 (1.20, 1.62)
Oberlander 2006 <i>Low</i>	Respiratory distress	SSRIs (any time)	Unexposed - depression	1 (cohort)	1,622	RD 0.044 (0.013, 0.077)
Oberlander 2006	Respiratory distress, infants born by vaginal birth	SSRIs (any time)	Unexposed - depression	1 (cohort)	NR	RD 0.049 (0.017, 0.088)
Oberlander 2008b	Respiratory distress	SSRI (early exposure) ³⁶⁶	SSRI (late exposure) ³⁶⁷	1 (cohort)	858	9.3% vs 10.3%; p≥0.05

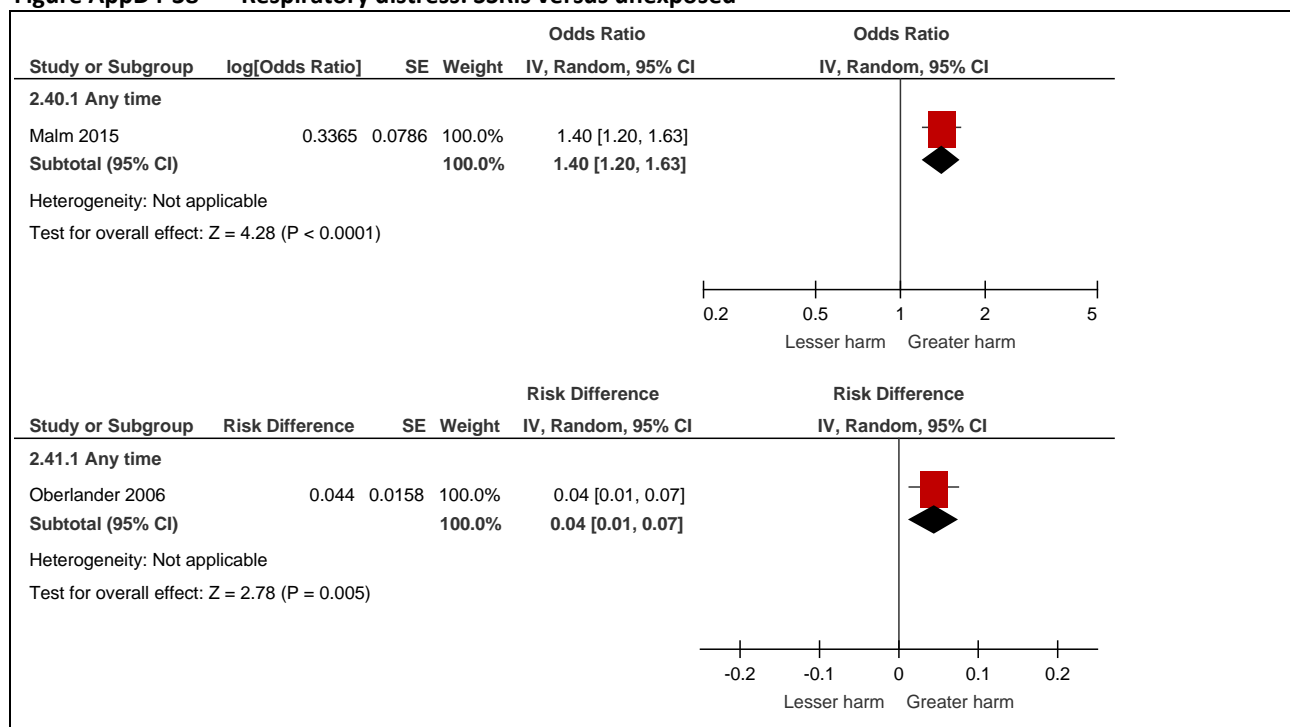
Abbreviations: AD, antidepressant; CI, confidence interval; RE, risk estimate; OR, odds ratio; RD, risk difference; SSRI, selective serotonin reuptake.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Two studies examined the association between SSRIs and respiratory distress, as shown in **Figure AppD4-38**. Malm 2015 examined the association between SSRI exposure and neonatal breathing problems and found the risk significantly increased (OR 1.40; 95% CI 1.20, 1.62). Similarly, Oberlander 2006 found a statistically significant increased absolute risk of respiratory distress in all neonates (RD 0.044; 95% CI 0.013, 0.077) and infants born by vaginal birth only (RD 0.049; 95% CI 0.017, 0.088), following exposure to SSRIs at any time during pregnancy.

³⁶⁶ Discontinued use in first or second trimester.

³⁶⁷ Continued use into third trimester.

Figure AppD4-38 Respiratory distress: SSRIs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

One study (Oberlander 2008b) compared the risk of respiratory distress in neonates following early versus late exposure to SSRIs and found no difference between the two groups (9.3% versus 10.3%; $p \geq 0.05$).

AppD4.1.1.13 Tremors – antidepressants

AppD4.1.1.13.1 Results based on systematic reviews

No SRs were identified that provided analyses of the association between antidepressants and tremors based on either data adjusted for potential confounding or used the appropriate comparator population. *As such, an examination of the results of individual studies has been undertaken for this outcome.*

AppD4.1.1.13.2 Results based on individual studies

No individual studies were identified that provided analyses of the association between antidepressants and tremors based on data adjusted for potential confounding and using the appropriate comparator population or adjusted for confounding by indication.

AppD4.1.1.14 Convulsions – antidepressants

AppD4.1.1.14.1 Results based on systematic reviews

The results of the analyses of the association between antidepressants and convulsions presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-22**. Only one SR (reporting one case-control study) provided data for this outcome, and suggested a strong relative association between exposure to TCAs and convulsions, and no absolute association between exposure to SSRIs and convulsions when an appropriate comparator group was used. Due to the inconsistency in these findings, and the lack of appropriate comparator population for the TCA result, *these findings has not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-22 Antidepressants – convulsions outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
SSRIs								
McDonagh 2014	Neonatal convulsions	SSRIs	Unexposed - disease	1 (CC)	15,685	-	RD 0.0005 (-0.0015, 0.0025)	NA
TCAs								
McDonagh 2014	Neonatal convulsions	TCAs	Unexposed - any	1 (CC)	582,796	OR 6.8 (2.2, 16.0)	-	NR

Abbreviations: AD, antidepressant; CI, confidence interval; NR, not reported; OBS, observational studies (type not specified); OR, odds ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

AppD4.1.1.14.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and convulsions is presented in **Table AppD4-23**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of PPHN in the depressed/unexposed population (0.25% in Huybrechts 2015), it is assumed that the OR approximates the RR and where possible, these risk estimates have been pooled together in order to calculate a single relative effect estimate.

Table AppD4-23 Antidepressants – convulsions outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
SSRIs						
Hayes 2012	Convulsions	SSRIs – one prescription filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – two prescriptions filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – three+ prescription filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – one prescription filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – two prescriptions filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	SSRIs – three+ prescription filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012 <i>Low</i>	Convulsions	SSRIs – one prescription filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 1.4 (0.7, 2.8)
Hayes 2012 <i>Low</i>	Convulsions	SSRIs – two prescriptions filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 2.8 (1.4, 5.5)
Hayes 2012 <i>Low</i>	Convulsions	SSRIs – three+ prescription filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	OR 4.9 (2.6, 9.5)

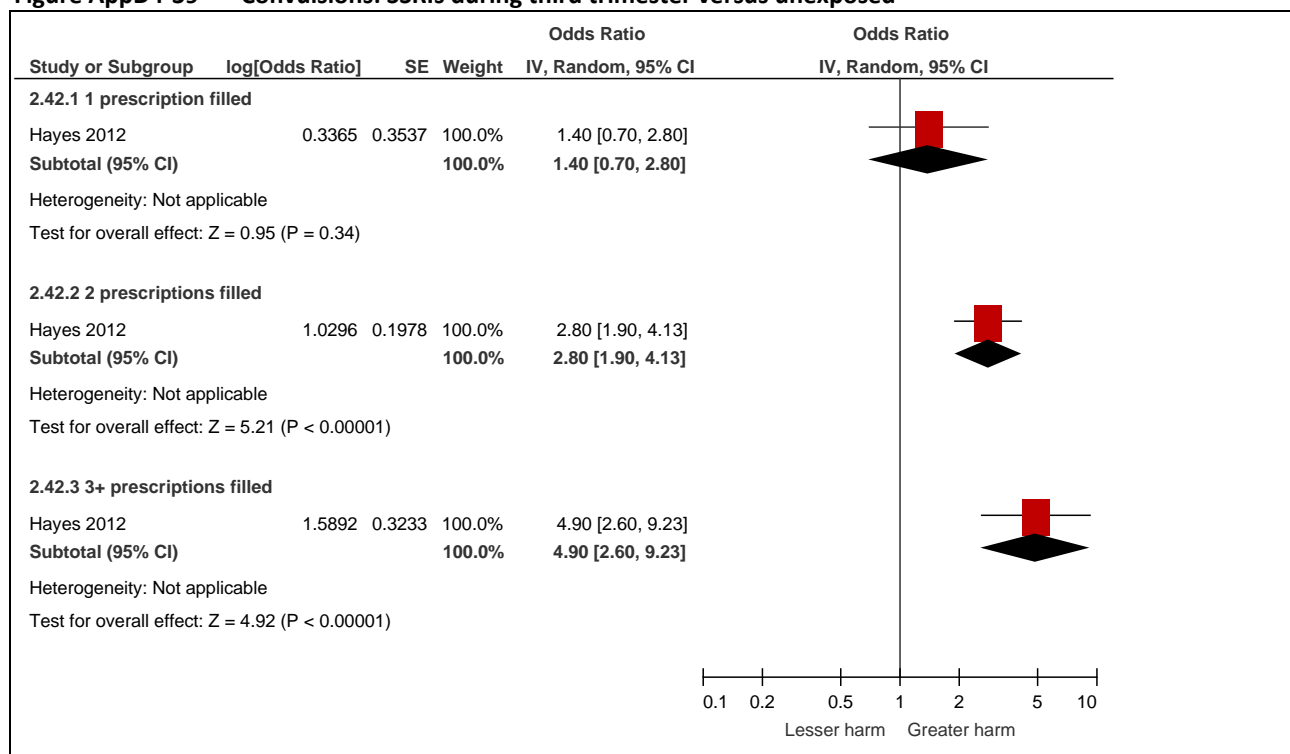
Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Oberlander 2006 <i>Low</i>	Convulsions	SSRI	Unexposed - depression	1 (cohort)	1,622	RD 0.00077 (-0.0010, 0.0036)
Non-SSRIs						
Hayes 2012	Convulsions	Non-SSRIs – one prescription filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – two prescriptions filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – three+ prescription filled (first trimester)	Unexposed in first trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – one prescription filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – two prescriptions filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – three+ prescription filled (second trimester)	Unexposed in second trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – one prescription filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – two prescriptions filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS
Hayes 2012	Convulsions	Non-SSRIs – three+ prescription filled (third trimester)	Unexposed in third trimester – adjusted for psychiatric confounders	1 (cohort)	228,876	NS

Abbreviations: CI, confidence interval; NS, not significant; RD, risk difference; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

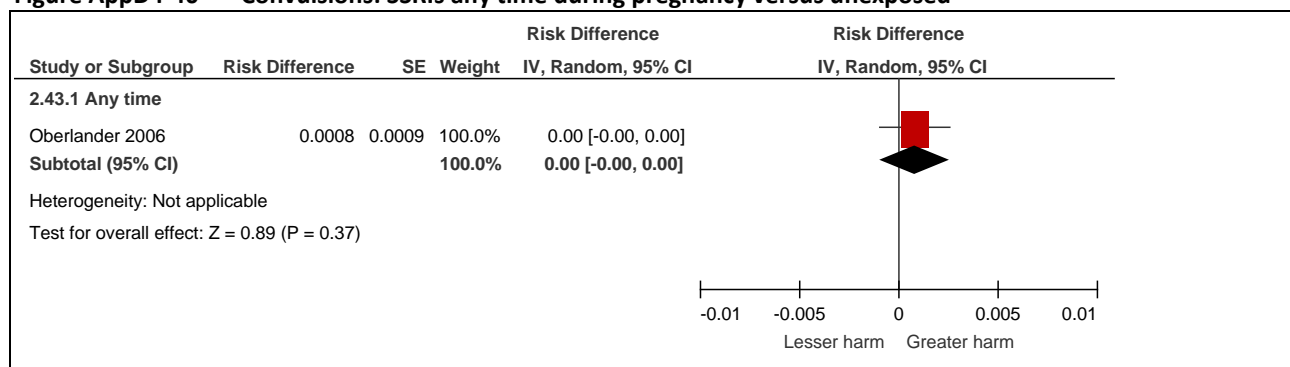
Hayes 2012 examined the association between SSRI use during different trimesters and neonatal convulsions, taking into account the number of antidepressant prescriptions filled (**Figure AppD4-39**). There was no increased risk for infants exposed during the first trimester compared with those not exposed during the first trimester, regardless of the number of antidepressant scripts filled; the result was the same for second trimester exposure. Exposure versus non-exposure to antidepressants in the third trimester significantly increased the risk of convulsions when 2, or 3 or more prescriptions, were filled (OR 2.8; 95% CI 1.9, 5.5 and OR 4.9; 95% CI 2.6, 9.5). These results suggest a dose-response effect: that increasing exposure to SSRIs in the third trimester increases the risk of convulsions in the infant.

Oberlander 2006 found no increase in absolute risk of convulsions (RD 0.00077; 95% CI -0.0010, 0.0036) following exposure to SSRIs at any time during pregnancy (**Figure AppD4-40**).

Figure AppD4-39 Convulsions: SSRIs during third trimester versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-40 Convulsions: SSRIs any time during pregnancy versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.1.15 Postpartum haemorrhage – antidepressants

AppD4.1.1.15.1 Results based on systematic reviews

The results of the analysis of the association between antidepressants and postpartum haemorrhage presented in the Jiang 2016 SR are presented in **Table AppC4.1-1**, grouped by antidepressant type. Findings shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section D3.1.1** of the Part D Technical Report.

While the prevalence of post-partum haemorrhage in an unexposed population with depression/psychiatric diagnoses was not available in the identified SRs and their individual included studies, the risks in the general population comparator groups of the individual studies included in Jiang SR ranged from 4% to 14%. As such, the baseline risk in the depressed population is likely to be > 5 % and it cannot be assumed that the odds ratio (OR) approximates the relative risk (RR).

The majority of analyses included in the Jiang 2016 SR show that exposure to antidepressants during pregnancy results in an increased risk of postpartum haemorrhage. However, it should be noted that a number of the analyses are subject to substantial heterogeneity.

Table AppC4.1-1 Antidepressants – postpartum haemorrhage outcomes from systematic reviews

Study ID Risk of bias	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any ADs								
Jiang 2016 Low	Postpartum haemorrhage	ADs (any time)	Unexposed - adjusted ³⁶⁸	8 (17) ³⁶⁹ (OBS)	NR	RR 1.32 (1.17, 1.48)	-	<0.001 (85%)
Jiang 2016 Low	Postpartum haemorrhage	ADs (any time)	Unexposed - adjusted ³⁶⁸	8 (17) ³⁷⁰ (OBS)	NR	OR 1.25 (1.1, 1.5)	-	<0.001 (87%)
Jiang 2016 Low	Postpartum haemorrhage – <u>similar definition of PPH</u>	ADs (any time)	Unexposed - adjusted ³⁶⁸	3 (11) ¹⁶⁶	NR	OR 1.24 (1.09, 1.41)	-	<0.001 (90%)
Jiang 2016 Low	Postpartum haemorrhage – <u>vaginal delivery</u>	ADs (any time)	Unexposed - adjusted ³⁶⁸	2 (3) ¹⁶⁶	NR	OR 1.43 (1.15, 1.78)	-	0.32 (1%)
Jiang 2016 Low	Postpartum haemorrhage – <u>caesarean section</u>	ADs (any time)	Unexposed - adjusted ³⁶⁸	2 (3) ¹⁶⁶	NR	OR 2.02 (1.61, 2.54)	-	0.31 (12%)
Jiang 2016 Low	Postpartum haemorrhage	ADs (any time)	Unexposed – <u>adjusted for disease severity</u>	5 (13) ¹⁶⁶	NR	OR 1.31 (1.14, 1.50)	-	0.31 (88%)
Jiang 2016 Low	Postpartum haemorrhage	ADs (past users)	Unexposed - adjusted ³⁶⁸	2 (3) ¹⁶⁶	NR	OR 1.08 (0.88, 1.31)	-	0.46 (68%)
Jiang 2016 Low	Postpartum haemorrhage	ADs (recent users)	Unexposed - adjusted ³⁶⁸	5 (11) ¹⁶⁶	NR	OR 1.32 (1.15, 1.51)	-	<0.01 (81%)
Jiang 2016 Low	Postpartum haemorrhage	ADs (current users)	Unexposed - adjusted ³⁶⁸	4 (6) ¹⁶⁶	NR	OR 1.37 (1.09, 1.71)	-	<0.001 (83%)
SRIs								
Jiang 2016 Low	Postpartum hemorrhage	SRIs ³⁷¹ (any time)	Unexposed - adjusted ³⁶⁸	4(10) ¹⁶⁶	NR	OR 1.23 (1.06, 1.44)	-	<0.001 (87%)
Jiang 2016 Low	Postpartum hemorrhage	SRIs ³⁷¹ (recent users)	Unexposed - adjusted ³⁶⁸	3 (7) ¹⁶⁶	NR	OR 1.30 (1.06, 1.60)	-	<0.001 (84%)
Jiang 2016 Low	Postpartum hemorrhage	SRIs ³⁷¹ (recent users)	Unexposed - adjusted ³⁶⁸	2 (4) ¹⁶⁶	NR	OR 1.39 (0.96, 1.61)	-	<0.001 (89%)
Non-SRIs								
Jiang 2016	Postpartum hemorrhage	Non-SRI (any time)	Unexposed - adjusted ³⁶⁸	2 (4) ¹⁶⁶	NR	OR 1.31 (1.10, 1.56)	-	0.33 (12%)
SSRIs								
Jiang 2016 Low	Postpartum hemorrhage	SSRI (any time)	Unexposed - adjusted ³⁶⁸	5 (10) ¹⁶⁶	NR	OR 1.20 (1.04, 1.38)	-	<0.001 (86%)
Jiang 2016 Low	Postpartum hemorrhage	SSRI (recent users)	Unexposed - adjusted ³⁶⁸	3 (5) ¹⁶⁶	NR	OR 1.19 (1.02, 1.37)	-	<0.001 (78%)
Jiang 2016 Low	Postpartum hemorrhage	SSRI (current users)	Unexposed - adjusted ³⁶⁸	2 (2) ¹⁶⁶	NR	OR 1.24 (1.02, 1.37)	-	<0.001 (92%)
SNRIs								
Jiang 2016 Low	Postpartum hemorrhage	SNRI (any time)	Unexposed - adjusted ³⁶⁸	2 (6) ¹⁶⁶	NR	OR 1.62 (1.41, 1.85)	-	0.26 (24%)

³⁶⁸ Most included studies included adjustment for depression/psychiatric illness.

³⁶⁹ Number of estimates included in meta-analysis.

³⁷⁰ Number of estimates included in meta-analysis.

³⁷¹ Includes SSRIs and SNRIs.

Study ID Risk of bias	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Jiang 2016 Low	Postpartum hemorrhage	SNRI (recent users)	Unexposed - adjusted ³⁶⁸	2 (4) ¹⁶⁶	NR	OR 1.73 (1.50, 2.00)	-	0.66 (0%)
Jiang 2016 Low	Postpartum hemorrhage	SNRI (current users)	Unexposed - adjusted ³⁶⁸	2 (2) ¹⁶⁶	NR	OR 1.79 (1.53, 2.10)	-	0.68 (0%)

Abbreviations: AD, antidepressant; CI, confidence interval; OR, odds ratio; SNRI, serotonin-noradrenaline reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; RE, risk estimate.

Note: Risk estimates shown in bold black text are statistically significant.

AppD4.1.1.16 Autism spectrum disorder – antidepressants

AppD4.1.1.16.1 Results based on systematic reviews

The results of the analyses of the association between antidepressants and autism spectrum disorder (ASD) presented in the included SRs that were based on either data adjusted for potential confounding or used the appropriate comparator population are presented in **Table AppD4-24**.

One SR (Kobayashi et al. 2016) provides the results of analyses in which both adjusted data and an appropriate comparator population have been used (shown in shading). These results show no significant association between SSRIs and autism spectrum disorder. Conversely, analyses based on adjusted data from the same SR, and two other SRs that were not limited to an appropriate comparator population, showed a significant association between SSRIs and autism spectrum disorder.

While the Kobayashi 2016 SR provides a ‘higher quality’ analysis of the association between SSRIs at any time during pregnancy, it actually includes unadjusted data for one of the included studies, and there are discrepancies between the results presented in the SR, and those presented in two of the original studies (El Marroun 2014 and Hviid 2013).³⁷² In addition, the El Marroun study examines the association between pervasive developmental delay, which is just one of the disorders included under the umbrella of ASD. For these reasons the Kobayashi SR has not been used as a basis for the current Review.

Thus, no SRs were identified that provided analyses of the association between antidepressants and other neurodevelopmental outcomes based on either data adjusted for potential confounding or used the appropriate comparator population. *As such, an examination of the results of individual studies have been undertaken for other neurodevelopmental outcomes.*

Table AppD4-24 Antidepressants – autism spectrum disorder outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
SSRIs								
Kaplan 2016	ASD (≥0 years)	SSRIs	Unexposed – any	5 (CC)	1,225,692	OR 1.66 (1.23, 2.23)	-	0.18 (37%)
Kaplan 2016	ASD (≥2 years)	SSRIs (preconception)	Unexposed – any	3 (CC)	635,612	OR 1.84 (1.48, 2.28)	-	0.40 (0%)
Kaplan 2016	ASD (≥2 years)	SSRIs (first trimester)	Unexposed – any	4 (CC)	636,578	OR 1.90 (1.28, 2.83)	-	0.16 (42%)
Kaplan 2016	ASD (≥2 years)	SSRIs (second trimester)	Unexposed – any	4 (CC)	636,578	OR 1.73 (1.15, 2.61)	-	0.24 (29%)
Kaplan 2016	ASD (≥2 years)	SSRIs (third trimester)	Unexposed – any	4 (CC)	636,578	OR 1.64 (0.83, 3.24)	-	0.02 (68%)
Kaplan 2016	ASD (≥2 years)	SSRIs (third–trimester – sensitivity 1)	Unexposed – any	3 (CC)	631,179	OR 2.48 (1.73, 3.57)	-	0.45 (0%)

³⁷² The authors have been contacted for c but have not responded.

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies/ estimates (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Kaplan 2016	ASD (≥2 years)	SSRIs (third-trimester – sensitivity 2)	Unexposed – any	3 (CC)	8,170	OR 1.11 (0.66, 1.88)	-	0.36 (3%)
Man 2015	ASD (≥0 years)	SSRIs	Unexposed – any	4 (cohort/ CC)	107,688	OR 1.81 (1.47, 2.24)	-	0.90 (0%) 0.87 (0%)
Kobayashi 2016	ASD (Unknown or ≥2 years)	SSRIs (Study set A)	Unexposed – condition	3 (cohort/ CC)	633,663	OR 0.96 (0.57, 1.63)	-	0.22 (35%)
Kobayashi 2016	ASD (≥2 years)	SSRIs (Study set A)	Unexposed – condition	1 (CC)	812	OR 1.86 (0.76, 4.58)	-	NA
Kobayashi 2016	ASD (Unknown)	SSRIs (Study set A)	Unexposed – condition	2 (cohort)	632,851	OR 0.79 (0.51, 1.23)	-	0.58 (0%)
Kobayashi 2016	ASD (Unknown or ≥2 years)	SSRIs (Study set B)	Unexposed – condition	3 (cohort/ CC)	661,076	1.22 (0.72, 2.08)	-	0.22 (34%)
Kobayashi 2016	ASD (≥2 years)	SSRIs (Study set B)	Unexposed – condition	1 (CC)	812	OR 1.86 (0.76, 4.58)	-	NA
Kobayashi 2016	ASD (unknown)	SSRIs (Study set B)	Unexposed – condition	2 (cohort)	660,264	OR 1.03 (0.49, 2.15)	-	0.15 (52%)
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs (Study set A) ³⁷³	Unexposed (other ADs or no ADs) – any	7 (cohort/ CC)	988,245	OR 1.45 (1.15, 1.82)	-	0.19 (31%)
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs (Study set A)	Unexposed (other ADs or no ADs) – any	5 (CC)	355,394	OR 1.37 (1.08, 1.74)	-	0.53 (0%)
Kobayashi 2016	ASD (Unknown)	SSRIs (Study set A)	Unexposed (other ADs or no ADs) – any	2 (cohort)	632,851	OR 1.69 (0.80, 3.57)	-	0.02 (82%)
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs (Study set B) ³⁷⁴	Unexposed (other ADs or no ADs) – any	7 (cohort/ CC)	1,015,658	OR 1.55 (1.28, 1.88)	-	0.29 (19%)
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs (Study set B)	Unexposed (other ADs or no ADs) – any	5 (CC)	355,394	OR 1.37 (1.08, 1.74)	-	0.53 (0%)
Kobayashi 2016	ASD (unknown)	SSRIs (Study set B)	Unexposed (other ADs or no ADs) – any	2 (cohort)	660,264	OR 1.89 (1.21, 2.95)	-	0.12 (58%)
Kobayashi 2016	ASD (Unknown or ≥0 years)	SSRIs	Unexposed (other ADs) – disease	3 (cohort/ CC)	703,799	OR 1.14 (0.67, 1.96)	-	0.74 (0%)
Kobayashi 2016	ASD (≥0 years)	SSRIs	Unexposed (other ADs) – disease	2 (CC)	49,511	OR 0.98 (0.39, 2.43)	-	0.52 (0%)
Kobayashi 2016	ASD (Unknown)	SSRIs	Unexposed (other ADs) – disease	1 (cohort)	654,288	OR 1.24 (0.63, 2.43)	-	NA
Non-SSRIs								
Kaplan 2016	ASD (≥0 years)	Non-SSRIs	Unexposed – any	3 (CC)	596,318	OR 2.05 (1.20, 3.49)	-	0.77 (0%)

Abbreviations: AD, antidepressant; ASD, Autism Spectrum Disorder; CC, case control; CI, confidence interval; NA, not applicable; NR, not reported; OR, odds ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor.

³⁷³ Includes Hviid 2013 for Danish dataset.

³⁷⁴ Includes Sørensen 2013 for Danish dataset.

AppD4.1.1.16.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and autism spectrum disorder (ASD) is presented in **Table AppD4-25**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of ASD in the depressed or psychiatric diagnosis/unexposed population (0.9%),³⁷⁵ it is assumed that the odds ratio (OR) approximates the relative risk (RR) and where possible, these risk estimates have been pooled together in order to calculate a single relative effect estimate.

Table AppD4-25 Antidepressants – autism spectrum disorder outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Any ADs						
Clements 2015	Autism spectrum disorder (2-19 years)	Any ADs (any time)	Unexposed – adjusted for major depression	1 (CC)	5,399	OR 1.10 (0.70, 1.70)
Rai 2013	Autism spectrum disorder (> 3 years)	Any ADs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (CC)	18,524	OR 1.90 (1.15, 3.14)
Rai 2013	Autism spectrum disorder – <u>with</u> intellectual disability (> 3 years)	Any ADs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (CC)	NR	OR 1.09 (0.41, 2.88)
Rai 2013	Autism spectrum disorder – <u>without</u> intellectual disability (> 3 years)	Any ADs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (CC)	NR	OR 2.54 (1.37, 4.68)
Sørensen 2013	Autism spectrum disorder (mean 8.8 years)	Any ADs (any time)	Unexposed – hospital-diagnosed affective disorder	1 (cohort)	6,080	HR 1.2 (0.7, 2.1)
Sørensen 2013	Autism spectrum disorder (mean 8.8 years)	Any ADs (any time)	Unexposed – sibling study	1 (cohort)	6,142	HR 1.1 (0.5, 2.3)
Croen 2011	Autism spectrum disorder (median 4 years)	Any ADs (year before delivery)	Unexposed – adjusted for history of any mental health disorder in year before delivery	1 (CC)	1,805	OR 2.1 (1.0, 4.4)
Clements 2015	Autism spectrum disorder (2-19 years)	Any ADs (first trimester)	Unexposed – adjusted for major depression	1 (CC)	5,399	OR 1.43 (0.85, 2.38)
Croen 2011	Autism spectrum disorder (median 4 years)	Any ADs (first trimester)	Unexposed – adjusted for history of any mental health disorder in year before delivery	1 (CC)	1,799	OR 3.5 (1.5, 7.9)
Clements 2015	Autism spectrum disorder (2-19 years)	Any ADs (second trimester)	Unexposed – adjusted for major depression	1 (CC)	5,399	OR 1.34 (0.77, 2.27)
Croen 2011	Autism spectrum disorder (median 4 years)	Any ADs (second trimester)	Unexposed – adjusted for history of any mental health disorder in year before delivery	1 (CC)	1,774	OR 1.5 (0.5, 5.0)
Clements 2015	Autism spectrum disorder (2-19 years)	Any ADs (third trimester)	Unexposed – adjusted for major depression	1 (CC)	5,399	OR 1.08 (0.61, 1.88)
Croen 2011	Autism spectrum disorder (median 4 years)	Any ADs (third trimester)	Unexposed – adjusted for history of any mental health disorder in year before delivery	1 (CC)	1,775	OR 2.2 (0.7, 6.9)
Boukhris 2016	Autism spectrum disorder (mean 4 years)	Any ADs (second and/or third trimester)	Unexposed - depression	1 (cohort)	16,442	HR 1.75 (1.03, 2.97)
SSRIs						
Gidaya 2014	Autism spectrum disorder (2-14 years)	SSRIs (any time)	Unexposed – adjusted for history of maternal depression	1 (CC)	57,365	OR 1.8 (1.4, 2.3)³⁷⁶
Malm 2016 <i>Moderate</i>	Autism spectrum disorder (up to 14 years)	SSRIs (any time - mono or polytherapy)	Unexposed – previous SSRIs	1 (cohort)	23,709	HR 1.30 (0.88, 1.92)

³⁷⁵ Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

³⁷⁶ Gidaya 2013 performed a Monte Carlo simulation to take into account the likely under reporting of depression in the cohort, and the subsequent impact of adjusting for that as a confounder. These results are described in the text.

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Malm 2016	Autism spectrum disorder (up to 14 years)	SSRIs (any time – mon- or polytherapy)	Unexposed – psychiatric disorder	1 (cohort)	25,380	HR 0.88 (0.65, 1.20)
Harrington 2014 <i>Moderate</i>	Autism spectrum disorder (mean 3.8 years at diagnosis)	SSRIs (any time)	Unexposed – history of mood/anxiety disorder	1 (CC)	229	OR 1.86 (0.76, 4.58)
Harrington 2014	Autism spectrum disorder – boys only (mean 3.8 years at diagnosis)	SSRIs (any time)	Unexposed – history of mood/anxiety disorder	1 (CC)	NR	OR 3.17 (0.91, 11.00)
Hviid 2013	Autism spectrum disorder (up to 10 years – median age 5.6 years)	SSRIs (–4 weeks pregnancy to delivery)	Unexposed – adjusted for psychiatric diagnoses before delivery	1 (cohort)	4,991,3 03 py	RR 1.20 (0.90, 1.61)
Hviid 2013	Autism spectrum disorder (up to 10 years – median age 5.6 years)	SSRIs (any time)	Unexposed – adjusted for psychiatric diagnoses before delivery	1 (cohort)	4,965,8 67 py	RR 1.40 (0.92, 2.13)
Rai 2013	Autism spectrum disorder (> 3 years)	SSRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (CC)	18,524	OR 1.65 (0.90, 3.03)
Rai 2013	Autism spectrum disorder – <u>with</u> intellectual disability (> 3 years)	SSRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (CC)	NR	OR 1.01 (0.34, 2.98)
Rai 2013	Autism spectrum disorder – <u>without</u> intellectual disability (> 3 years)	SSRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (CC)	NR	OR 2.34 (1.09, 5.06)
Sørensen 2013 <i>Moderate</i>	Autism spectrum disorder (mean 8.8 years)	SSRIs (any time)	Unexposed – hospital- diagnosed affective disorder	1 (cohort)	5,799	HR 1.4 (0.8, 2.4)
Sørensen 2013	Autism spectrum disorder (mean 8.8 years)	SSRIs (any time)	Unexposed – sibling study	1 (cohort)	6,117	HR 0.9 (0.4, 2.0)
Gidaya 2014	Autism spectrum disorder (2-14 years)	SSRIs (first trimester)	Unexposed – adjusted for history of maternal depression	1 (CC)	57,360	OR 2.0 (1.5, 2.6)
Harrington 2014 <i>Moderate</i>	Autism spectrum disorder (mean 3.8 years at diagnosis)	SSRIs (first trimester)	Unexposed – history of mood/anxiety disorder	1 (CC)	229	OR 1.70 (0.66, 4.37)
Harrington 2014	Autism spectrum disorder – boys only (mean 3.8 years at diagnosis)	SSRIs (first trimester)	Unexposed – history of mood/anxiety disorder	1 (CC)	NR	OR 3.52 (0.93, 13.34)
Hviid 2013	Autism spectrum disorder (up to 10 years – median age 5.6 years)	SSRIs (first trimester)	Unexposed – adjusted for psychiatric diagnoses before delivery	1 (cohort)	4,977,8 50 py	RR 1.35 (0.97, 1.87)
Gidaya 2014	Autism spectrum disorder (2-14 years)	SSRIs (second trimester)	Unexposed – adjusted for history of maternal depression	1 (CC)	57,333	OR 2.1 (1.5, 3.0)
Harrington 2014 <i>Moderate</i>	Autism spectrum disorder (mean 3.8 years at diagnosis)	SSRIs (second trimester)	Unexposed – history of mood/anxiety disorder	1 (CC)	229	OR 1.12 (0.40, 3.11)
Harrington 2014	Autism spectrum disorder – boys only (mean 3.8 years at diagnosis)	SSRIs (second trimester)	Unexposed – history of mood/anxiety disorder	1 (CC)	NR	OR 1.80 (0.39, 8.37)
Gidaya 2014	Autism spectrum disorder (2-14 years)	SSRIs (third trimester)	Unexposed – adjusted for history of maternal depression	1 (CC)	57,328	OR 2.5 (1.7, 3.7)
Harrington 2014 <i>Moderate</i>	Autism spectrum disorder (mean 3.8 years at diagnosis)	SSRIs (third trimester)	Unexposed – history of mood/anxiety disorder	1 (CC)	229	OR 1.43 (0.52, 3.95)
Harrington 2014	Autism spectrum disorder – boys only (mean 3.8 years at diagnosis)	SSRIs (third trimester)	Unexposed – history of mood/anxiety disorder	1 (CC)	NR	OR 2.45 (0.54, 11.22)
Boukhris 2016 ³⁷⁷ <i>Moderate</i>	Autism spectrum disorder – full -term delivery (median 4 years)	SSRIs (2 nd or 3 rd trimester)	Unexposed – adjusted for prior AD use and other psychiatric disorders	1 (cohort)	144,507	HR 2.17 (1.20, 3.93)

³⁷⁷ Includes the same cohort as Bérard 2016.

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Citalopram						
Bérard 2016 ³⁷⁸ <i>Moderate</i>	Autism spectrum disorder – full -term delivery (median 4 years)	Citalopram (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	143,137	HR 2.23 (1.01, 4.92)
Fluoxetine						
Bérard 2016 ¹⁸⁴ <i>Moderate</i>	Autism spectrum disorder – full -term delivery (median 4 years)	Fluoxetine (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	142,887	HR 4.99 (1.45, 17.1)
Fluvoxamine						
Bérard 2016 ¹⁸⁴ <i>Moderate</i>	Autism spectrum disorder – full -term delivery (median 4 years)	Fluvoxamine (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	142,751	HR 7.30 (0.30, 178)
Paroxetine						
Bérard 2016 ¹⁸⁴ <i>Moderate</i>	Autism spectrum disorder – full -term delivery (median 4 years)	Paroxetine (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	143,460	HR 1.99 (1.00, 3.96)
Sertraline						
Bérard 2016 ¹⁸⁴ <i>Moderate</i>	Autism spectrum disorder – full -term delivery (median 4 years)	Sertraline (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	143,008	HR 0.45 (0.05, 4.26)
SNRIs						
Boukhris 2016 ¹⁸⁶ <i>Moderate</i>	Autism spectrum disorder – full -term delivery (median 4 years)	SNRIs (2 nd or 3 rd trimester)	Unexposed – adjusted for prior AD use and other psychiatric disorders	1 (cohort)	143,371	HR 1.04 (0.20, 5.46)
TCAs						
Rai 2013	Autism spectrum disorder (> 3 years)	Non-selective MRIs ³⁷⁹ (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (CC)	18,524	OR 2.69 (1.04, 6.96)
Rai 2013	Autism spectrum disorder – <u>with</u> intellectual disability (> 3 years)	Non-selective MRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (CC)	NR	OR 1.72 (0.20, 15.0)
Rai 2013	Autism spectrum disorder – <u>without</u> intellectual disability (> 3 years)	Non-selective MRIs (any time)	Unexposed – adjusted for any maternal psychiatric disorder	1 (CC)	NR	OR 2.93 (0.98, 8.82)
Boukhris 2016 ¹⁸⁶ <i>Moderate</i>	Autism spectrum disorder – full -term delivery (median 4 years)	TCAs (2 nd or 3 rd trimester)	Unexposed – adjusted for prior AD use and other psychiatric disorders	1 (cohort)	143,153	HR 1.03 (0.23, 4.61)
Other ADs						
Bérard 2016 ¹⁸⁴	Autism spectrum disorder – full -term delivery (median 4 years)	SNRI/TCA/MAOI, other ³⁸⁰ (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	143,495	HR 0.85 (0.28, 2.54)
Co-exposure						
Bérard 2016 ¹⁸⁴	Autism spectrum disorder – full -term delivery (median 4 years)	≥ 2 ADs (2 nd or 3 rd trimester)	Unexposed – adjusted for depression/anxiety and other psychiatric disorders	1 (cohort)	142,799	HR 4.95 (0.66, 36.8)
Boukhris 2016 ¹⁸⁶	Autism spectrum disorder – full -term delivery (median 4 years)	≥ 2 ADs (2 nd or 3 rd trimester)	Unexposed – adjusted for prior AD use and other psychiatric disorders	1 (cohort)	143,091	HR 4.39 (1.44, 13.3)

Abbreviations: AD, antidepressant; CC, case control; CI, confidence interval; HR, hazard ratio; MAOI, monoamine oxidase inhibitor; MRI, non-selective, monoamine reuptake inhibitor; OR, odds ratio; RD, risk difference; RE, risk estimate; RR, relative risk; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Eight studies examine the association between SSRIs and ASD. Seven studies are based on registry data, with five from large population-based cohorts (Denmark, Finland, Sweden) and two from a state-wide public health insurance plan cohort (Quebec, Canada). Five of the studies present results from two population-based cohorts: Gidaya 2014, Hviid 2013 and Sørensen 2013 from the Danish cohort and Bérard 2016 and Boukhris 2016 from the Quebec cohort. Two studies represent each of the Finnish and Swedish cohorts (Rai 2013 and Malm 2016, respectively). The remaining study, by Harrington 2014, uses data from a

³⁷⁸ Includes the same study cohort as Boukhris 2016.

³⁷⁹ Defined as tricyclic antidepressants (TCAs) in Rai 2013.

³⁸⁰ Other includes bupropion, amoxapine, maprotiline, mirtazapine, trazodone and nefazodone.

specific childhood autism cohort, the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, conducted in the US.

The studies are a mix of cohort and case-control design: Bérard 2016, Boukhris 2016, Malm 2016, Hviid 2013, Sørensen 2013 are cohort studies and Harrington 2014, Gidaya 2014 and Rai 2013 are case-control studies.

The other main differences between the studies are the methods they have used to take into account confounding by indication. Bérard 2016, Boukhris, Gidaya 2014, Hviid 2013 and Rai 2013 all adjusted, by varying degrees, for maternal depression/other psychiatric conditions in their analysis. In the Danish, Finnish and Swedish cohorts, data on psychiatric diagnoses was only available from inpatient and outpatient hospital services – diagnoses from general practice only were unavailable; as such, depression is likely to be substantially underreported in these studies and there is likely to be substantial residual confounding by indication. It should be noted that Gidaya 2014 attempt to address this by performing a sensitivity analysis to explore the underreporting of SSRI and depression in the dataset using a Monte Carlo simulation. The finding of this analysis are described below.

In the remaining studies, the included population was either limited to those with depression/other psychiatric illness, or the comparison was made against a depressed/psychiatric illness but unexposed population. Both methods have different limitations. While limiting the included population is likely most effective for minimising confounding by indication, it may result in a reduction in generalisability depending on the definition of the population; for example, in the subgroup analysis from Sorensen 2013 (Danish cohort) that has been included in this Review, the population is limited to those with hospital-diagnosed affective disorder which may represent a cohort with more severe illness. However, this method does not limit the internal validity of the findings. On the other hand, limiting only the comparator group may provide a more generalisable population, but may impact on the validity of the study. In the study by Malm 2016 (Finnish cohort), the exposed population includes all women dispensed a prescription for SSRIs – this population would include women who received their prescription via general practice. However, one of the comparator populations (psychiatric disorder/no medication) was limited to unexposed women with a diagnosis of a psychiatric disorder, which would only have come from a hospital-based service (due to the nature of the registers used in the study). Thus, the two populations are not truly comparable: hospital and general practice-managed women are included in the exposed population and hospital only-managed women are included in the unexposed population. Thus, the comparison is at risk of selection bias. For this reason, the primary findings from the Malm 2016 study included in this Review are those that compare SSRI-exposed women with women who discontinued SSRIs during pregnancy; both groups in this comparison would include women with general practice only-managed psychiatric illness as well as hospital-managed psychiatric illness.

The final point to note is that none of these studies collect data on severity of disease either during pregnancy or in the years after pregnancy, prior to the diagnosis of ASD in the child. This means that there is likely to be substantial residual confounding by indication present in all studies, even in those studies that have limited their assessment to a depressed population, and is why all studies were considered within the current Review to have a high risk of bias.

A summary of these methodological considerations is presented in **Table AppD4-26**. While the results of these studies are meta-analysed below, interpretation of the findings has been made with these methodological limitations in mind.

Table AppD4-26 Methodological characteristics of studies examining the association between SSRIs and ASD

Study	Location	Study type	Population included/ limited in analysis included in review	Method used for confounding by indication in analysis used in review	Adjustment for disease severity during and after pregnancy?	Includes diagnoses from general practice	Risk of bias ³⁸¹	Generalisability
Bérard 2016	Quebec, Canada	Cohort	Publicly insured	Adjustment for maternal depression/ anxiety	No	Yes	High	Moderate
Boukhris 2016	Quebec, Canada	Cohort	Publicly insured	Adjustment for history of maternal psychiatric conditions	No	Yes	High	Moderate
Malm 2016	Finland	Cohort	General	Limited comparator population to those who discontinued SSRIs and adjusted for maternal and paternal history of other psychiatric diagnosis	No	Yes	High	Moderate
Harrington 2014	California, US	Case control	History of anxiety mood disorder	Limited population	No	Yes	High	Moderate
Gidaya 2014	Denmark	Case control	General	Adjustment for history of maternal depression and other SSRI conditions	No	No	High	High
Hviid 2013	Denmark	Cohort	General	Adjustment for psychiatric diagnoses before delivery	No	No	High	High
Rai 2013	Sweden	Nested case control	General	Adjustment for psychiatric disorders in the parents	No	No	High	High
Sørensen 2013	Denmark	Cohort	Hospital-diagnosed affective disorder	Limited population	No	No	High	Low

Abbreviations: ASD, autism spectrum disorder; SSRI, selective serotonin reuptake inhibitor.

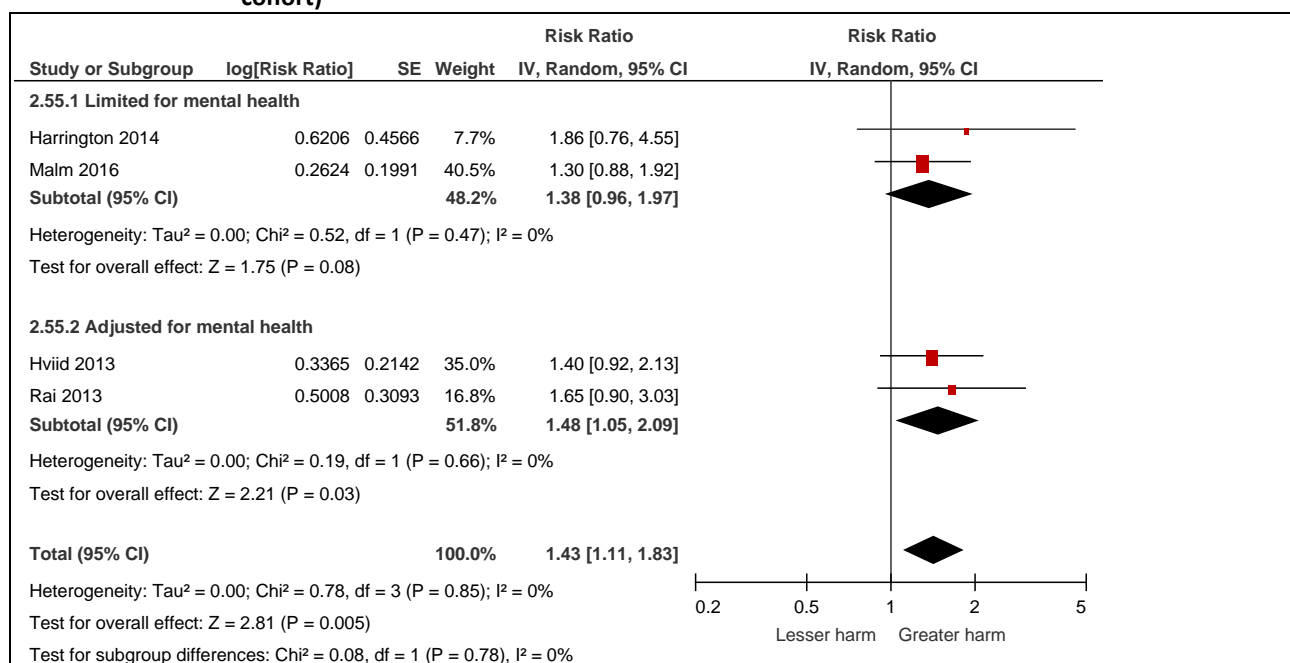
³⁸¹ All studies considered to be at a high risk of bias for ASD, at a minimum due to their retrospective nature and lack of adjustment for severity of disease during and after pregnancy.

The results of three meta-analyses of the association between exposure to SSRIs at any time during pregnancy and ASD (which include one each of the three Danish cohort studies) are presented in **Figure AppD4-41**, **Figure AppD4-42** and **Figure AppD4-43**.

The analysis shown in **Figure AppD4-41** includes the Hviid 2013 study to represent the Danish cohort. The overall result shows a significant association between SSRIs and ASD (RR 1.43; 95% CI 1.11, 1.83).

Harrington 2014, also performed a subgroup analysis on boys only and found no significant association (RR 3.17; 95% CI 0.91, 11.00), while Rai 2013 presented additional subgroup analyses based on the presence or absence of intellectual disability and found no significant association in the population with intellectual disability (RR 1.01; 95% CI 0.34, 2.98), and a significant association in the population without intellectual disability (RR 2.34; 95% CI 1.09, 5.06).

Figure AppD4-41 Autism spectrum disorder: SSRIs in pregnancy versus unexposed (including Hviid 2013/Danish cohort)

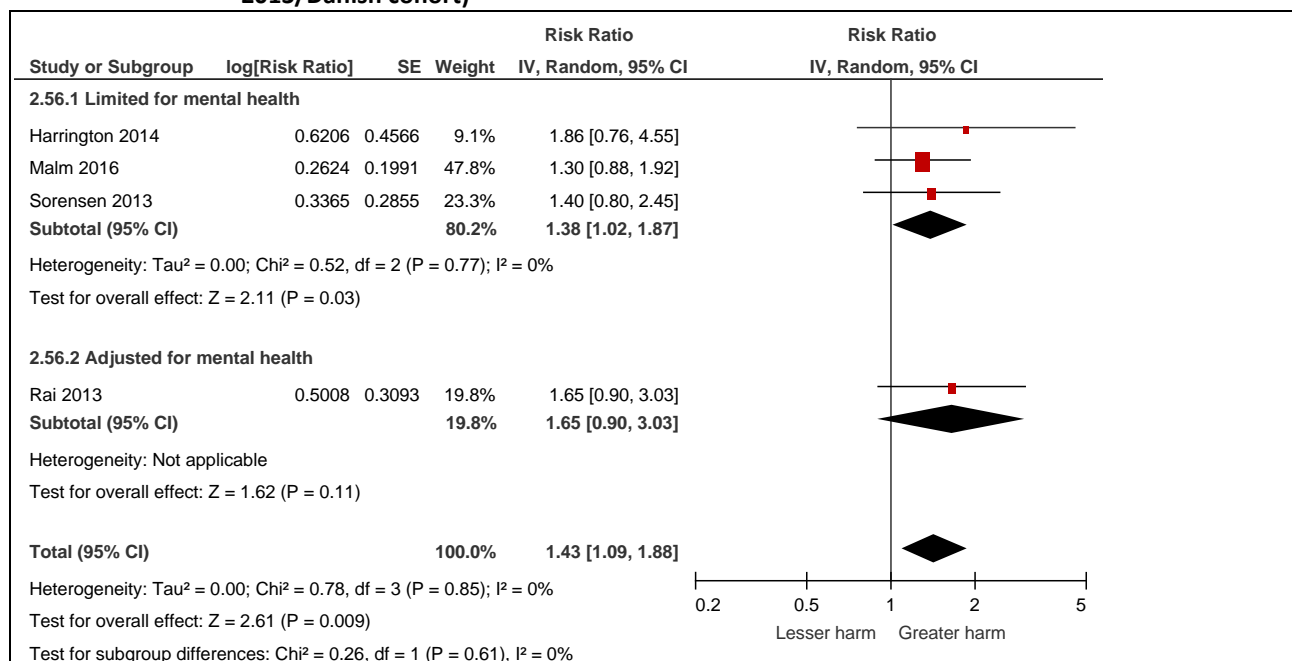


Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Similarly, the analysis shown in **Figure AppD4-42** (which includes Sorensen 2013 to represent the Danish cohort) also shows a significant association between SSRIs and ASD (RR 1.43; 95% CI 1.09, 1.88).

Sørensen 2013 also performed an analysis using a sibling comparator group and showed no significantly increased risk (RR 0.90; 95% CI 0.40, 2.02).

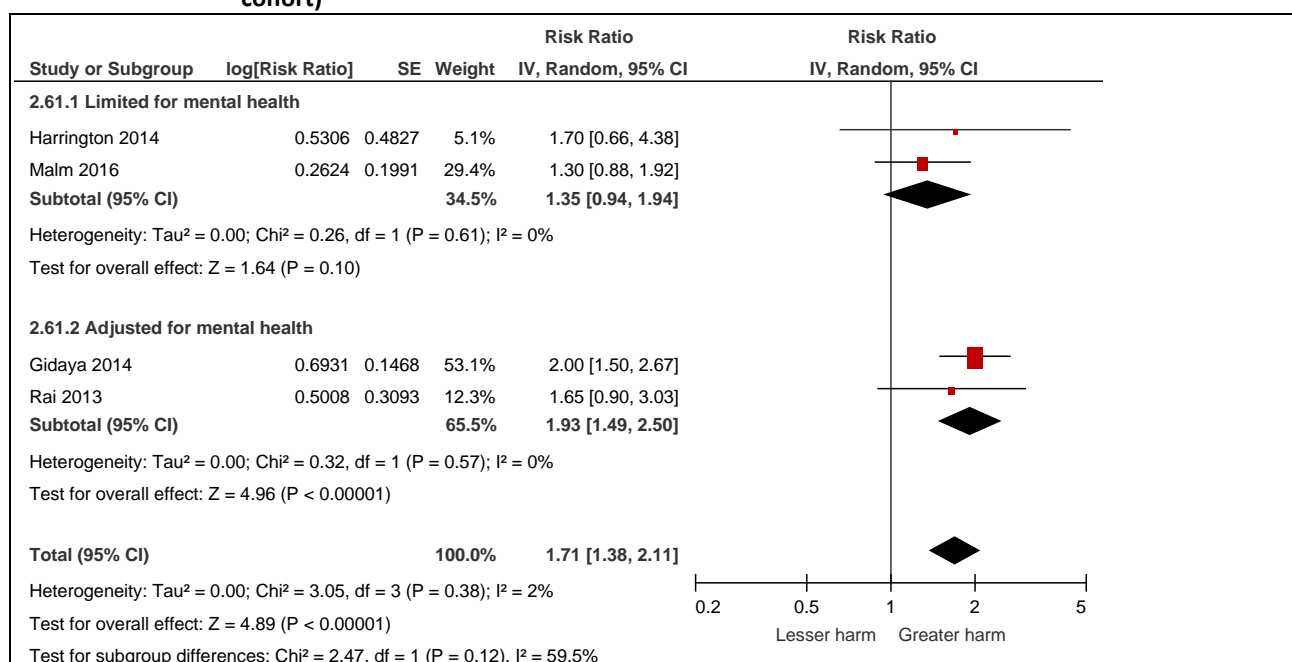
Figure AppD4-42 Autism spectrum disorder: SSRIs in pregnancy versus unexposed (including Sørensen 2013/Danish cohort)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Finally, the analysis shown in **Figure AppD4-43** (which includes Gidaya 2014 to represent the Danish cohort), also shows a significant association between SSRIs and ASD (RR 1.71; 95% CI 1.38, 2.11).

Interestingly, Gidaya 2014 performed a Monte Carlo simulation to adjust for the under reporting of depression in the Danish cohort. When they assumed the prevalence of depression was 15%, the result remained statistically significant (RR 1.9; 95% CI 1.5, 2.4). However, when they then restricted the simulated analysis to those with depression, the association between SSRIs and ASD was no longer significant (RR 1.4; 95% CI 0.9, 2.4).

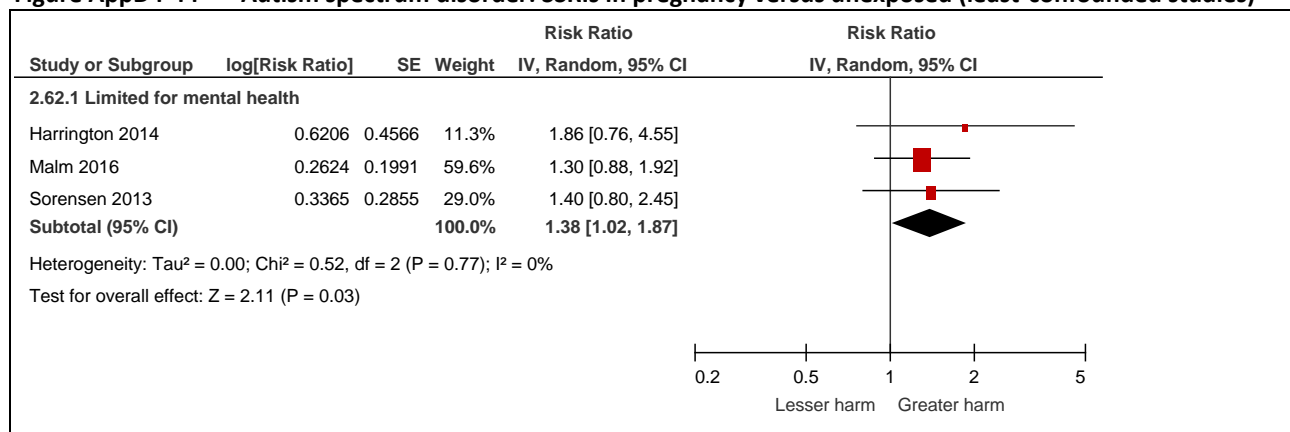
Figure AppD4-43 Autism spectrum disorder: SSRIs in pregnancy versus unexposed (including Gidaya 2014/Danish cohort)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

In order to minimise the potential for confounding by indication, the studies that identified the population or variables via hospital-based data only have been excluded from the analysis. While Malm 2016 (Finland) and Sorensen 2013 (Denmark) used data from these cohorts, they presented comparisons that are less likely to be affected by residual confounding by indication (as described above) and so have been included. Harrington 2014 has also been included because they include an analysis that was limited to those with a history of and anxiety/mood disorder. As shown in **Figure AppD4-44**, including only these studies results in a significant association between SSRIs at any time during pregnancy and ASD (RR 1.38; 95% CI 1.02, 1.87).

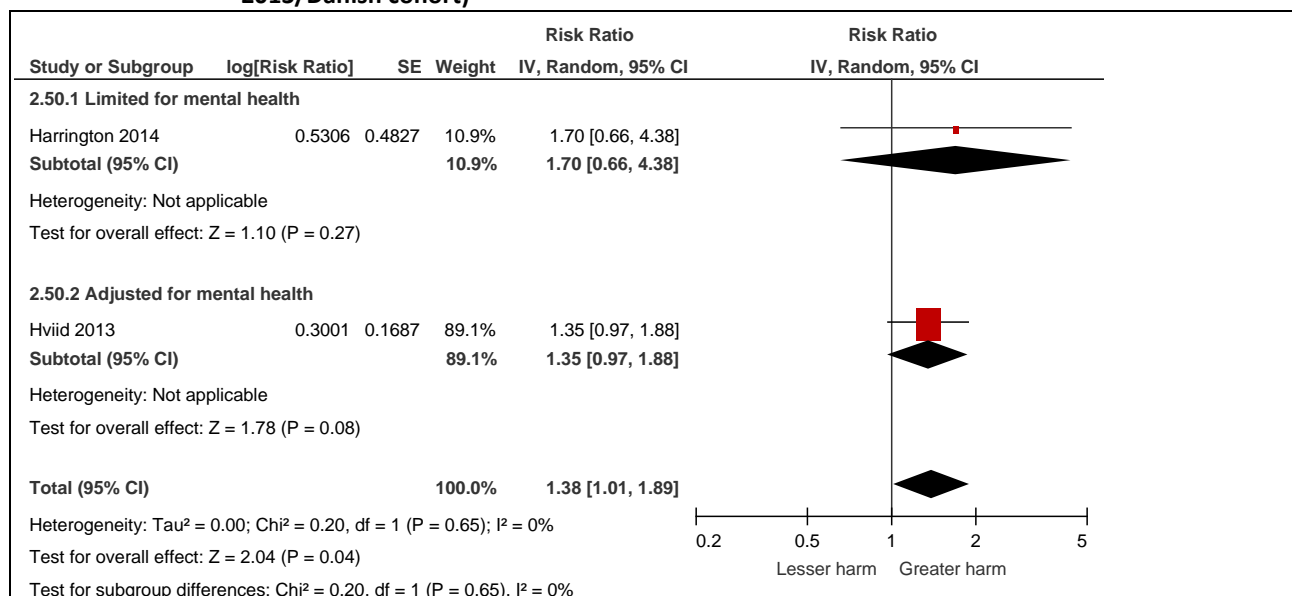
Figure AppD4-44 Autism spectrum disorder: SSRIs in pregnancy versus unexposed (least-confounded studies)



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

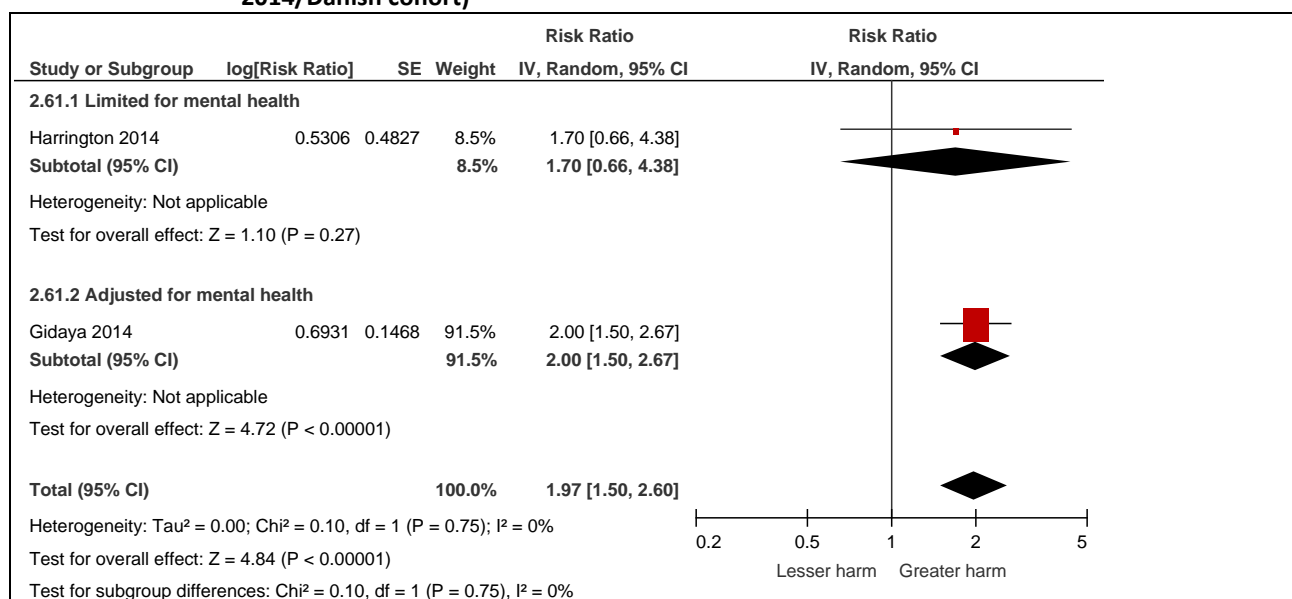
Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Three studies assessed the association between exposure to SSRIs during the first trimester and ASD. Two of these studies were from the same Danish cohort and are analysed separately. As shown in **Figure AppD4-45**, meta-analysis of the Harrington 2014 and Hviid 2013 studies suggests a significant association between SSRIs in first trimester and ASD. A stronger association is seen when the Gidaya study is included in the analysis; however, once again this study is subject to a high risk of bias. Harrington 2014, who limited the comparator group to those with a history of mood/anxiety disorder found no significant association (RR 1.70; 0.66, 4.38), although this finding is subject to substantial imprecision because the 95% CI includes a measure of appreciable benefit and harm (RR 0.75/1.25). Harrington 2014 also performed a subgroup analysis on boys only and found no significant association (OR 3.52; 95% CI 0.93, 13.34); this was also subject to imprecision.

Figure AppD4-45 Autism spectrum disorder: SSRIs in first trimester versus unexposed (including Hviid 2013/Danish cohort)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

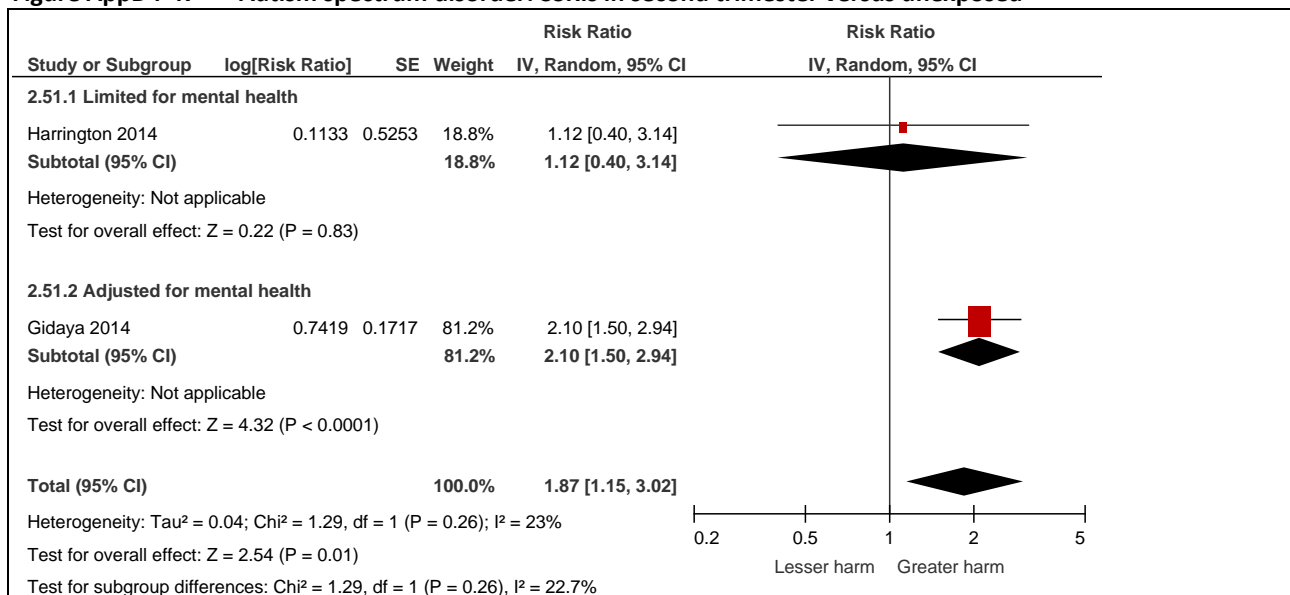
Figure AppD4-46 Autism spectrum disorder: SSRIs in first trimester versus unexposed (including Gidaya 2014/Danish cohort)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Two studies assessed the association between SSRIs during the second trimester and ASD using ORs, as shown in **Figure AppD4-47**. The pooled results showed a significantly increased risk of ASD (RR 1.87; 95% CI 1.15, 3.02), although this is largely driven by the Gidaya 2014 study which is at high risk of bias. Harrington 2014 limited the comparator group to those with a history of mood/anxiety disorder and found no significant association, although the finding is subject to substantial imprecision because the 95% CI includes a measure of appreciable benefit and harm.³⁸² Harrington 2014 also performed a subgroup analysis on boys only and found no significant association (OR 1.80; 95% CI 0.39, 8.37), although this result was also subject to imprecision (RR 0.75/1.25).

³⁸² Because the prevalence of autism spectrum disorder is low (e.g. 0.8% in Hviid 2016 in the overall population), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

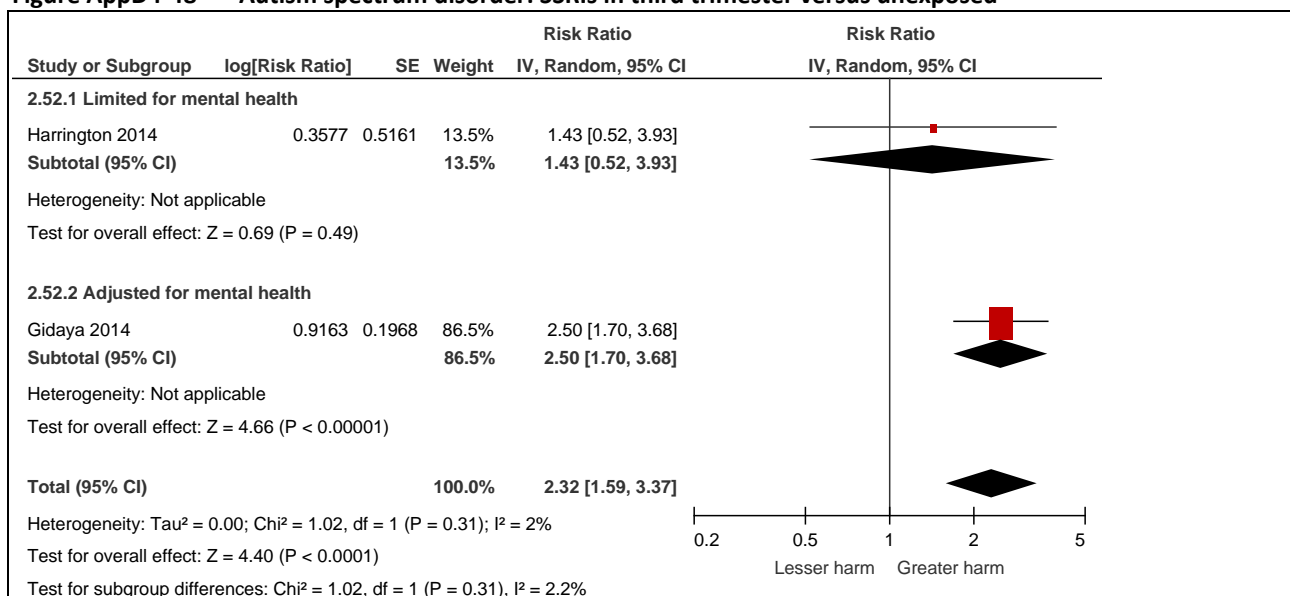
Figure AppD4-47 Autism spectrum disorder: SSRIs in second trimester versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Two studies assessed the association between SSRIs during the third trimester and ASD using ORs, as shown in **Figure AppD4-48**. Harrington 2014 limited the comparator group to those with a history of mood/anxiety disorder and found no significant association, although the finding is subject to imprecision because the 95% CI includes a measure of appreciable benefit and harm (RR 0.75/1.25). The much larger Gidaya 2014 study, which is at a high risk of bias, showed a highly significant association between first-trimester SSRI exposure and ASD. The pooled result, largely driven by the Gidaya 2014 result, showed a significantly increased risk (RR 2.32; 95% CI 1.59, 3.37).

Harrington 2014 also performed a subgroup analysis on boys only and found no significant association (OR 2.45; 95% CI 0.54, 11.22), although this was also subject to imprecision.

Figure AppD4-48 Autism spectrum disorder: SSRIs in third trimester versus unexposed

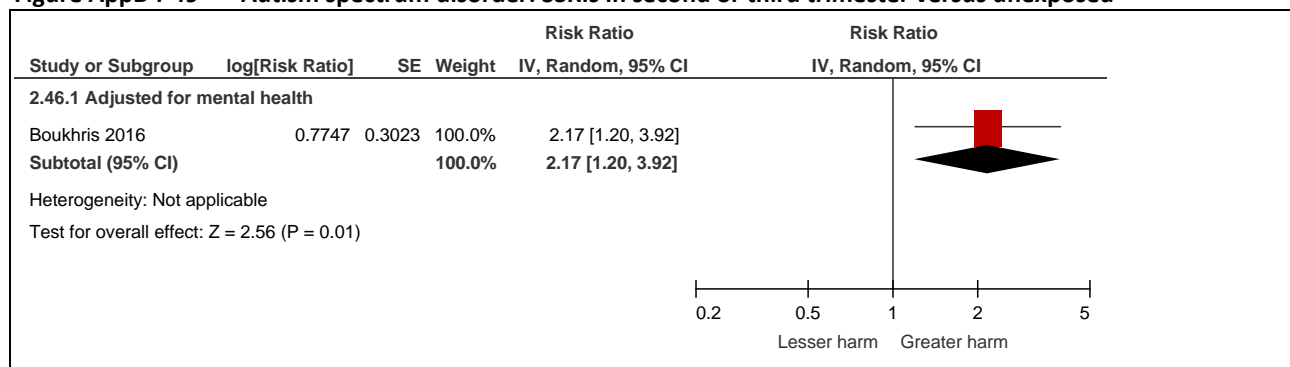
Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Finally, Boukhris 2016 examined the association between second or third trimester SSRI exposure and ASD in full-term deliveries and found a significantly increased risk (RR 2.17; 95% CI 1.20, 3.93). This analysis was

not limited to an appropriate comparator population but was instead adjusted for prior antidepressant use and other psychiatric disorders.

Figure AppD4-49 Autism spectrum disorder: SSRIs in second or third trimester versus unexposed

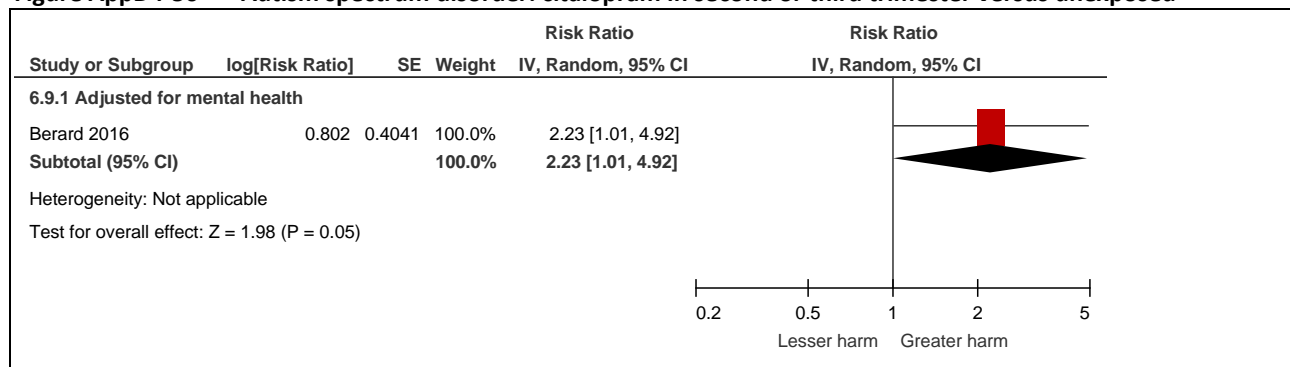


Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Bérard 2016 examined the association between second or third trimester citalopram exposure and ASD in full-term deliveries and found a significantly increased risk (RR 2.23; 95% CI 1.01, 4.92; **Figure AppD4-50**). This analysis was not limited to an appropriate comparator population but was instead adjusted for depression/anxiety and other psychiatric disorders.

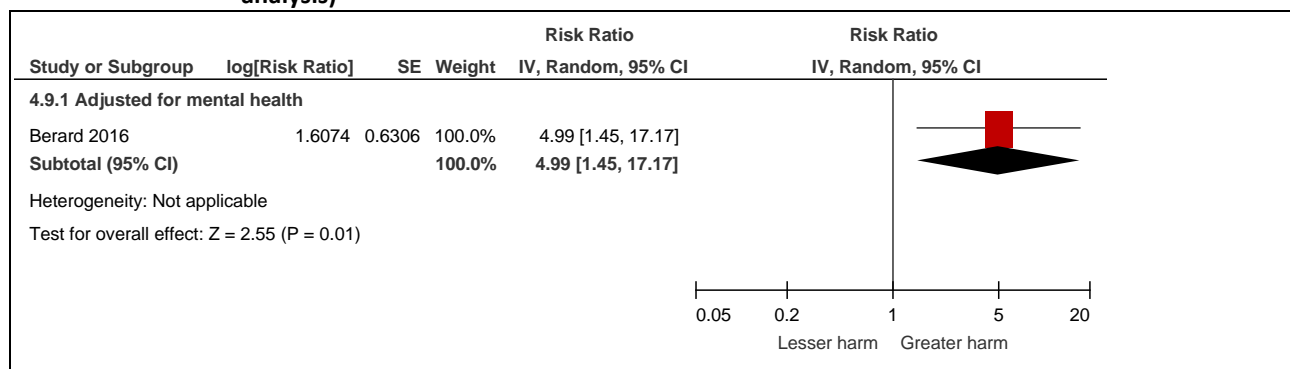
Figure AppD4-50 Autism spectrum disorder: citalopram in second or third trimester versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

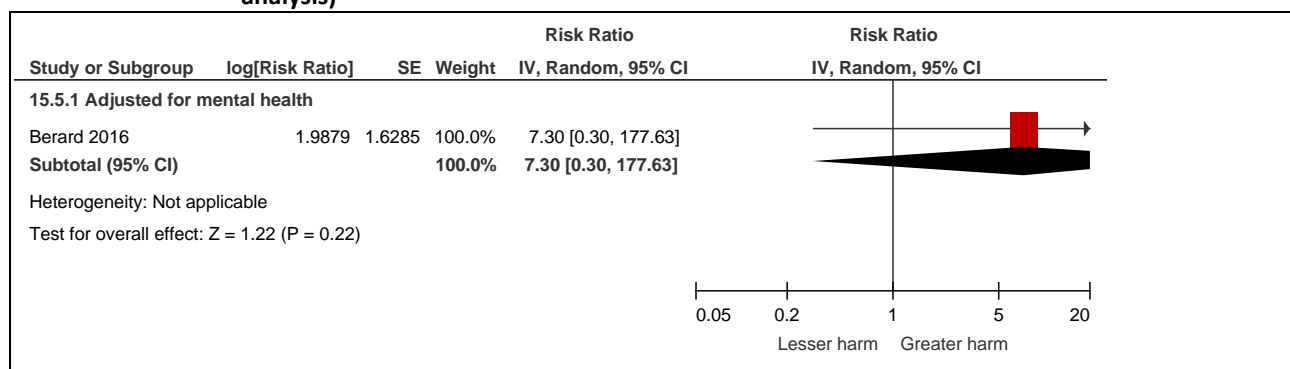
Bérard 2016 examined the association between second or third trimester fluoxetine exposure and ASD in full-term deliveries and found a significantly increased risk (RR 4.99; 95% CI 1.45, 17.2; **Figure AppD4-51**). This analysis was not limited to an appropriate comparator population but was instead adjusted for depression/anxiety and other psychiatric disorders.

Figure AppD4-51 Autism spectrum disorder: fluoxetine in second or third trimester versus unexposed (HR analysis)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Bérard 2016 examined the association between second or third trimester fluvoxamine exposure and ASD in full-term deliveries and found no significantly increased risk (RR 7.30; 95% CI 0.30, 178; **Figure AppD4-52**); however, this analysis was imprecise.³⁸³ This analysis was not limited to an appropriate comparator population but was instead adjusted for depression/anxiety and other psychiatric disorders.

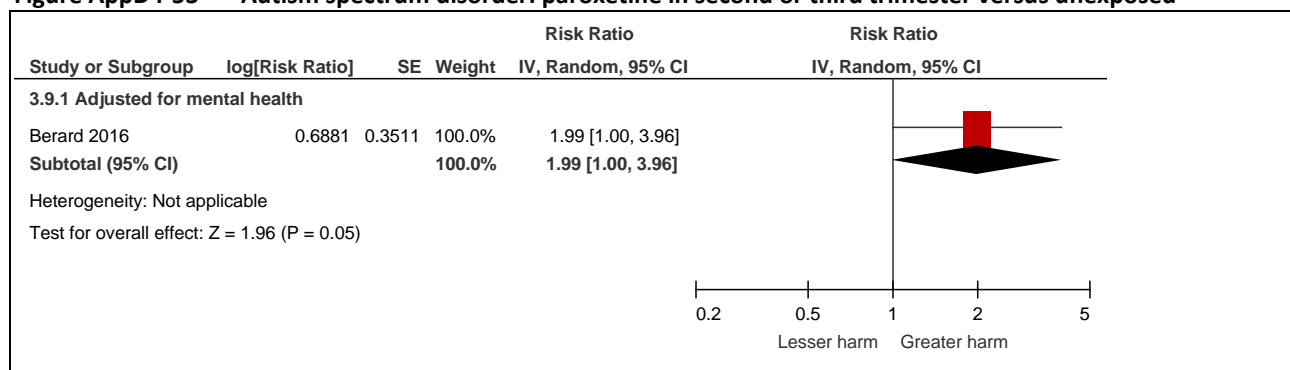
Figure AppD4-52 Autism spectrum disorder: fluvoxamine in second or third trimester versus unexposed (HR analysis)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Bérard 2016 examined the association between second or third trimester paroxetine exposure and ASD in full-term deliveries and found a borderline significantly increased risk (RR 1.99; 95% CI 1.00, 3.96; **Figure AppD4-53**). This analysis was not limited to an appropriate comparator population but was instead adjusted for depression/anxiety and other psychiatric disorders.

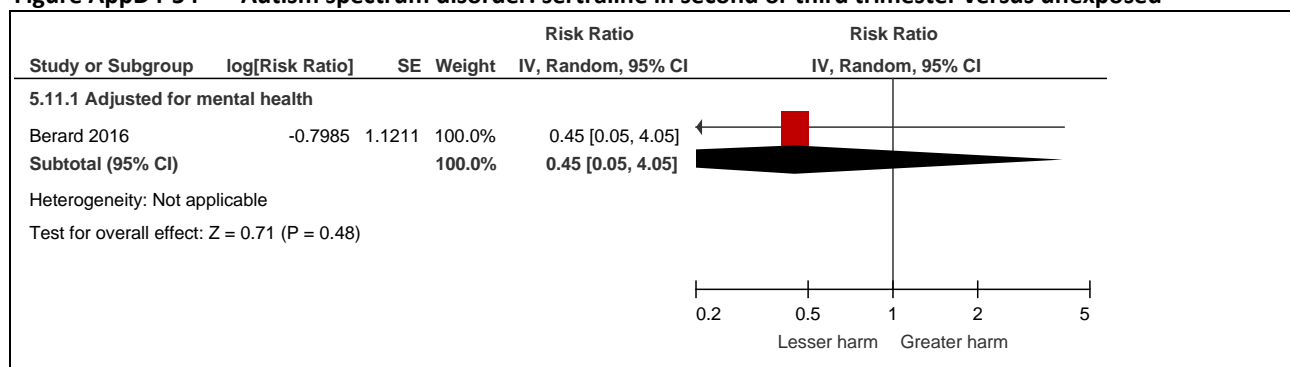
³⁸³ Because the prevalence of autism spectrum disorder is low (e.g. 0.8% in Hviid 2016 in the overall population), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-53 Autism spectrum disorder: paroxetine in second or third trimester versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

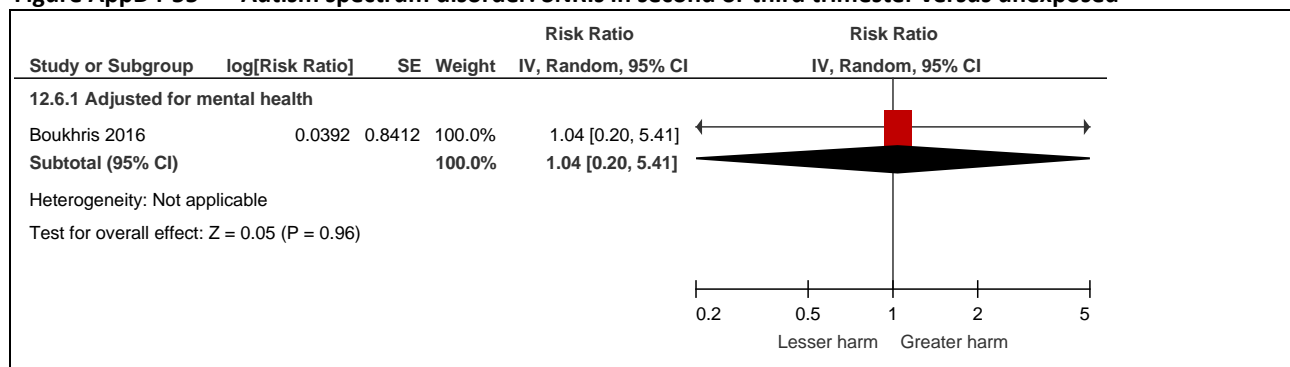
Bérard 2016 examined the association between second or third trimester sertraline exposure and ASD in full-term deliveries and showed no significantly increased risk (RR 0.45; 95% CI 0.05, 4.26; **Figure AppD4-54**). This finding is subject to imprecision (RR 0.75/1.25). This analysis was not limited to an appropriate comparator population but was instead adjusted for depression/anxiety and other psychiatric disorders.

Figure AppD4-54 Autism spectrum disorder: sertraline in second or third trimester versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Boukhris 2016 examined the association between second or third trimester SNRI exposure and ASD in full-term deliveries and showed no significantly increased risk (RR 1.04; 95% CI 0.20, 5.46; **Figure AppD4-55**). This finding is subject to imprecision (RR 0.75/1.25). This analysis was not limited to an appropriate comparator population but was instead adjusted for prior antidepressant use and other psychiatric disorders.

Figure AppD4-55 Autism spectrum disorder: SNRIs in second or third trimester versus unexposed

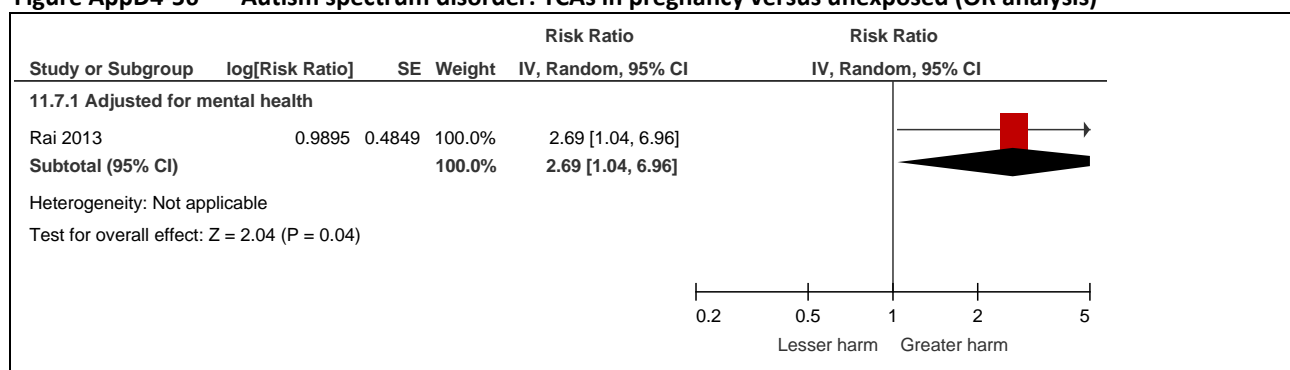
Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Rai 2013 examined the association between TCAs³⁸⁴ in pregnancy and ASD and found no significantly increased risk (RR 2.69; 95% CI 1.04, 6.96; **Figure AppD4-56**); however, this analysis was imprecise (RR 0.75/1.25) and at a high risk of bias due to under ascertainment of depression diagnoses because the Swedish cohort did not include data from general practice.

Rai 2013 also presented additional subgroup analyses based on the presence or absence of intellectual disability and found no significant association in the population with intellectual disability (OR 1.72; 95% CI 0.20, 15.0), or without intellectual disability (OR 2.93; 95% CI 0.98, 8.82). Both findings are subject to substantial imprecision.³⁸⁵

Figure AppD4-56 Autism spectrum disorder: TCAs in pregnancy versus unexposed (OR analysis)

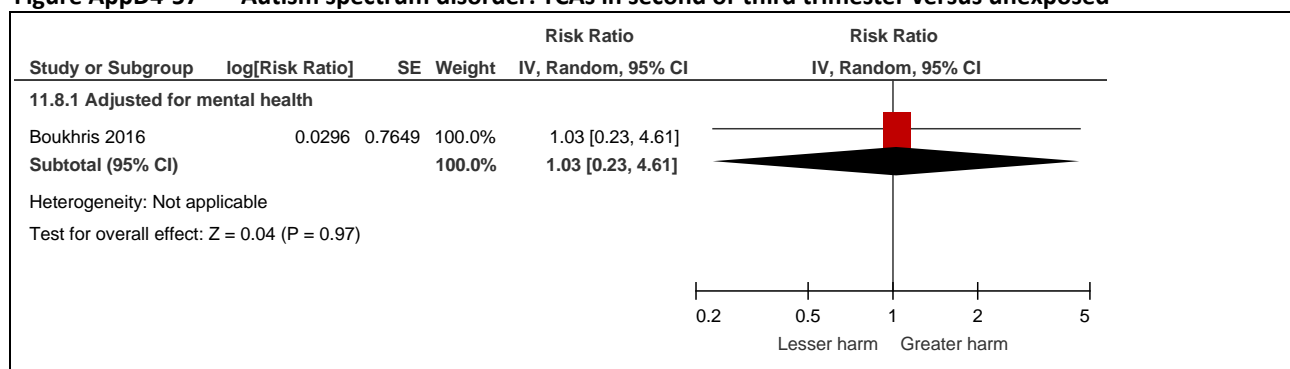


Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Boukhris 2016 examined the association between TCAs in second or third trimester and ASD in full-term deliveries and found no significantly increased risk (RR 1.03; 95% CI 0.23, 4.61; **Figure AppD4-56**); however, this analysis was imprecise (RR 0.75/1.25). This analysis was not limited to an appropriate comparator population but was instead adjusted for prior antidepressant use and other psychiatric disorders.

Figure AppD4-57 Autism spectrum disorder: TCAs in second or third trimester versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

A number of studies examined other outcomes associated with autism spectrum disorder; each are described below.

Childhood autism

A summary of the results regarding the association between antidepressant use and childhood autism (ICD-10 F84.0) is presented in **Table AppD4-27**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other

³⁸⁴ Called non-selective monoamine reuptake inhibitors in the publication, as defined as being TCAs.

³⁸⁵ Because the prevalence of autism spectrum disorder is low (e.g. 0.8% in Hviid 2016 in the overall population), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of childhood autism in the depressed or psychiatric diagnosis/unexposed population,³⁸⁶ it is assumed that the odds ratio (OR) approximates the relative risk (RR) and where possible, these risk estimates have been pooled together in order to calculate a single relative effect estimate.

Table AppD4-27 Antidepressants – childhood autism outcomes from observational studies

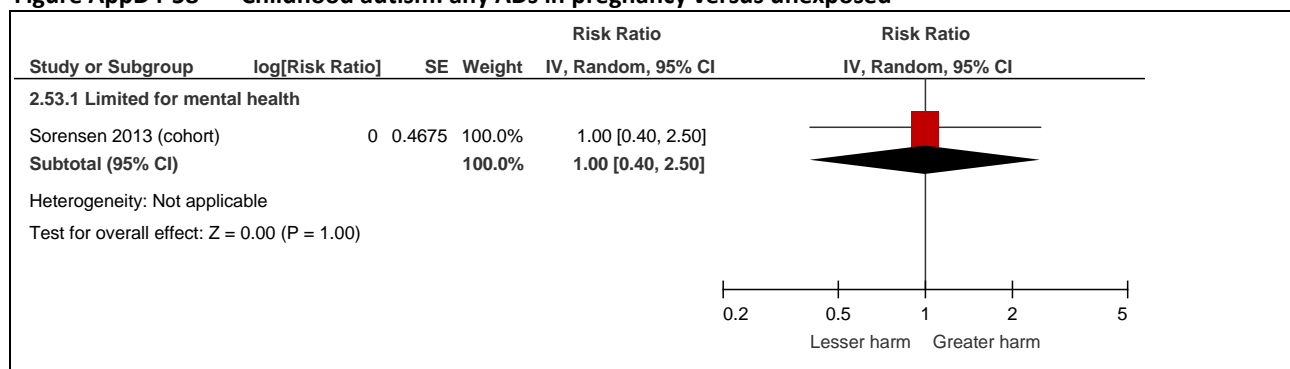
Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Sørensen 2013	Childhood autism (mean 8.8 years)	Any ADs (any time)	Unexposed – hospital-diagnosed affective disorder	1 (cohort)	6,080	HR 0.8 (0.3, 2.1)
Sørensen 2013 <i>Moderate</i>	Childhood autism (mean 8.8 years)	SSRIs (any time)	Unexposed – hospital-diagnosed affective disorder	1 (cohort)	5,799	HR 1.0 (0.4, 2.6)

Abbreviations: AD, antidepressant; CI, confidence interval; HR, hazard ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Sørensen 2013 (from the Danish cohort) provided data on the association between exposure to SSRIs at any time during pregnancy and childhood autism; the study limited the population to those with a hospital-diagnosed affective disorder (**Figure AppD4-58**). The result showed no significant association (HR 1.0; 95% CI 0.4, 2.6); however, this was imprecise because the 95% CI includes a measure of appreciable benefit or harm (RR 0.75/1.25).

Figure AppD4-58 Childhood autism: any ADs in pregnancy versus unexposed



Abbreviations: AD, antidepressant; CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Pervasive developmental disorder

While an ICD code for pervasive developmental disorder was an outcome included in the studies described above for ASD, two smaller prospective cohort studies specifically examined pervasive developmental disorder using the Child Behaviour Checklist (CBCL). These are described here.

A summary of the results regarding the association between exposure to SSRIs and pervasive developmental disorder (PDD) is presented in **Table AppD4-29**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the

³⁸⁶ There was no data available specifically regarding the prevalence of childhood autism in offspring of the depressed maternal population; however, it is likely to be very low based on the on the pooled prevalence from Sørensen 2013 and Malm 2016 of ASD in this population.

Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of childhood in the depressed or psychiatric diagnosis/unexposed population,³⁸⁷ it is assumed that the odds ratio (OR) approximates the relative risk (RR) and where possible, these risk estimates have been pooled together in order to calculate a single relative effect estimate.

Table AppD4-28 Antidepressants – pervasive developmental disorder outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
SSRIs						
El Marroun 2014 <i>High</i>	Pervasive developmental problems (mother-rated) ³⁸⁸ (1.5–6 years)	SSRIs (any time)	Unexposed – depression and adjusted for maternal depressive symptoms at 3 years postnatal	1 (cohort)	445	OR 1.33 (0.68, 2.57)
Johnson 2016 <i>High</i>	Pervasive developmental disorder (mother-rated) ³⁸⁹ (2.5 – 5.5 years)	SSRIs (any time)	Unexposed – attended mental health clinic	1 (cohort)	178	OR 1.05 (1.01, 1.08)
Johnson 2016 <i>High</i>	Pervasive developmental disorder (alternate caregiver-rated) ²⁸⁴ (2.5 – 5.5 years)	SSRIs (any time)	Unexposed – attended mental health clinic	1 (cohort)	178	OR 1.01 (0.98, 1.05)

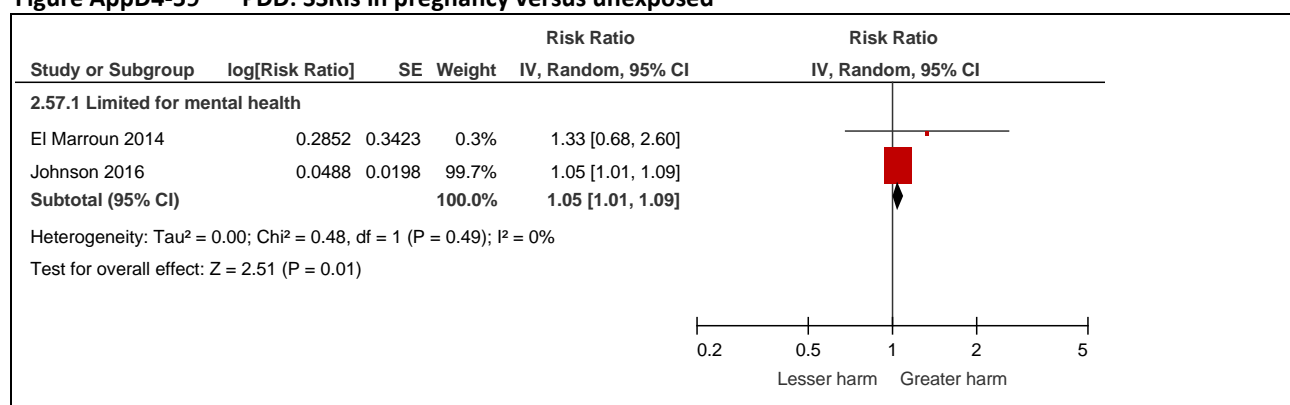
Abbreviations: CI, confidence interval; OR, odds ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Two studies provided data on the association between exposure to SSRIs at any time during pregnancy and PDD (as measured by the mother); both studies limited the population to those with depression/attending a mental health clinic (**Figure AppD4-59**). The result showed a significant association (RR 1.05; 95% CI 1.01, 1.09). Of interest, the analysis is mostly influenced by the data from the Johnson 2016 study because it is the more precise study.

Johnson 2016 also examined the association between exposure to SSRIs at any time during pregnancy and PDD as measured by an alternative caregiver (e.g., father, babysitter, teacher, grandmother) and found no significant association (RR 1.01; 95% CI 0.98, 1.05).

Figure AppD4-59 PDD: SSRIs in pregnancy versus unexposed



Abbreviations: AD, antidepressant; CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

³⁸⁷ There was no data available specifically regarding the prevalence of PDD in offspring of the depressed maternal population; however, it is likely to be very low based on the pooled prevalence from Sørensen 2013 and Malm 2016 of ASD in this population.

³⁸⁸ Measured using the PDD subscale of the Dutch version of the CBCL. At risk children were those with a score > 7.

³⁸⁹ Measured using the PDD subscale of the CBCL. At risk children were those with a score > 65.

Autistic traits

A summary of the results regarding the association between exposure to SSRIs and autistic traits is presented in **Table AppD4-29**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

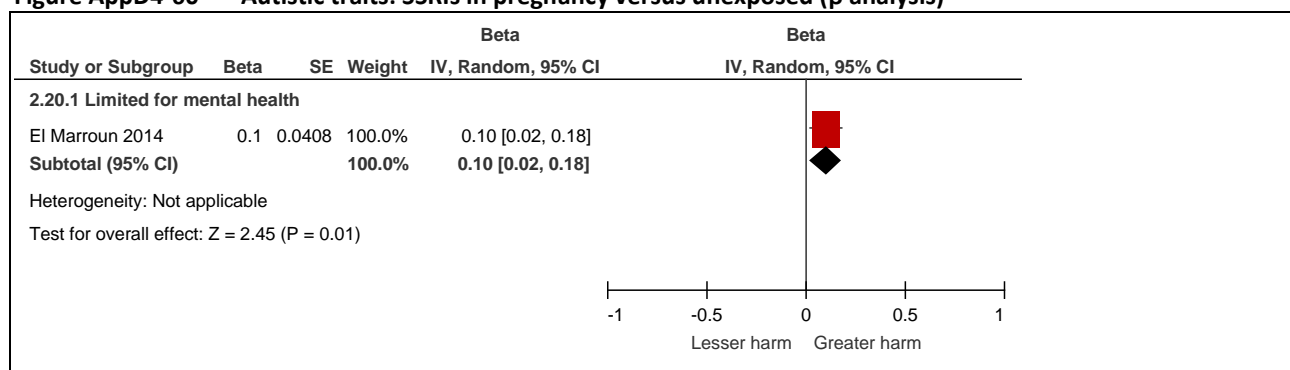
Table AppD4-29 Antidepressants – autistic traits outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
El Marroun 2014 <i>High</i>	Autistic traits – SRS ³⁹⁰ (6 years)	SSRIs (any time)	Unexposed – depression	1 (cohort)	445	β 0.10 (0.02, 0.18)

Abbreviations: AD, antidepressant; CI, confidence interval; HR, hazard ratio; RE, risk estimate; SRS, social Responsiveness Scale; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

One study provided data on the association between exposure to SSRIs during pregnancy and autistic traits as measured by the Social Responsiveness Scale (SRS); the study limited the population to those with depression (**Figure AppD4-60**). The result showed a significant association (β 0.10; 95% CI 0.02, 0.18).

Figure AppD4-60 Autistic traits: SSRIs in pregnancy versus unexposed (β analysis)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Social cognition

A summary of the results regarding the association between exposure to SSRIs and social cognition is presented in **Table AppD4-30**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

³⁹⁰ Measured using the adapted 18-item version of the Social Responsiveness Scale (SRS) at age 6 years, which is a quantitative measure of autistic traits for children aged between 4 and 18 years. The 18-item questionnaire contained items from three subscales: social cognition, social communication and autistic mannerism. The (weighted) sum score of autistic traits ranged between 0 and 2.83.

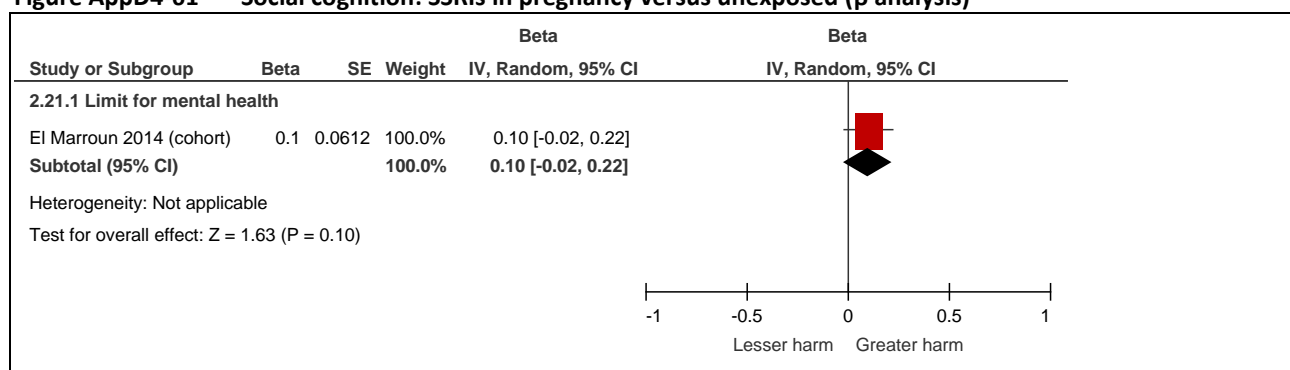
Table AppD4-30 Antidepressants – social cognition outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
El Marroun 2014 <i>High</i>	Social cognition - SRS (6 years)	SSRIs (any time)	Unexposed – depression	1 (cohort)	445	β 0.10 (-0.02, 0.22)

Abbreviations: AD, antidepressant; CI, confidence interval; HR, hazard ratio; RE, risk estimate; SRS, social Responsiveness Scale; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

One study provided data on the association between exposure to SSRIs during pregnancy and social cognition, as measured by a subscale of the SRS; the study limited the population to those with depression (**Figure AppD4-61**). The result showed no significant association (β 0.10; 95% CI -0.02, 0.22).

Figure AppD4-61 Social cognition: SSRIs in pregnancy versus unexposed (β analysis)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Social communication

A summary of the results regarding the association between exposure to SSRIs and social communication is presented in **Table AppD4-31**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

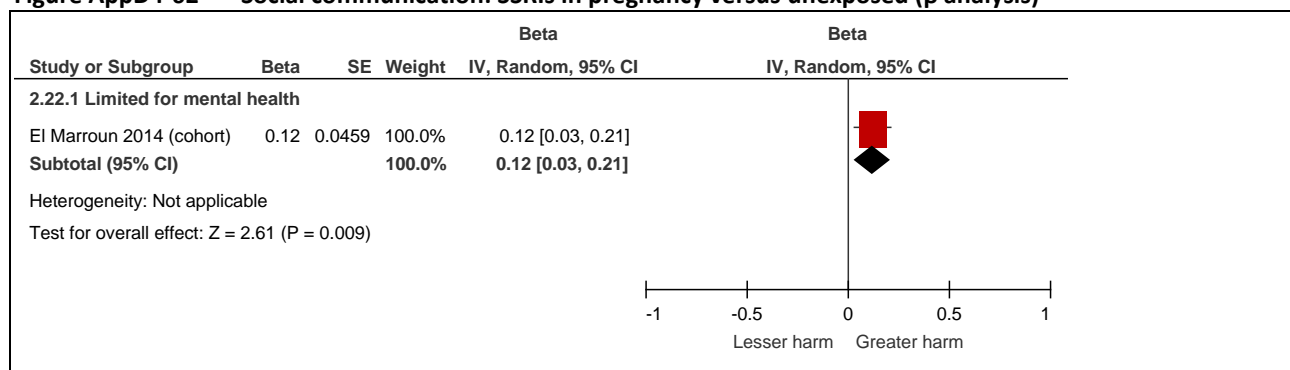
Table AppD4-31 Antidepressants – social communication outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
El Marroun 2014 <i>High</i>	Social communication – SRS (6 years)	SSRIs (any time)	Unexposed – depression	1 (cohort)	445	β 0.12 (0.03, 0.21)

Abbreviations: AD, antidepressant; CI, confidence interval; HR, hazard ratio; RE, risk estimate; SRS, social Responsiveness Scale; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

One study provided data on the association between exposure to SSRIs during pregnancy and social communication, as measured by a subscale of the SRS; the study limited the population to those with depression (**Figure AppD4-62**). The result showed a significant association (β 0.12; 95% CI 0.03, 0.21).

Figure AppD4-62 Social communication: SSRIs in pregnancy versus unexposed (β analysis)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Autistic mannerism

A summary of the results regarding the association between exposure to SSRIs and autistic mannerism is presented in **Table AppD4-32**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

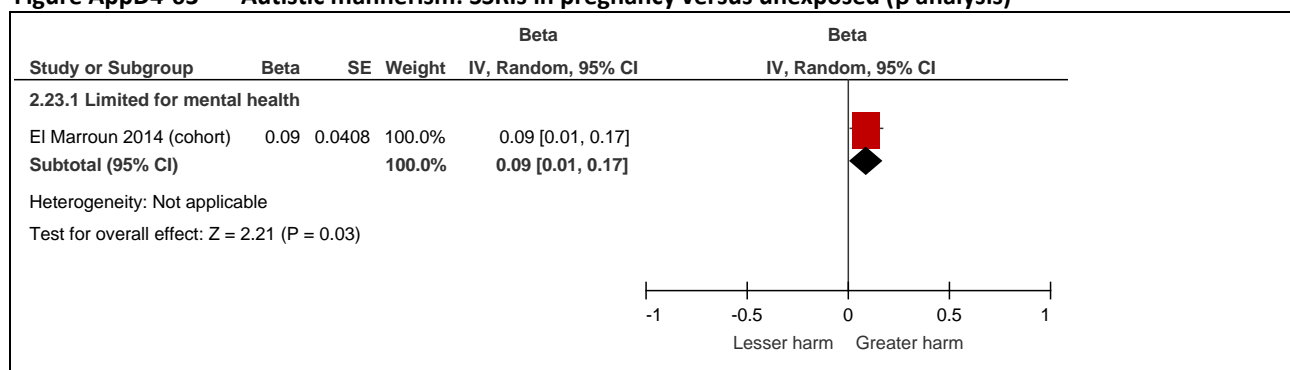
Table AppD4-32 Antidepressants – autistic mannerism outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
El Marroun 2014 <i>High</i>	Autistic mannerism (6 years)	SSRIs (any time)	Unexposed – depression	1 (cohort)	445	β 0.09 (0.01, 0.17)

Abbreviations: AD, antidepressant; CI, confidence interval; HR, hazard ratio; RE, risk estimate; SRS, social Responsiveness Scale; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

One study provided data on the association between exposure to SSRIs during pregnancy and autistic mannerism, as measured by a subscale of the SRS; the study limited the population to those with depression (**Figure AppD4-63**). The result showed a significant association (β 0.09; 95% CI 0.01, 0.17).

Figure AppD4-63 Autistic mannerism: SSRIs in pregnancy versus unexposed (β analysis)

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.1.17 Attention-deficit hyperactivity disorder (ADHD) – antidepressants**AppD4.1.1.17.1 Results based on systematic reviews**

No SRs were identified that provided analyses of the association between antidepressants and ADHD based on either data adjusted for potential confounding or used the appropriate comparator population. *As such, an examination of the results of individual studies has been undertaken for this outcome.*

AppD4.1.1.17.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and attention-deficit hyperactivity disorder (ADHD) is presented in **Table AppD4-33**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of ADHD in the psychiatric diagnosis/unexposed population (~1.0%),³⁹¹ it is assumed that the odds ratio (OR) approximates the relative risk (RR) and where possible, these risk estimates have been pooled together in order to calculate a single relative effect estimate.

Table AppD4-33 Antidepressants – ADHD outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Any ADs						
Clements 2015	ADHD (2-19 years)	Any ADs (any time)	Unexposed – adjusted for major depression	1 (CC)	7,874	OR 1.81 (1.22, 2.70)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Any ADs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	877,778	HR 1.2 (1.1, 1.4)
Clements 2015	ADHD (2-19 years)	Any ADs (first trimester)	Unexposed – adjusted for major depression	1 (CC)	7,874	OR 2.03 (1.19, 3.44)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Any ADs (first trimester)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	NR	HR 1.2 (1.0, 1.4)
Clements 2015	ADHD (2-19 years)	Any ADs (second trimester)	Unexposed – adjusted for major depression	1 (CC)	7,874	OR 0.98 (0.56, 1.68)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Any ADs (second trimester)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	NR	HR 1.5 (0.9, 2.4)
Clements 2015	ADHD (2-19 years)	Any ADs (third trimester)	Unexposed – adjusted for major depression	1 (CC)	7,874	OR 1.29 (0.76, 2.15)
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Any ADs (third trimester)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	NR	HR 0.8 (0.3, 2.0)
SSRIs						
Malm 2016 <i>Moderate</i>	ADHD (up to 14 years)	SSRIs (mono or polytherapy; any time)	Unexposed – previous SSRIs	1 (cohort)	23,709	OR 0.98 (0.75, 1.27)
Malm 2016 <i>High</i>	ADHD (up to 14 years)	SSRIs (mono or polytherapy; any time)	Unexposed – psychiatric disorder	1 (cohort)	25,380	OR 0.98 (0.77, 1.24)
Laugesen 2013 <i>High</i>	ADHD (up to 14 years – median 8 years)	SSRIs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	874,491	HR 1.2 (1.0, 1.5)

³⁹¹ Based on the prevalence from Malm 2016.

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Figueroa 2010 <i>High</i>	ADHD (up to 5 years)	SSRIs (any time)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.91 (0.51, 1.60)
Figueroa 2010 <i>Moderate</i>	ADHD (up to 5 years)	SSRIs (first trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 1.62 (0.79, 3.32)
Figueroa 2010 <i>Moderate</i>	ADHD (up to 5 years)	SSRIs (second trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 1.59 (0.58, 4.35)
Figueroa 2010 <i>Moderate</i>	ADHD (up to 5 years)	SSRIs (third trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.38 (0.14, 1.03)
Figueroa 2010 <i>Moderate</i>	ADHD (up to 5 years)	SSRIs (after pregnancy)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 2.04 (1.43, 2.91)
SNRIs						
Laugesen 2013 <i>High</i>	ADHD (up to 14 years – median 8 years)	SNRIs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	863,533	HR 1.0 (0.4, 2.5)
TCAs						
Laugesen 2013 <i>High</i>	ADHD (up to 14 years – median 8 years)	TCAs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	863,486	HR 1.1 (0.6, 2.0)
Bupropion						
Figueroa 2010 <i>Moderate</i>	ADHD (up to 5 years)	Bupropion (any time)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 3.63 (1.20, 11.0)
Figueroa 2010 <i>Moderate</i>	ADHD (up to 5 years)	Bupropion (first trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 2.06 (0.35, 12.2)
Figueroa 2010 <i>Moderate</i>	ADHD (up to 5 years)	Bupropion (second trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 14.66 (3.27, 65.73)
Figueroa 2010 <i>Moderate</i>	ADHD (up to 5 years)	Bupropion (third trimester)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.00 (0.00, 1.00)
Figueroa 2010 <i>Moderate</i>	ADHD (up to 5 years)	Bupropion (after pregnancy)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.90 (0.32, 2.53)
Other ADs						
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Other ADs ³⁹² (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	863,374	HR 1.6 (0.8, 3.0)
Figueroa 2010	ADHD (up to 5 years)	Other ADs ³⁹³ (any time)	Unexposed – adjusted for parental mental health diagnoses and visits	1 (cohort)	38,074	OR 0.65 (0.09, 4.79)
Combined ADs						
Laugesen 2013	ADHD (up to 14 years – median 8 years)	Combined ADs (any time)	Unexposed – adjusted for parental psychiatric diagnoses	1 (cohort)	863,974	HR 0.8 (0.4, 1.7)

Abbreviations: AD, antidepressant; CI, confidence interval; HR, hazard ratio; RE, risk estimate; SRS, social Responsiveness Scale; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

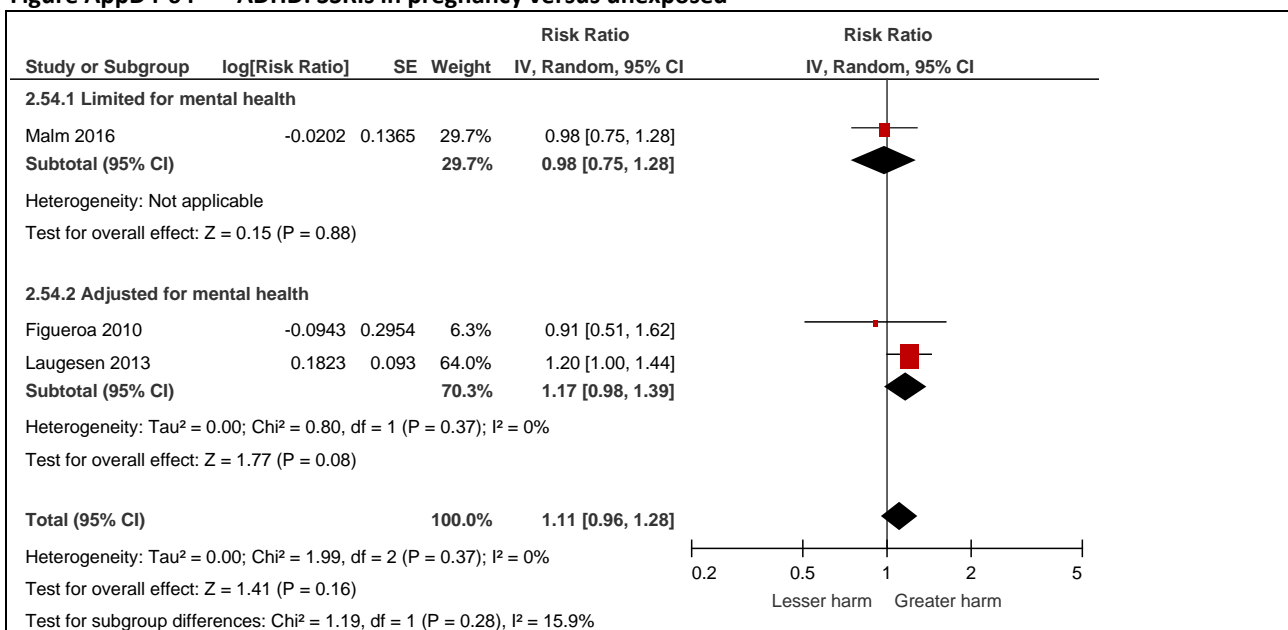
Figure AppD4-64 presents the findings of the association between SSRIs during pregnancy and ADHD. Based on three studies – one that limited the population to those with a psychiatric disorder, and two that adjusted for parental mental health diagnoses – there was no significant association between SSRIs and

³⁹² Not defined but excludes SSRIs, SNRIs, TCAs and combined antidepressants.

³⁹³ Tricyclic antidepressants, tetracyclic antidepressants, mirtazapine and venlafaxine.

ADHD (RR 1.11; 95% CI 0.96, 1.28). The Malm 2016 analysis comparing the offspring of women exposed to SSRIs with the offspring of women who discontinued use of SSRIs during pregnancy is the study likely to be least impacted by confounding by indication, and showed no significant association (RR 0.98; 95% CI 0.75, 1.28).

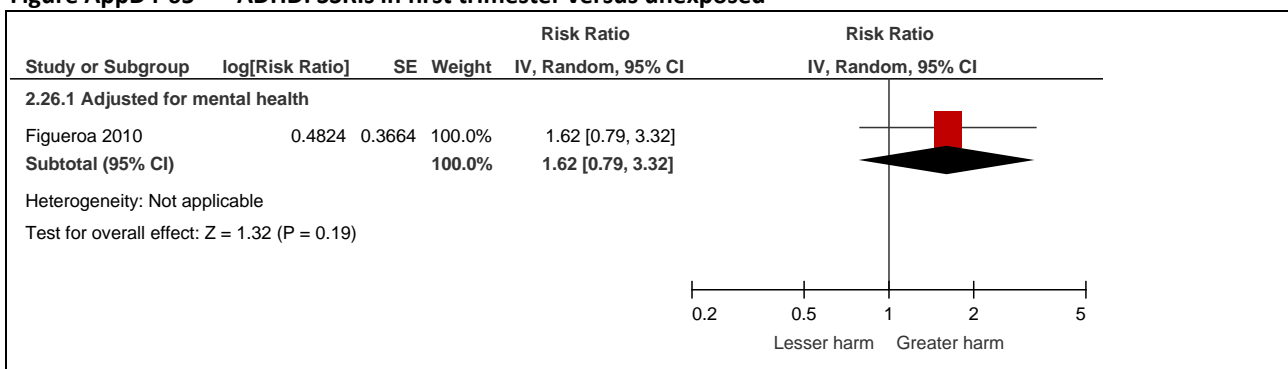
Figure AppD4-64 ADHD: SSRIs in pregnancy versus unexposed



Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.
Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

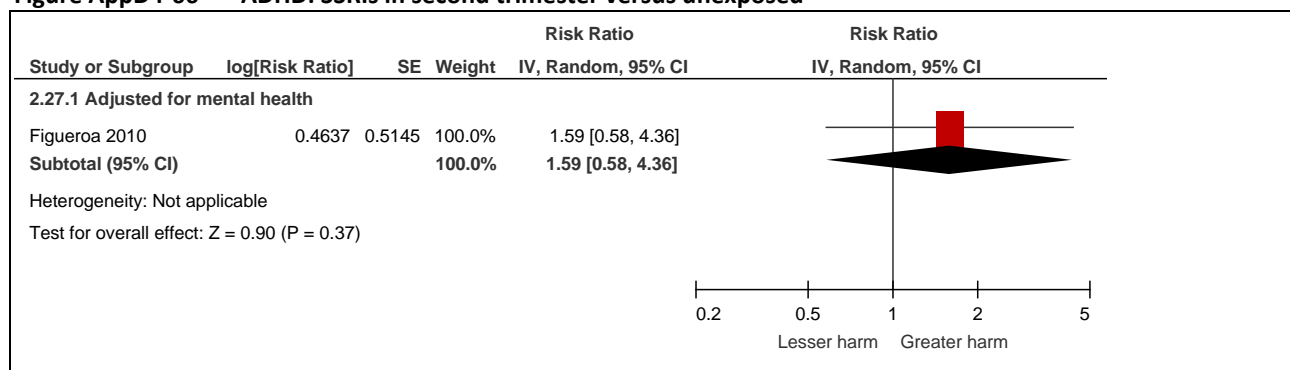
Figure AppD4-65 presents the findings of the association between first-trimester exposure to SSRIs and ADHD. Based on one study that adjusted for parental mental health diagnoses, there was no association between SSRIs and ADHD (RR 1.62; 95% CI 0.79, 3.32). However, this finding is subject to imprecision because the 95% CI includes a measure of appreciable harm (RR 1.25).

Figure AppD4-65 ADHD: SSRIs in first trimester versus unexposed



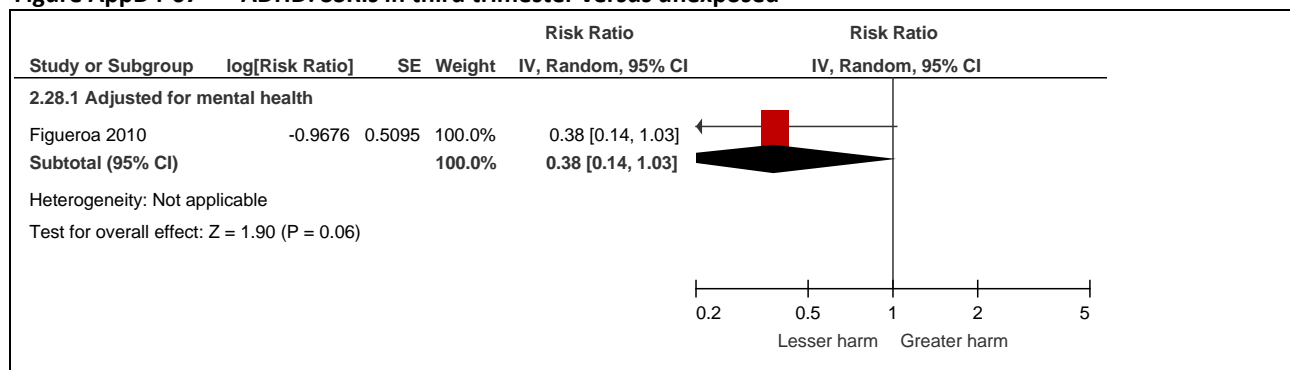
Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.
Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-66 presents the findings of the association between second trimester exposure to SSRIs and ADHD. Based on one study that adjusted for parental mental health diagnoses, there was no association between SSRIs and ADHD (OR 1.59; 95% CI 0.58, 4.35). However, this finding is subject to imprecision because the 95% CI includes a measure of appreciable harm (RR 1.25).

Figure AppD4-66 ADHD: SSRIs in second trimester versus unexposed

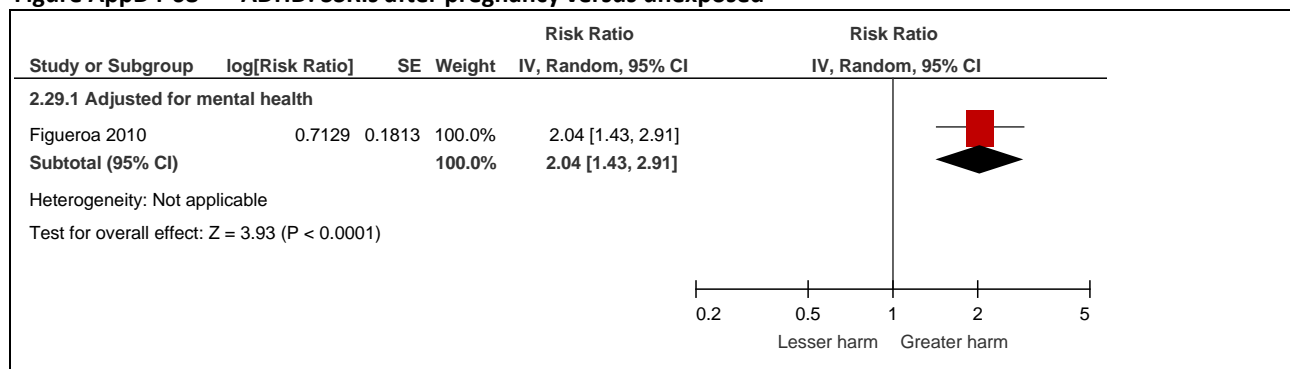
Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.
 Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-67 presents the findings of the association between third trimester exposure to SSRIs and ADHD. Based on one study that adjusted for parental mental health diagnoses, there was no association between SSRIs and ADHD (RR 0.38; 95% CI 0.14, 1.03). However, this finding is subject to imprecision because the 95% CI includes a measure of appreciable benefit (RR 0.75).

Figure AppD4-67 ADHD: SSRIs in third trimester versus unexposed

Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.
 Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

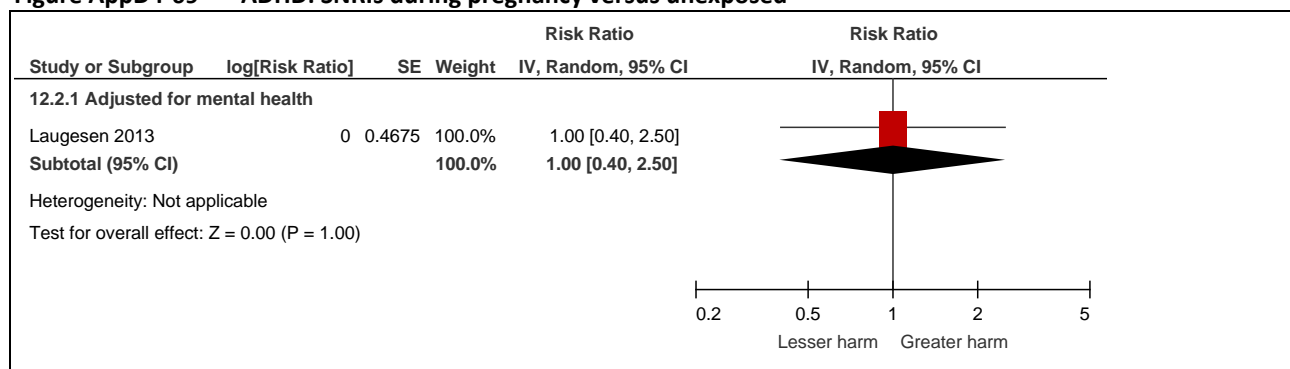
Figure AppD4-68 presents the findings of the association between after-pregnancy exposure to SSRIs and ADHD. Based on one study that adjusted for parental mental health diagnoses, there was a significant association between SSRIs and ADHD (OR 2.04; 95% CI 1.43, 2.91).

Figure AppD4-68 ADHD: SSRIs after pregnancy versus unexposed

Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.
 Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-69 presents the findings of the association between SNRI use during pregnancy and ADHD. Based on one study that adjusted for parental psychiatric diagnoses, there was no significant association between SNRIs and ADHD (RR 1.0; 95% CI 0.4, 2.5).

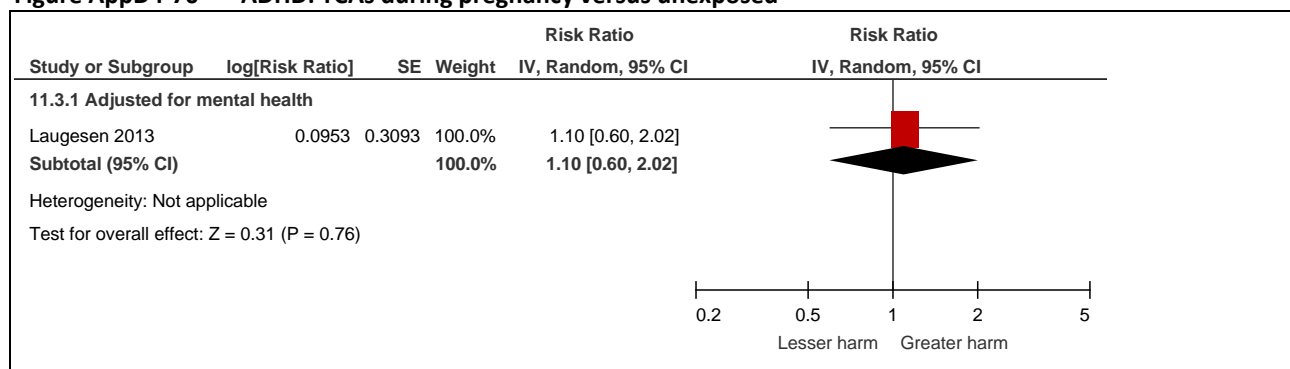
Figure AppD4-69 ADHD: SNRIs during pregnancy versus unexposed



Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.
Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-70 presents the findings of the association between TCA use during pregnancy and ADHD. Based on one study that adjusted for parental psychiatric diagnoses, there was no significant association between TCAs and ADHD (OR 1.1; 95% CI 0.6, 2.0).

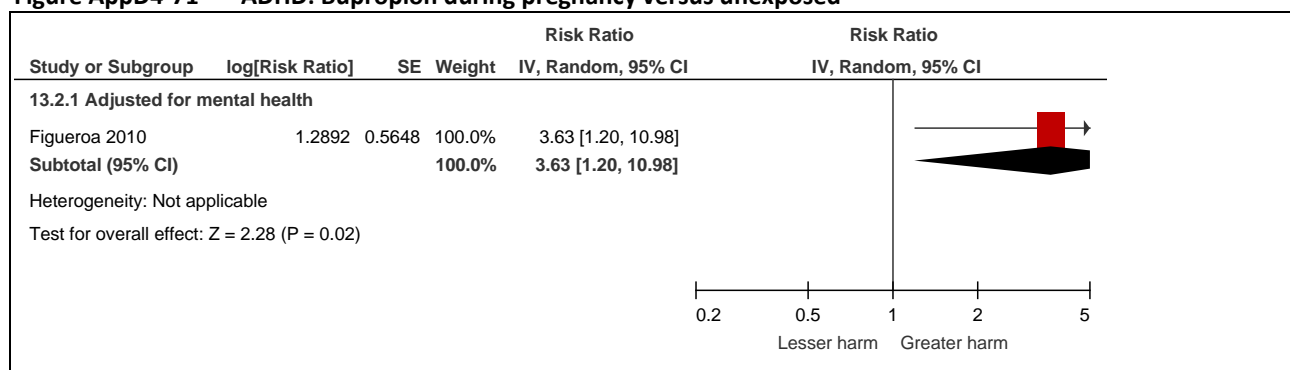
Figure AppD4-70 ADHD: TCAs during pregnancy versus unexposed



Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.

Figure AppD4-71 presents the findings of the association between bupropion use during pregnancy and ADHD. Based on one study that adjusted for parental mental health diagnoses, there was a significant association between bupropion and ADHD (RR 3.63; 95% CI 1.20, 11.0).

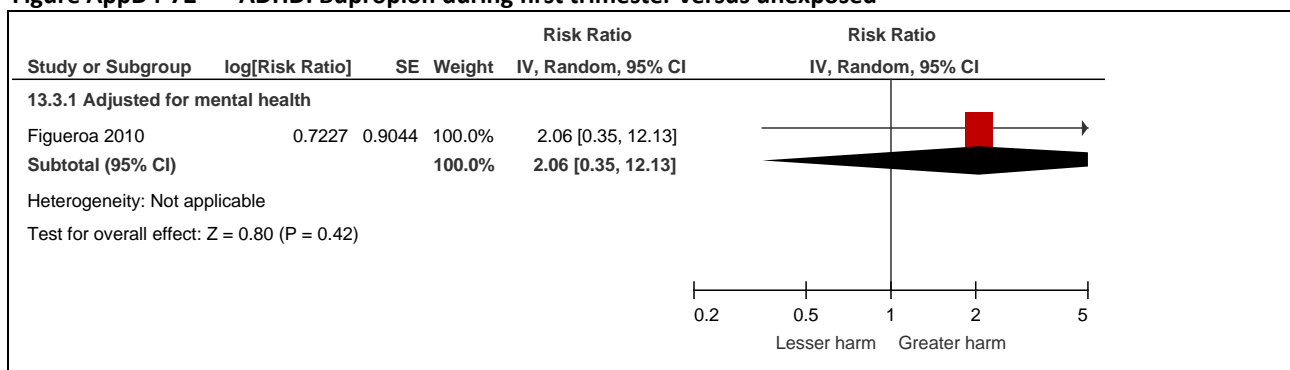
Figure AppD4-71 ADHD: Bupropion during pregnancy versus unexposed



Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.
Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-72 presents the findings of the association between first-trimester exposure to bupropion and ADHD. Based on one study that adjusted for parental mental health diagnoses, there was no significant association between bupropion and ADHD (RR 2.06; 95% CI 0.35, 12.2). This finding is subject to imprecision because the 95% CI includes a measure of appreciable benefit and harm.³⁹⁴

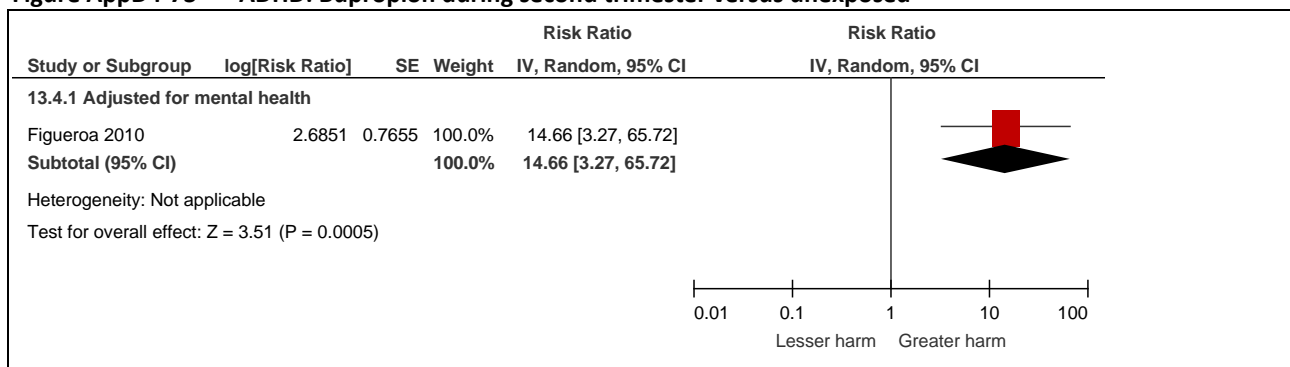
Figure AppD4-72 ADHD: Bupropion during first trimester versus unexposed



Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.
Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-73 presents the findings of the association between second trimester exposure to bupropion and ADHD. Based on one study that adjusted for parental mental health diagnoses, there was a highly significant association between bupropion and ADHD (RR 14.7; 95% CI 3.27, 65.7).

Figure AppD4-73 ADHD: Bupropion during second trimester versus unexposed

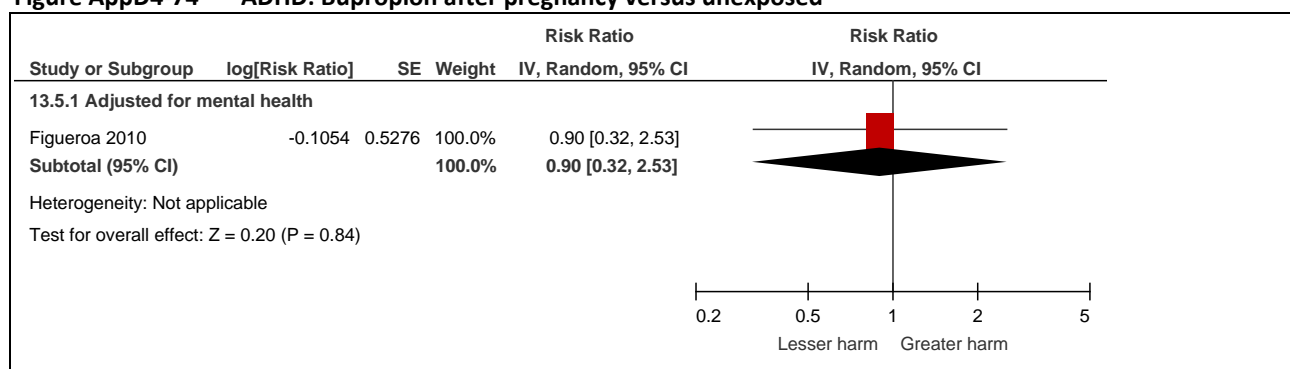


Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.
Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Based on one study that adjusted for parental mental health diagnoses, there was no significant association between third trimester exposure to bupropion and ADHD (OR 0.00; 95% CI 0.00, 1.00). There were no children with ADHD in the bupropion in third trimester group.

Figure AppD4-74 presents the findings of the association between after-pregnancy exposure to bupropion and ADHD. Based on one study that adjusted for parental mental health diagnoses, there was no significant association between bupropion and ADHD (OR 0.90; 95% CI 0.32, 2.53). This finding is imprecise because the 95% CI includes measures of appreciable benefit and harm (RR 0.75/1.25).

³⁹⁴ Because the prevalence of autism spectrum disorder is low (quoted as 5% in Laugensen 2013), the OR can be assumed to approximate the RR. The values of appreciable benefit or harm are RR 0.75 and 1.25, respectively.

Figure AppD4-74 ADHD: Bupropion after pregnancy versus unexposed

Abbreviations: AD, antidepressant; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.1.18 Other disorders – antidepressants

AppD4.1.1.18.1 Results based on systematic reviews

No SRs were identified that provided analyses of the association between antidepressants and other neurodevelopmental disorders based on either data adjusted for potential confounding or using the appropriate comparator population. *As such, an examination of the results of individual studies has been undertaken for this outcome.*

AppD4.1.1.18.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and other disorders is presented in **Table AppD4-34**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

The results are presented as HRs but are interpreted as RRs.

Table AppD4-34 Antidepressants – neurodevelopmental outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Brown 2016 <i>High</i>	Speech/language disorder ³⁹⁵ (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	25,133	HR 1.20 (0.97, 1.49)
Brown 2016 <i>High</i>	Speech/language disorder ³⁹⁵ – 1 purchase (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 0.86 (0.67, 1.10)
Brown 2016 <i>High</i>	Speech/language disorder ³⁹⁵ – ≥ 2 purchases (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 1.37 (1.11, 1.70)
Brown 2016 <i>High</i>	Speech/language disorder ³⁹⁵ – ≥ 2 purchases (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with <u>monotherapy</u> SSRI use	1 (cohort)	NR	HR 1.34 (1.07, 1.68)
Brown 2016 <i>High</i>	Speech/language disorder ³⁹⁵ – ≥ 2 purchases (mean 4.4 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use <u>and adjusted for maternal suicidal behavior</u>	1 (cohort)	NR	HR 1.34 (1.07, 1.68)
Brown 2016 <i>High</i>	Scholastic disorder ³⁹⁵ (mean 3.6 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	25,133	HR 1.00 (0.63, 1.59)

³⁹⁵ ICD-10.

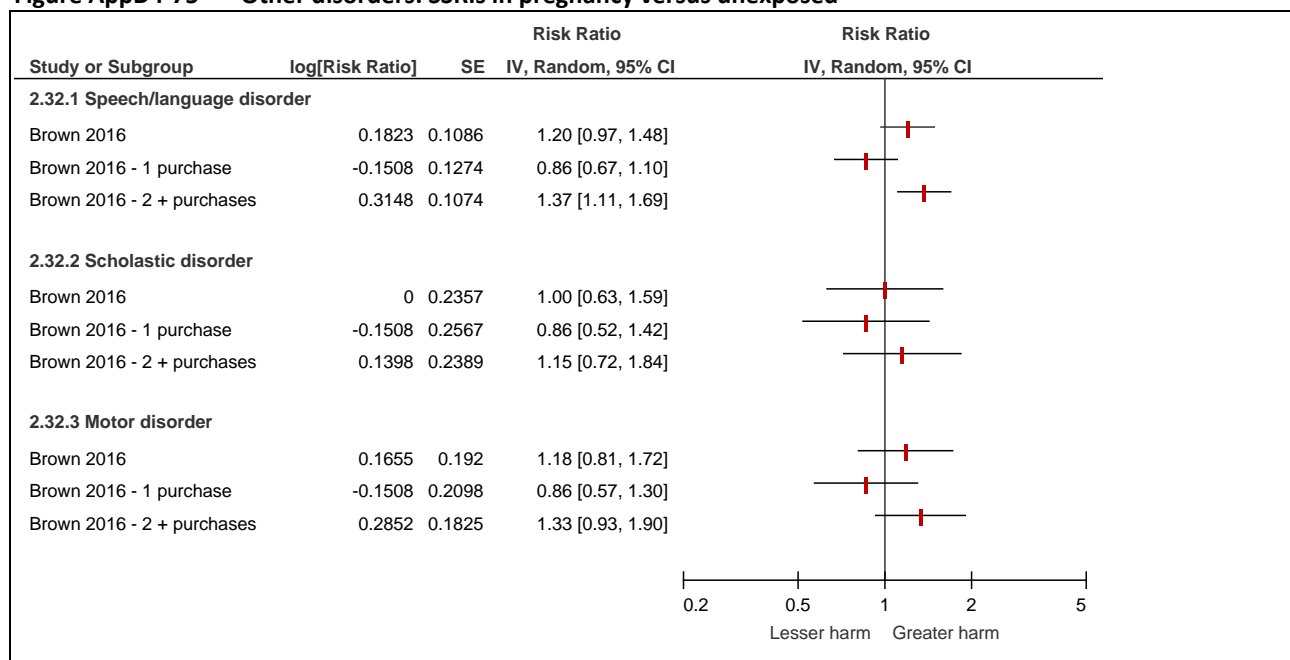
Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Brown 2016 <i>High</i>	Scholastic disorder ³⁹⁵ – one purchase (mean 3.6 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 0.86 (0.52, 1.42)
Brown 2016 <i>High</i>	Scholastic disorder ³⁹⁵ – ≥ 2 purchases (mean 3.6 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 1.15 (0.72, 1.84)
Brown 2016 <i>High</i>	Motor disorder ³⁹⁵ (mean 7.7 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	25,133	HR 1.18 (0.81, 1.72)
Brown 2016 <i>High</i>	Motor disorder ³⁹⁵ – 1 purchase (mean 7.7 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 0.86 (0.57, 1.30)
Brown 2016 <i>High</i>	Motor disorder ³⁹⁵ – ≥ 2 purchases (mean 7.7 years)	SSRIs (any time)	Unexposed – depression or psychiatric diagnosis associated with SSRI use	1 (cohort)	NR	HR 1.33 (0.93, 1.91)

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Figure AppD4-75 presents the findings of the association between SSRIs at any time during pregnancy and other disorders. Based on the findings of one study that limited the comparator population who were unexposed but had depression or a psychiatric illness associated with SSRI use (from the Finnish cohort so at risk of selection bias), there was no statistically significant association between SSRIs and speech/language, scholastic or motor disorders (RR 1.20 95% CI 0.97, 1.49; RR 1.00 95% CI 0.63, 1.59; and RR 1.18 95% CI 0.81, 1.72, respectively). When the analyses were restricted to subgroups with either one purchase of SSRIs during pregnancy, or two or more purchases, with the exception of one analysis (the association between two or more purchases during pregnancy and speech/language disorder) there was also no significant association; however, the findings do suggest there may be a dose effect, with increasing exposure resulting in higher risk estimates.

All non-significant findings were subject to imprecision because the 95% CIs included measures of appreciable benefit and/or harm.

Figure AppD4-75 Other disorders: SSRIs in pregnancy versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; RR, relative risk; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.1.19 Intelligence Quotient – antidepressants

AppD4.1.1.19.1 Results based on systematic reviews

No SRs were identified that provided analyses of the association between antidepressants and intelligence quotient (IQ) based on either data adjusted for potential confounding or used the appropriate comparator population. *As such, an examination of the results of individual studies has been undertaken for this outcome.*

AppD4.1.1.19.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and other disorders is presented in **Table AppD4-35**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-35 Antidepressants – intelligence quotient outcomes from observational studies

Study ID Risk of bias	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
SRIs³⁹⁶						
Nulman 2015 <i>Low</i>	Full Scale IQ (WPPSI-III)	SRIs (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05
Nulman 2015 <i>Low</i>	Verbal IQ (WPPSI-II)	SRIs (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05
Nulman 2015 <i>Low</i>	Performance IQ (WPPSI-II)	SRIs (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05

Abbreviations: CI, confidence interval; IQ, intelligence quotient; RE, risk estimate; SRI, selective reuptake inhibitors; WPPSI-II, Wechsler Preschool and Primary Scale of Intelligence-II.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Nulman 2015 examined total, verbal and performance IQ using the Wechsler Preschool and Primary Scale of Intelligence in exposed and unexposed siblings of women diagnosed with depression. After adjusting for child's age, birth order and severity of depression during pregnancy, they found no difference in any of the IQ scales (all $P \geq 0.05$).

AppD4.1.1.20 Behavioural problems – antidepressants

AppD4.1.1.20.1 Results based on systematic reviews

No SRs were identified that provided analyses of the association between antidepressants and behavioural problems based on either data adjusted for potential confounding or used the appropriate comparator population. *As such, an examination of the results of individual studies has been undertaken for this outcome.*

AppD4.1.1.20.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and behavioural problems as measured by total difficulties via the Strengths and Difficulties Questionnaire (SDQ) is presented in **Table AppD4-36**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-36 Antidepressants – behavioural problem outcomes from observational studies

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Any ADs						
Grzeskowiak 2015	Total difficulties – abnormal score (SDQ) ³⁹⁷	Any ADs (any time)	Unexposed - depression	1 (cohort)	441	RR 0.54 (0.23, 1.30)
Pedersen 2013	Total difficulties – abnormal score (SDQ) ³⁹⁷	Any ADs (any time)	Unexposed - depression	1 (cohort)	225	OR 1.3 (0.3, 6.0)
Grzeskowiak 2015	Total difficulties – abnormal score (SDQ) ³⁹⁷	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.84 (0.31, 2.31)

³⁹⁶ Includes SSRIs and SNRIs.

³⁹⁷ According to the Australian Mental Health Outcome and Classification Network: Strengths and Difficulties Questionnaire Training Manual (accessed from <http://www.readbag.com/amhocr-static-files-assets-d666a3f8-sdq-manual>), a total difficulties score is abnormal if it is ≥ 17 .

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Grzeskowiak 2015	Internalising problems – abnormal emotional symptoms score (SDQ) ³⁹⁸	Any ADs (any time)	Unexposed - depression	1 (cohort)	441	RR 0.74 (0.47, 1.14)
Pedersen 2013	Internalising problems – abnormal emotional symptoms score (SDQ) ³⁹⁸	Any ADs (any time)	Unexposed - depression	1 (cohort)	225	OR 1.6 (0.8, 8.9)
Grzeskowiak 2015	Internalising problems – abnormal emotional symptoms score (SDQ) ³⁹⁸	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.80 (0.50, 1.28)
Grzeskowiak 2015	Internalising problems – abnormal peer problems score (SDQ) ³⁹⁹	Any ADs (any time)	Unexposed - depression	1 (cohort)	441	RR 0.65 (0.30, 1.42)
Pedersen 2013	Internalising problems – abnormal peer problems score (SDQ) ³⁹⁹	Any ADs (any time)	Unexposed - depression	1 (cohort)	225	OR 0.9 (0.2, 4.8)
Grzeskowiak 2015	Internalising problems – abnormal peer problems score (SDQ) ³⁹⁹	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.76 (0.32, 1.85)
Grzeskowiak 2015	Externalising problems – abnormal conduct problems score (SDQ) ⁴⁰⁰	Any ADs (any time)	Unexposed - depression	1 (cohort)	441	RR 0.82 (0.47, 1.43)
Pedersen 2013	Internalising problems – abnormal conduct problems score (SDQ) ⁴⁰⁰	Any ADs (any time)	Unexposed - depression	1 (cohort)	225	OR 0.6 (0.3, 1.3)
Grzeskowiak 2015	Externalising problems – abnormal conduct problems score (SDQ) ⁴⁰⁰	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.90 (0.49, 1.67)
Grzeskowiak 2015	Externalising problems – abnormal hyperactivity-inattention score (SDQ) ⁴⁰¹	Any ADs (any time)	Unexposed - depression	1 (cohort)	441	RR 0.57 (0.28, 1.19)
Pedersen 2013	Externalising problems – abnormal hyperactivity-inattention score (SDQ) ⁴⁰¹	Any ADs (any time)	Unexposed - depression	1 (cohort)	225	OR 1.8 (0.6, 5.6)
Grzeskowiak 2015	Externalising problems – abnormal hyperactivity-inattention problems score (SDQ) ⁴⁰¹	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.75 (0.34, 1.64)
Grzeskowiak 2015	Other measures – abnormal pro-social score (SDQ) ⁴⁰²	Any ADs (any time)	Unexposed - depression	1 (cohort)	441	RR 0.23 (0.05, 1.18)
Pedersen 2013	Other measures – abnormal pro-social score (SDQ) ⁴⁰²	Any ADs (any time)	Unexposed - depression	1 (cohort)	225	OR 0.5 (0.2, 1.7)
Grzeskowiak 2015	Other measures – abnormal pro-social score (SDQ) ⁴⁰²	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.19 (0.05, 0.77)
Grzeskowiak 2015	Other measures – abnormal impact score (SDQ)	Any ADs (any time)	Unexposed - depression	1 (cohort)	441	RR 0.66 (0.36, 1.20)
Grzeskowiak 2015	Other measures – abnormal impact score (SDQ)	Any ADs (any time)	Unexposed – depression and adjusted for antenatal mood	1 (cohort)	441	RR 0.76 (0.40, 1.46)
SRIs⁴⁰³						
Nulman 2015	Total problems (CBCL)	SRIs (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05

Abbreviations: AD, antidepressant; CI, confidence interval; RE, risk estimate; OR, odds ratio; RR, relative risk; SDQ, Strengths and Difficulties Questionnaire.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

³⁹⁸ According to the Australian Mental Health Outcome and Classification Network: Strengths and Difficulties Questionnaire Training Manual, an emotional symptoms score is abnormal if it is ≥ 5.

³⁹⁹ According to the Australian Mental Health Outcome and Classification Network: Strengths and Difficulties Questionnaire Training Manual, a peer problem score is abnormal if it is ≥ 4.

⁴⁰⁰ According to the Australian Mental Health Outcome and Classification Network: Strengths and Difficulties Questionnaire Training Manual, a conduct problem score is abnormal if it is ≥ 4.

⁴⁰¹ According to the Australian Mental Health Outcome and Classification Network: Strengths and Difficulties Questionnaire Training Manual, a hyperactivity score is abnormal if it is ≥ 7.

⁴⁰² According to the Australian Mental Health Outcome and Classification Network: Strengths and Difficulties Questionnaire Training Manual, a prosocial behaviour score is abnormal if it is ≤ 4.

⁴⁰³ Includes SSRIs and SNRIs.

Nulman 2015 assessed the association between SRIs (SSRIs and SNRIs) during pregnancy and total behavioural problems as measured by the CBCL. After adjusting for the child's age, birth order and severity of depression during pregnancy, they found no significant difference between exposed and unexposed children ($P \geq 0.05$).

Internalising behaviours

A summary of the results regarding the association between antidepressant use and internalising behaviour is presented in **Table AppD4-37**. Only results relating to specific classes of antidepressants or individual antidepressants are discussed in detail below. Results for antidepressants as a group, or other groupings of antidepressants, are presented in the table only. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-37 Antidepressants – internalising behaviour outcomes from observational studies

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Any ADs						
Brandlistuen 2015	Internalising behaviour (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.16 (–0.14, 0.46)
Brandlistuen 2015	Internalising behaviour - anxiety (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.14 (–0.19, 0.47)
Brandlistuen 2015	Internalising behaviour – emotional reactivity (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.05 (–0.28, 0.38)
Brandlistuen 2015	Internalising behaviour – somatic (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β –0.05 (–0.41, 0.30)
Brandlistuen 2015	Internalising behaviour - sleep (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.20 (–0.11, 0.51)
Brandlistuen 2015	Internalising behaviour (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β 0.34 (–0.01, 0.68)
Brandlistuen 2015	Internalising behaviour - anxiety (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β 0.64 (0.26, 1.02)
Brandlistuen 2015	Internalising behaviour – emotional reactivity (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β –0.06 (–0.42, 0.30)
Brandlistuen 2015	Internalising behaviour - somatic (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β 0.04 (–0.36, 0.43)
Brandlistuen 2015	Internalising behaviour - sleep (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β 0.25 (–0.11, 0.60)
SRI⁴⁰⁴						
Nulman 201 Low	Internalising behaviour (CBCL)	SRI (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05

Abbreviations: AD, antidepressant; CBCL, Child Behaviour Checklist; CI, confidence interval; RE, risk estimate.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

⁴⁰⁴ Includes SSRIs and SNRIs.

Nulman 2015 assessed the association between SRIs (SSRIs and SNRIs) during pregnancy and internalising behaviour as measured by the CBCL. After adjusting for the child's age, birth order and severity of depression during pregnancy, they found no significant difference between exposed and unexposed children ($P \geq 0.05$).

Externalising behaviours

A summary of the results regarding the association between antidepressant use and externalising behaviour is presented in **Table AppD4-38**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-38 Antidepressants – externalising behaviour outcomes from observational studies

Study ID	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Any ADs						
Brandlistuen 2015	Externalising behaviour (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.26 (–0.05, 0.56)
Brandlistuen 2015	Externalising behaviour - attention (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.15 (–0.16, 0.47)
Brandlistuen 2015	Externalising behaviour – aggression (CBCL) (18 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	20,180	β 0.30 (–0.03, 0.64)
Brandlistuen 2015	Externalising behaviour (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β –0.08 (–0.44, 0.27)
Brandlistuen 2015	Externalising behaviour - attention (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β –0.01 (–0.38, 0.36)
Brandlistuen 2015	Externalising behaviour – aggression (CBCL) (36 months)	Any ADs (any time)	Unexposed – adjusted for lifetime history of depression/sibling matched	1 (cohort)	14,352	β –0.11 (–0.49, 0.27)
Any ADs						
Nulman 2015 <i>Low</i>	Externalising behaviour (CBCL)	SRIs ⁴⁰⁵ (any time)	Unexposed – depression (sibling analysis)	1 (cohort)	90	≥ 0.05

Abbreviations: AD, antidepressant; CBCL, Child Behaviour Checklist; CI, confidence interval; RE, risk estimate.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Nulman 2015 assessed the association between SRIs (SSRIs and SNRIs) during pregnancy and externalising behaviour as measured by the CBCL. After adjusting for the child's age, birth order and severity of depression during pregnancy, they found no significant difference between exposed and unexposed children ($P \geq 0.05$).

AppD4.1.1.21 Depression – antidepressants

AppD4.1.1.21.1 Results based on systematic reviews

No SRs were identified that provided analyses of the association between antidepressants and depression in the offspring based on either data adjusted for potential confounding or that used the appropriate comparator population. *As such, an examination of the results of individual studies has been undertaken for this outcome.*

⁴⁰⁵ Includes SSRIs and SNRIs.

AppD4.1.1.21.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and depression in the offspring is presented in **Table AppD4-39**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

The results are presented as HRs but have been interpreted as RRs.

Table AppD4-39 Antidepressants – child depression outcomes from observational studies

Study ID Risk of bias	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Malm 2016 <i>Moderate</i>	Depression (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – SSRIs discontinued	1 (cohort)	23,709	HR 1.84 (1.14, 2.97)
Malm 2016	Depression (up to 14 years)	SSRIs (monotherapy only)	Unexposed – psychiatric disorder	1 (cohort)	NR	HR 1.85 (1.15, 2.98)
Malm 2016	Depression (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – psychiatric disorder	1 (cohort)	25,380	HR 1.78 (1.12, 2.82)

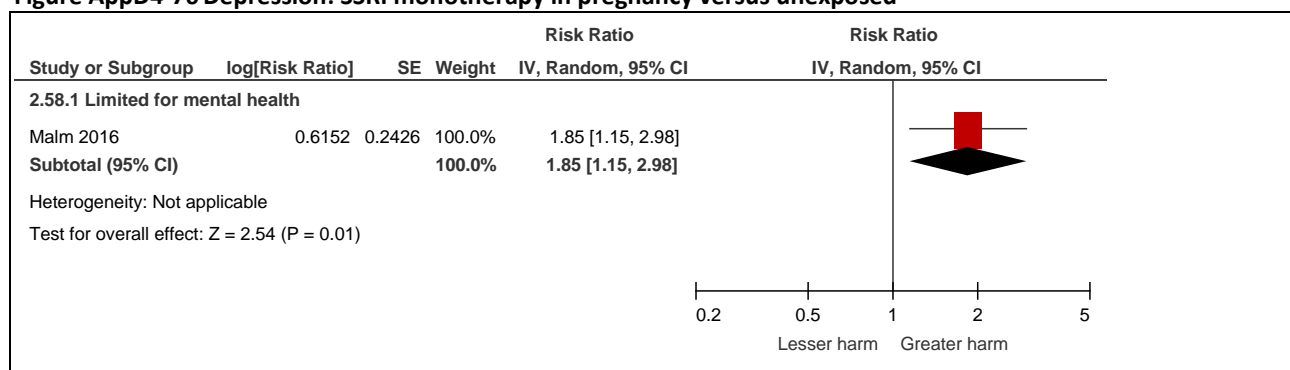
Abbreviations: CI, confidence interval; HR, hazard ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Figure AppD4-76 presents the findings of the association between SSRI monotherapy during pregnancy and depression in the offspring. Based on the findings of one study that limited the comparator population to those who had discontinued SSRIs before pregnancy, there was a statistically significant association between SSRI monotherapy and depression in the offspring (RR 1.85; 95% CI 1.15, 2.98).

Analysis of the comparison between SSRI-exposed women and women with a psychiatric disorder is likely to be subject to selection bias (Finnish cohort; as previously described) and showed a significant association for monotherapy (HR 1.85; 95% CI 1.15, 2.98) and mono/polytherapy (HR 1.78; 95% CI 1.12, 2.82).

Figure AppD4-76 Depression: SSRI monotherapy in pregnancy versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.1.22 Anxiety – antidepressants

AppD4.1.1.22.1 Results based on systematic reviews

No SRs were identified that provided analyses of the association between antidepressants and anxiety in the offspring based on either data adjusted for potential confounding or that used the appropriate comparator population. *As such, an examination of the results of individual studies has been undertaken for this outcome.*

AppD4.1.1.22.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and anxiety in the offspring is presented in **Table AppD4-40**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

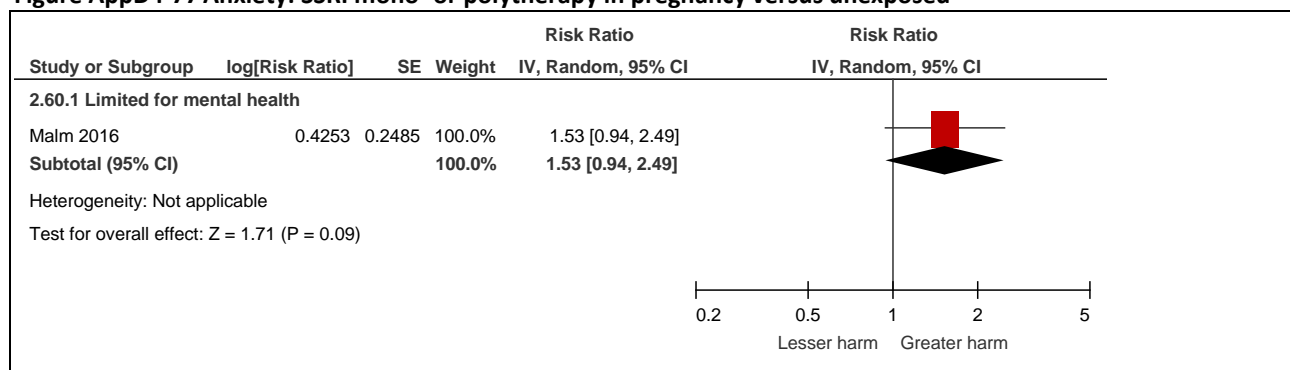
Table AppD4-40 Antidepressants – child anxiety outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome (follow-up)	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)
Malm 2016 <i>Moderate</i>	Anxiety (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – previous SSRIs	1 (cohort)	23,709	HR 1.53 (0.94, 2.50)
Malm 2016	Anxiety (up to 14 years)	SSRIs (mono or polytherapy)	Unexposed – psychiatric disorder	1 (cohort)	25,380	HR 1.30 (0.84, 2.01)

Abbreviations: CI, confidence interval; HR, hazard ratio; RE, risk estimate; SSRI, selective serotonin reuptake inhibitor.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.1** of the Technical Report.

Figure AppD4-77 presents the findings of the association between SSRI mono- or polytherapy during pregnancy and anxiety in the offspring. Based on the findings of one study that limited the comparator population to those who had discontinued SSRIs before pregnancy, there was no significant association between SSRI monotherapy and anxiety in the offspring (RR 1.53; 95% CI 0.94, 2.50). A similar result was seen for the comparison of women with a psychiatric disorder that is likely to be affected by selection bias (Finnish cohort; see previous discussion). However, the findings are subject to imprecision because the 95% CI includes measures of appreciable harm (RR 1.25).

Figure AppD4-77 Anxiety: SSRI mono- or polytherapy in pregnancy versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.2 Antipsychotics**AppD4.1.2.1 Included systematic reviews – antipsychotics**

None of the identified quantitative systematic reviews were eligible for inclusion in the Technical Report as none restricted their analyses to adjusted data, nor restricted comparator groups to unexposed women with a mental health disorder diagnosis.

AppD4.1.2.2 Included individual studies – antipsychotics

Due to the lack of data from higher quality studies, for all outcomes it was necessary to use data from individual studies; data from individual studies was only eligible for inclusion if it was adjusted for potential confounders, and greater weight was given to evidence where an attempt was made to minimise confounding by indication.

Adjusted risk estimates were reported by 11 individual studies, and were assessed for inclusion in the body of evidence for antipsychotics. The characteristics of the included individual studies are summarised in **Table AppD4-41**. The risk-of-bias rating shown in this table refers to excess risk over and above that assumed from the observational design (see Section AppD5.1.2 for the risk assessment of these 11 studies), and this additional risk will be referred to simply as risk-of-bias.

Lack of cohort comparability is the main limitation in these studies, as the majority of comparator groups were not limited to women with a mental health disorder diagnosis. A number of studies did not account for differences in indication between groups. These comparability issues were captured under indirectness when assessing the body of evidence as a whole in the Evidence Profile Tables. Some studies did adjust for indication, but where adjustment was suspected to be biased between groups (i.e. incomplete ascertainment of diagnosis in the comparator group), this was captured in the risk of bias (under comparability of cohorts).

Seven studies were population-based cohort analyses, and all were low risk of bias for non-malformation outcomes, and moderate risk of bias for malformation outcomes (due to selection bias for this outcome): one US (Huybrechts 2016), one Danish (Sorensen 2015), one Canadian (Vigod 2015), one Taiwanese (Lin 2010) and three Swedish studies of the same collection of databases (Källén 2013, Bodén 2012b, Reis 2008).

One HTA presented a retrospective analysis of a cohort of mother-child dyads from linked UK primary care databases (Petersen 2016a), and had moderate risk of bias for major malformations and high risk for neurodevelopment disorders. The remaining three studies investigated small, prospective cohorts from US clinical centres (Cohen 2016, Johnson 2012; both moderate risk of bias) and a German teratology information service in Berlin (Habermann et al 2013; low risk of bias except for malformations).

The outcomes reported in this section are a selected subset of those from the data extraction section (Section AppD3.1.2.2). Only outcomes shown in shading are considered primary evidence, and these are included in the body of evidence and taken through the GRADE process; where a large difference in the quality of the evidence existed for a particular outcome, the higher quality evidence only was chosen for evaluation (e.g. studies adjusting to a high degree for indications versus studies not adjusting for indication).

Table AppD4-41 Characteristics of the included comparative observational studies of antipsychotic harms

Study ID Risk of bias	Study characteristics Country Timeframe	Population (N)	Exposure/s <u>Timing</u>	Comparator/s	Outcomes in PICO
Cohen 2016 <i>Moderate risk</i>	Prospective hospital-based pregnancy registry for SGAs US 2008–2014	Pregnant women aged 18-45, recruited through provider referral, self-referral, and the Center's web site. Analysis based on live births. (N = 303)	SGAs <u>Timing</u> : 1 st trimester (<13 weeks)	Majority with a psychiatric illness history, being treated with psychotropic medications other than SGAs. ⁴⁰⁶	Major malformations
Huybrechts 2016 <i>Moderate risk</i>	Retrospective cohort nested in the nationwide Medicaid Analytic Extract database US 2000-2010	Women aged 12-55 enrolled in Medicaid from 3 months before their last menstrual period through at least 1 month after delivery of live-born infant. Infants were required to have coverage through Medicaid for the first 3 months of life unless they died sooner. (N = 1,341,715)	SGAs FGAs <u>Timing</u> : 1 st trimester	Two comparator groups: <ul style="list-style-type: none"> • Unexposed • Unexposed, restricted to schizophrenia, bipolar disorder or psychosis⁴⁰⁷ 	Major malformations Cardiac malformations
Petersen 2016a <i>Moderate risk</i> (<i>High for neurodev. disorders</i>)	Retrospective cohort, linked primary care databases ⁴⁰⁸ The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD) UK 1995–2012	Mother-infant pairs: live-birth singleton infants of mothers registered at practice for at least 6-months prior to pregnancy and throughout pregnancy (N = 211,748)	Any antipsychotic; SGAs; FGAs <u>Timing</u> : early and late cohorts with 4-24 months' prior exposure: <ul style="list-style-type: none"> • 31-105 days from start of pregnancy; • within 92 days of delivery date both exposed between 4 and 24 months before start of pregnancy	Two comparator groups: <ul style="list-style-type: none"> • Unexposed; • 4-24 months' prior exposure, discontinued at pregnancy (i.e. unexposed with mental health disorder) 	Major congenital malformation Neurodevelopment/behaviour disorders
Sorensen 2015 <i>Low risk</i>	Retrospective, linked, population-based cohort Denmark 1997–2008	Clinically recognised pregnancies in nationwide health registry (N = 1,005,319)	Any antipsychotics Individual antipsychotics ⁴⁰⁹ <u>Timing</u> : 30 days before start of pregnancy to one day prior to spontaneous abortion/ stillbirth/ birth	Two comparator groups: <ul style="list-style-type: none"> • Unexposed • Unexposed, restricted to bipolar disorder, including mania or schizophrenia⁴¹⁰ 	Stillbirth Miscarriage (spontaneous abortion)

⁴⁰⁶ Only 1.1% of women in the comparator group (1/89) was taking first generation antipsychotics.⁴⁰⁷ The exposed group was also restricted in this sensitivity analysis. Diagnoses were from inpatient and outpatient records.⁴⁰⁸ Two studies performed, one in a pregnant women cohort reporting maternal outcomes, and another in a mother-child cohort (live births), with the latter study reporting infant harms and extracted here.⁴⁰⁹ Adjusted results reported (and extracted here) for chlorprothixene, flupenthixol, perphenazine, zuclopenthixol, levomepromazine, quetiapine, olanzapine. Unadjusted results reported (not extracted here) for lithium, risperidone, aripiprazole, ziprasidone, haloperidone, prochlorperazine, fluphenazine, chlorpromazine.⁴¹⁰ The exposed group was also restricted in this sensitivity analysis. Excludes diagnoses made by general practitioners or private psychiatrists.

Study ID Risk of bias	Study characteristics Country Timeframe	Population (N)	Exposure/s Timing	Comparator/s	Outcomes in PICO
Vigod 2015 <i>Low risk</i>	Retrospective, linked, population-based, hdPS-matched cohort Ontario, Canada 2003–2012	Live-born or stillborn singleton infants of mothers covered under the provincial drug plan during the pregnancy ⁴¹¹ (N = 41,523; matched cohorts 1,021 each)	Any antipsychotic <u>Timing</u> : ≥2 consecutive prescriptions during pregnancy, at least one of which was filled in the 1 st or 2 nd trimester	Unexposed – matched for high-dimensional propensity score and age (±3 years)	Preterm (<37; <32; <28 weeks) Small for gestational age Large for gestational age Stillbirth Respiratory distress syndrome (not acute) ⁴¹² Poor neonatal adaptation syndrome Seizures Mortality <90 days
Habermann 2013 <i>Low risk (Moderate for malformations)</i>	Prospective cohort, matched controls Teratology Information Service Berlin, Germany 1997–2009	Women exposed to at least 1 SGA during pregnancy (FGAs allowed) (N = 1967)	SGAs FGAs (excluding SGAs) <u>Timing</u> : pregnancy	Unexposed, matched to SGA group	Major malformations Major malformations (<i>first-trimester exposure</i>) Cardiac malformations Miscarriage Stillbirth ⁴¹³ Neonatal death Preterm (<37 weeks)
Källén 2013 <i>Low risk (Moderate for malformations)</i>	Retrospective, linked, population-based cohort Medical Birth Register, Register of Birth Defects, Hospital Discharge Register, Register of Prescribed Drugs Sweden 1996–2011	Live-birth infants of mothers reporting use of antipsychotics (neuroleptics) during early pregnancy, or dispensed drug in later pregnancy (N = 1,575,847)	Antipsychotics ⁴¹⁴ or lithium Haloperidol Perphenazine Flupenthixol Olanzapine <u>Timing</u> : early pregnancy, 2 nd or 3 rd trimester	Unexposed	Relatively severe malformations (<i>may include malformations not strictly classifiable as major</i>) ⁴¹⁵ Cardiac defects Septal defects Preterm birth <37 weeks Small for gestational age Large for gestational age Respiratory diagnosis
Bodén 2012b <i>Low risk (Moderate for malformations)</i>	Retrospective, linked, population-based cohort Swedish Medical Birth Register, Prescribed Drug Register, National Patient Register Sweden 1997–2009	Singleton infants (or stillborns) of mothers dispensed antipsychotics during pregnancy. (N = 385,203)	Olanzapine and/or clozapine Other antipsychotic <u>Timing</u> : pregnancy	Unexposed	Stillbirth Neonatal death Preterm birth (<37 weeks) Small for gestational age (<i>three measures</i>) Large for gestational age (<i>three measures</i>)

⁴¹¹ To ensure that all participants were covered under the provincial drug plan during the index pregnancy, only those who had filled a provincially funded drug prescription within 180 days before pregnancy and one during pregnancy or within 180 days of delivery were included.

⁴¹² No instances of acute respiratory distress observed in either of the matched groups.

⁴¹³ The cumulative incidence of livebirths was also reported, but this outcome is impacted by elective abortion and miscarriage.

⁴¹⁴ Data aggregated for FGAs (chlorpromazine, chlorpromazine, flupenthixol, fluphenazine, haloperidol, levomepromazine, perphenazine, pimozide, thioridazine, zuclopenthixol) and SGAs (aripiprazole, clozapine, melperone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) and lithium (17% of infants exposed). Excludes dixyrazine and prochlorperazine.

⁴¹⁵ This excludes the following common and clinically little important conditions: preauricular appendices, tongue tie, patent ductus at preterm birth, single umbilical artery, undescended testicle, unstable hip or hip (sub)luxation, and nevus. Therefore, this outcome would likely include malformations not classifiable as major.

Study ID Risk of bias	Study characteristics Country Timeframe	Population (N)	Exposure/s Timing	Comparator/s	Outcomes in PICO
Johnson 2012 <i>Moderate risk</i>	Prospective cohort, Emory Psychological Center US 1999–2008	Infants from mothers with psychiatric history (unexposed control) (N = 107)	Any antipsychotic	Unexposed ⁴¹⁶ Any antidepressant	Infant Neurological International Battery (INFANIB)
Lin 2010 <i>Low risk</i>	Retrospective, population-based cohort National Health Insurance Research Database Taiwan 2001–2003	Live-birth singleton infants of mothers with schizophrenia prescribed antipsychotics (N = 696) ⁴¹⁷	SGAs for schizophrenia FGAs for schizophrenia Timing: pregnancy	Unexposed and schizophrenia ⁴¹⁸	Preterm birth (<37 weeks) Small for gestational age Large for gestational age
Reis 2008 <i>Low risk</i> (<i>Moderate for malformations</i>)	Retrospective, linked, population-based cohort Swedish Medical Birth Register, Register of Congenital Malformations, Hospital Discharge Register Sweden 1995–2005	Infants (or stillborns) of mothers reporting use of antipsychotics in early pregnancy. (N = 973,767 infants born to 958,729 women)	Antipsychotics Timing: early pregnancy	Unexposed	Relatively severe malformations (<i>may include malformations not strictly classifiable as major</i> ⁴¹⁹) Stillbirth Preterm birth (<37 weeks) Small for gestational age Large for gestational age

Abbreviations: FGAs, first generation antipsychotics; hdPS, high-dimensional propensity score; PICO, population–intervention–comparator–outcome; SGA, second generation antipsychotic.

Table AppD4-42 Comparison of characteristics of included studies investigating overlapping cohorts

Study ID	Databases	Period	N	Exposure groups reported
Källén 2013	<ul style="list-style-type: none"> Swedish Medical Birth Register Register of Birth Defects (previously Register of Congenital Malformations) Hospital Discharge Register Swedish Register of Prescribed Drugs 	1996–2011	Exposed: 1,344 Total: 1,575,847	<ul style="list-style-type: none"> Antipsychotics <u>or lithium</u> Perphenazine Haloperidol Flupenthixol Olanzapine
Reis 2008	<ul style="list-style-type: none"> Swedish Medical Birth Register Register of Congenital Malformations Hospital Discharge Register 	1995–2005	Exposed: 576 Total: 973,767	<ul style="list-style-type: none"> Antipsychotics
Bodén 2012b	<ul style="list-style-type: none"> Swedish Medical Birth Register Prescribed Drug Register National Patient Register 	2005–2009 ⁴²⁰ 1997–2009	Exposed: 169 Unexposed: 357,696	<ul style="list-style-type: none"> Antipsychotics (excluding olanzapine and clozapine) Olanzapine or clozapine⁴²¹

AppD4.1.2.3 Major malformations – antipsychotics

AppD4.1.2.3.1 Results based on systematic reviews

None of the three systematic reviews reporting quantitative data for major malformations were eligible for inclusion in the Technical Report as none restricted their analyses to adjusted data. Furthermore, Coughlin

⁴¹⁶ The comparator group was a mix of women with and without mental health disorders (32/85 had a psychiatric history).

⁴¹⁷ Results are also reported for healthy, unexposed matched controls (n = 3480), but risk assessed relative to schizophrenia patients unexposed to antipsychotics, which is not a relevant comparison for the current Report.

⁴¹⁸ Both exposed and unexposed groups had at least three consensus schizophrenia diagnoses in a hospital or ambulatory care setting.

⁴¹⁹ This excludes some common and variable mild conditions: preauricular tag, tongue tie, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testicle, unstable hip, and nevus.

⁴²⁰ Date range for Medical Birth Register data was also 2005–2009.

⁴²¹ Main outcomes were gestational diabetes and fetal growth, so highly anabolic drugs were analysed separately.

2015 included data incorrectly extracted from an original study⁴²² – while the pooled result remains significant when the correct data is used, the true OR is less than that reported. *Therefore, these published SR findings have not been used to generate recommendations and an examination of the results of individual studies has been undertaken for the current Guideline.*

AppD4.1.2.3.2 Results based on individual studies

Table AppD4-43 presents adjusted data from a selection of the most relevant analyses extracted in Section AppD3.1.2.2.1 regarding the association between antipsychotic use and major malformations. Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

Six studies reported adjusted risk estimates for major malformations. Three are population-based cohorts, one from the US Medicaid database (Huybrechts 2016), and two from national databases in Sweden (Källén 2013; Reis 2008). One is a UK primary care database study (Petersen 2016a) and two smaller studies are registries from the US (Cohen 2016; hospital-based pregnancy registry for SGAs) and Germany (Habermann 2013; Teratology Information Service). Only Huybrechts 2016 and Habermann 2013 report results for SGAs and FGAs, and only Huybrechts 2016 and Källén 2013 reported risk estimates for individual interventions.

Three of the six studies attempted to improve comparability of groups with regard to indication. Cohen 2016 (N = 303) partly limited the comparator group to women with a history of psychiatric illness (although results adjusted for indication-related covariates are reported and extracted here, the authors note that, due to the rarity of the outcome, they interpret only the crude results). Petersen 2016a (N = 211,748) compared an exposed cohort with a cohort of women who discontinued use prior to pregnancy, inferring this group is more likely to have mental health disorders than the entire unexposed cohort. Huybrechts 2016 (N = 1,341,715) adjusted for indication and associated medication, as well as for a high-dimensional propensity score addressing 200 potential confounders. The other three studies, Habermann 2013, Källén 2013 and Reis 2008, did not adjust for indication. As the exposed group in Källén 2013 included women using either antipsychotics or lithium, data from this study are included in the body of evidence only where no other evidence is available for a particular intervention.

The risk of malformations is potentially underestimated due to the impracticality of capturing malformations in spontaneous and elective terminations, and many study populations consisted of liveborns only, excluding malformation in stillbirths. This flaw in outcome ascertainment increases the risk of bias for malformation compared to other outcomes within the same study. Consequently, each of the six studies reporting adjusted results for major malformations are of moderate risk of bias for malformation outcomes.

Table AppD4-43 Antipsychotics – major malformation outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotic						
Petersen 2016a <i>Moderate</i>	Major congenital malformations	Any antipsychotics (early – 31-105 days)	Discontinued – no further adjustment for indication	Retrospective, primary care database	Exposed: 290 Unexposed: 492	RR 1.79 (0.72, 4.47)
Petersen 2016a <i>Moderate</i>	Major congenital malformations	Any antipsychotics (early – 31-105 days)	Unexposed – no adjustment for indication	Retrospective, primary care database	Exposed: 290 Unexposed: 210,966	RR 1.59 (0.84, 3.00)

⁴²² Data for Källén 2013 incorrectly extracted for major malformations: the numerator of 60 events relates to exposure early in pregnancy while the 592 denominator relates to late exposure. The correct denominator was not reported but is approximately 1,344. The pooled estimate remained significantly in favour of the unexposed group (OR 1.80, 95% CI: 1.18, 2.75).

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Källén 2013 <i>Moderate</i>	Relatively severe malformations ⁴²³	Antipsychotics or lithium ⁴²⁴ (anticonvulsants likely excluded) ⁴²⁵ (early pregnancy)	Unexposed (anticonvulsants likely excluded) – no adjustment for indication	Population-based cohort	Infant exposure instances: 1,344 Total: 1,575,847	OR 1.48 (1.13, 1.92)
Reis 2008 <i>Moderate</i>	Relatively severe malformations ⁴²⁶	Antipsychotics (early pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 576 Total: 973,767	OR 1.52 (1.05, 2.19)
Reis 2008 <i>Moderate</i>	Relatively severe malformations ⁴²⁶	Antipsychotics (anticonvulsants excluded) (early pregnancy)	Unexposed (anticonvulsants excluded) – no adjustment for indication	Population-based cohort	No. of infants not reported but ~ 558 ⁴²⁷ Total: ~973,767	OR 1.45 (0.99, 2.12 ⁴²⁸)
SGAs						
Cohen 2016 <i>Moderate</i>	Major malformations	SGAs (1 st trimester)	Unexposed, partially restricted by psychiatric illness – no further adjustment for indication	Prospective cohort,	Exposed: 214 Unexposed: 89	OR 0.69 (0.06, 8.09) ⁴²⁹
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	SGAs (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 9,258 Unexposed: 1,331,910	RR 1.36 (1.24, 1.50)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	SGAs (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 9,240 Unexposed: 1,331,896	RR 1.12 (1.02, 1.23)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	SGAs (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 9,237 Unexposed: 1,289,826	RR 1.05 (0.96, 1.16)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	SGAs, restricted to schizophrenia, bipolar disorder, psychosis (1 st trimester)	Unexposed, restricted to schizophrenia, bipolar disorder, psychosis – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 3,995 Unexposed: 11,606	RR 1.16 (0.99, 1.35)
Habermann 2013 <i>Moderate</i>	Major congenital malformations	SGAs (pregnancy)	Unexposed – no adjustment for indication	Cohort – matched	Exposed: 561 Unexposed: 1,122	OR 2.17 (1.20, 3.91)
SGAs vs FGAs						
Habermann 2013 <i>Moderate</i>	Major congenital malformations	SGAs (pregnancy)	FGAs – no further adjustment for indication	Cohort (not matched)	SGAs: 561 FGAs: 284	OR 1.27 (0.57, 2.82)
FGAs						
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	FGAs (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 733 Unexposed: 1,331,910	RR 1.17 (0.81, 1.68)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	FGAs (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 668 Unexposed: 1,331,449	RR 1.00 (0.69, 1.45)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	FGAs (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 727 Unexposed: 1,297,638	RR 0.90 (0.62, 1.31)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	FGAs, restricted to schizophrenia, bipolar disorder, psychosis (1 st trimester)	Unexposed, restricted to schizophrenia, bipolar disorder, psychosis – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 381 Unexposed: 10,418	RR 0.93 (0.57, 1.51)

⁴²³ This excludes the following common and clinically little important conditions: preauricular appendices, tongue tie, patent ductus at preterm birth, single umbilical artery, undescended testicle, unstable hip or hip (sub)luxation, and nevus. Therefore, this outcome would likely include malformations not classifiable as major.

⁴²⁴ Lithium is the most commonly used agent (17% of neuroleptic-exposed women in the database), confounding the data for antipsychotics.

⁴²⁵ While Reis et al 2008 presented a sensitivity analysis in which anticonvulsants were explicitly excluded, Källén et al 2013 excluded concomitantly used drugs with teratogenic properties 'in some analyses of congenital malformation risk', which presumably was applied to the main analysis (any antipsychotic) and presumably excluded anticonvulsants.

⁴²⁶ This excludes some common and variable mild conditions: preauricular tag, tongue tie, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testicle, unstable hip, and nevus. Therefore, this outcome may include malformations not classifiable as major.

⁴²⁷ The sensitivity analysis excluded infants from 18 exposed women.

⁴²⁸ Upper CI reported in Reis et al 2008 as 1.41, which is less than the point estimate. $p = 0.55$, used to calculate upper limit post hoc.

⁴²⁹ This estimate was derived from a sensitivity analysis using a hypothetical propensity score-adjusted model (the propensity score predicting exposure was calculated using first-trimester exposure to 10 medication classes and a primary diagnosis of bipolar disorder) However, due to rarity of outcome, authors interpreted only the crude analysis (unadjusted OR 1.25 (0.13, 12.19), and noted that adjusting for confounders indicated an upward bias in the results.

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Habermann 2013 <i>Moderate</i>	Major congenital malformations	FGAs (pregnancy)	Unexposed – no adjustment for indication	Cohort (not matched)	Exposed: 284 Unexposed: 1,122	OR 1.71 (0.78, 3.76)
Aripiprazole						
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Aripiprazole (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 1,756 Unexposed: 1,331,910	RR 1.31 (1.05, 1.63)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Aripiprazole (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 1,750 Unexposed: 1,325,710	RR 1.04 (0.83, 1.30)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Aripiprazole (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 1,752 Unexposed: 957,012	RR 0.95 (0.76, 1.19)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Aripiprazole, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 949 Unexposed: 10,174	RR 1.13 (0.86, 1.50)
Flupenthixol						
Källén 2013 <i>Moderate</i>	Relatively severe malformations	Flupenthixol (early pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 154 Total: 1,575,847	RR 1.94 (1.00, 3.40) ⁴³⁰
Haloperidol						
Källén 2013 <i>Moderate</i>	Relatively severe malformations	Haloperidol (early pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 115 Total: 1,575,847	RR 1.21 (0.39, 2.83) ⁴³⁰
Olanzapine						
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Olanzapine (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 1,394 Unexposed: 1,331,910	RR 1.3 (1.01, 1.66)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Olanzapine (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 1,335 Unexposed: 1,329,948	RR 1.05 (0.82, 1.36)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Olanzapine (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 1,392 Unexposed: 1,231,441	RR 1.09 (0.85, 1.41)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Olanzapine, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 648 Unexposed: 10,949	RR 1.19 (0.84, 1.67)
Källén 2013 <i>Moderate</i>	Relatively severe malformations	Olanzapine (early pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 205 Total: 1,575,847	RR 0.93 (0.40, 1.84) ⁴³⁰
Quetiapine						
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Quetiapine (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 4,221 Unexposed: 1,331,910	RR 1.32 (1.15, 1.52)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Quetiapine (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 4,213 Unexposed: 1,331,557	RR 1.09 (0.95, 1.26)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Quetiapine (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 4,213 Unexposed: 1,161,955	RR 1.01 (0.88, 1.17)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Quetiapine, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 1,747 Unexposed: 11,440	RR 1.13 (0.92, 1.41)
Risperidone						
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Risperidone (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 1,566 Unexposed: 1,331,910	RR 1.56 (1.26, 1.94)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Risperidone (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 1,472 Unexposed: 1,331,674	RR 1.31 (1.05, 1.63)

⁴³⁰ As the expected number of exposed outcome was less than 10, a RR was calculated instead of OR, calculated using the observed over expected number with 95% CI from exact Poisson distributions.

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Risperidone (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 1,565 Unexposed: 1,290,485	RR 1.26 (1.02, 1.56)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Risperidone, <u>restricted to psychosis, schizophrenia or bipolar disorder</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 740 Unexposed: 11,497	RR 1.19 (0.86, 1.64)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	Discontinued: no Rx from 8 weeks before pregnancy – no further adjustment for indication (PS-adjusted) ⁴³¹	Retrospective, Medicaid cohort	Exposed: 866 Unexposed: 496	RR 1.64 (0.90, 2.98)
Ziprasidone						
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Ziprasidone (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 697 Unexposed: 1,331,910	RR 1.14 (0.78, 1.67)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Ziprasidone (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 695 Unexposed: 1,270,722	RR 0.9 (0.61, 1.31)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Ziprasidone (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 696 Unexposed: 979,614	RR 0.88 (0.60, 1.28)
Huybrechts 2016 <i>Moderate</i>	Major congenital malformations	Ziprasidone, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 425 Unexposed: 10,971	RR 0.84 (0.51, 1.39)

Abbreviations: CI, confidence interval; FGAs, first generation antipsychotics; OR, odds ratio; PS, propensity score; RE, risk estimate; RR, risk ratio; Rx, prescription; SGA, second generation antipsychotic.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

Any antipsychotics

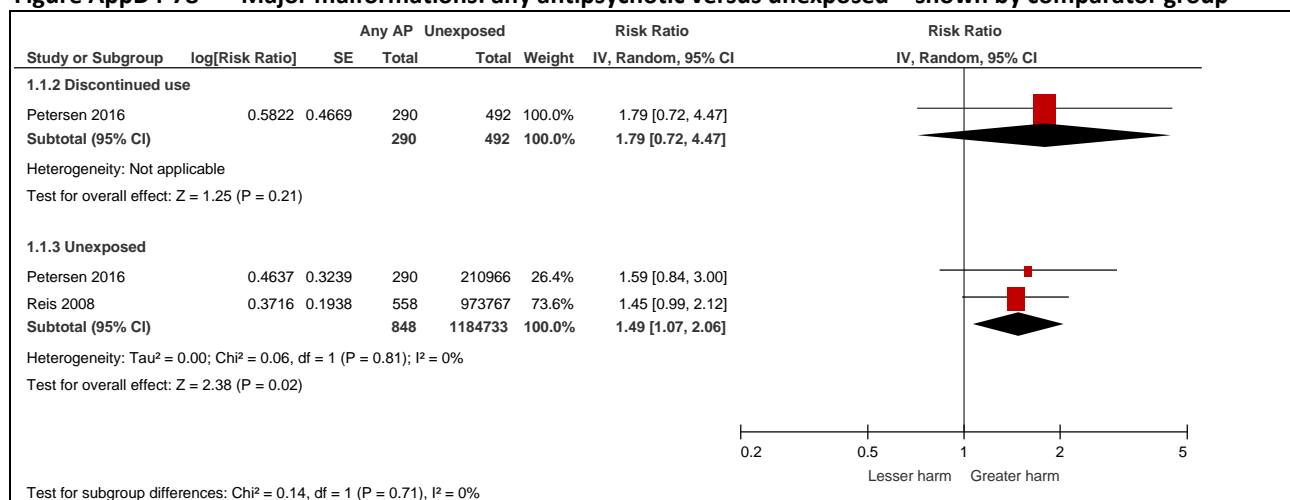
Results from two studies are included in the body of evidence for major malformation risk after exposure to any antipsychotic. Petersen et al 2016 compared a cohort exposed to any antipsychotic with an unexposed cohort, and also with a cohort restricted to women who discontinued use prior to pregnancy. Both comparisons found a substantial but statistically non-significant increase in the risk of major malformations.

Results from Reis 2008 were included in the body of evidence for exposure to any antipsychotic, as in the more recent Källén 2013 study of the same Swedish national databases, lithium was analysed together with antipsychotics.⁴²⁵ While Reis found a significant increase in the risk of major malformations, exclusion of anticonvulsant exposure led to a loss of significance (OR 1.45; 95% CI 0.99, 2.12⁴³²).

The pooled estimate from Petersen 2016a and Reis 2008 reaches statistical significance (RR 1.49; 95% CI 1.07, 2.06), but this estimate is not adjusted for differences in indication between groups.

⁴³¹ This analysis was adjusted for propensity score only. It is assumed the propensity score does not include indication variables as for other outcomes, indication was adjusted for separately prior to adjusting for propensity score. Therefore, it is assumed this PS-adjusted analysis does not adjusted for indication.

⁴³² Upper CI reported in Reis et al 2008 as 1.41, which is less than the point estimate. The reported p value of 0.55 was used to calculate upper limit post hoc.

Figure AppD4-78 Major malformations: any antipsychotic versus unexposed – shown by comparator group

Abbreviations: AP, antipsychotic; CI, confidence interval; IV, inverse variance; SE, standard error.

SGAs

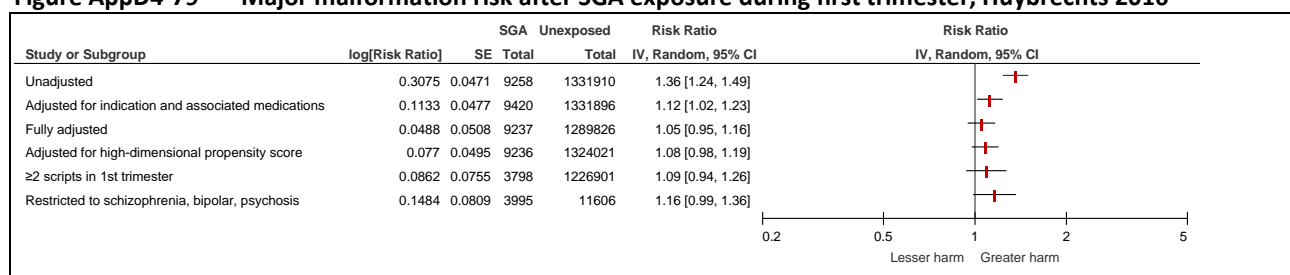
Three studies, Cohen 2016, Huybrechts 2016 and Habermann 2013, reported adjusted estimates for any SGA. Cohen 2016 mostly restricted the comparator groups to women with a mental health diagnosis. However, while adjusted results are presented, the authors interpreted only crude results, regarding the adjusted estimates simply as indicative of direction of bias from confounders. Consequently, while the adjusted estimate is shown here, it is not included in the body of evidence for malformations.

Habermann 2013 is a study of women who contacted a German teratology information service (TIS), from which three cohorts were identified: SGA-exposed, FGA-exposed and unexposed women. The authors found a large and significant increase in malformation risk in infants of mothers using SGAs during gestation compared with infants from a matched cohort of unexposed women (OR 2.17; 95% CI 1.20, 3.91). No accounting for indication was performed. A comparison of the SGA and FGA cohorts, both of which presumably would have consisted of women with a mental health disorder, found a non-significant increase in risk with SGAs (OR 1.27; 95% CI 0.57, 2.82).

Huybrechts 2016 is a US population-based study comparing three cohorts: SGA-exposed, FGA-exposed and unexposed women. A series of risk estimates is presented, starting with unadjusted results and sequentially adjusting, first for indication-related confounders (psychiatric and neurologic conditions, and psychotropic medication), then for a propensity score which accounts for a large number of other potential confounders. The impact on the risk of malformations is illustrated in **Figure AppD4-79**; the risk estimate is reduced by addressing indication-related confounding. When fully adjusted for other covariates, the estimate is reduced further and statistical significance is lost, while slightly improving the precision of the estimate. This estimate is referred to by the authors as fully adjusted.

Sensitivity and exploratory analyses are also presented: estimates using a high-dimensional propensity score (using 200 covariates), or restricting the exposure group to women who filled at least two scripts during their first trimester, were similar to the fully adjusted estimates, albeit precision was reduced for the latter comparison. Restricting the population to women with schizophrenia, bipolar disorder or psychosis (fully adjusted as per main analysis) found a higher risk than the analysis adjusting for indication confounders, but this estimate was not statistically significant.

The Huybrechts 2016 study adjusts for a greater number of covariates than other antipsychotic studies investigating malformations, and illustrates the substantial impact of lack of comparability of cohorts in these studies, especially confounding by indication and its related medications. This trend towards the null after substantial adjustment is of relevance to the interpretation of other studies comparing cohorts that differ in mental health status without sufficient treatment of confounders.

Figure AppD4-79 Major malformation risk after SGA exposure during first trimester, Huybrechts 2016

Note: Confidence intervals may differ slightly to reported results due to rounding. Restricted analysis: both exposed and unexposed groups were restricted to women with schizophrenia, bipolar disorder or psychosis.

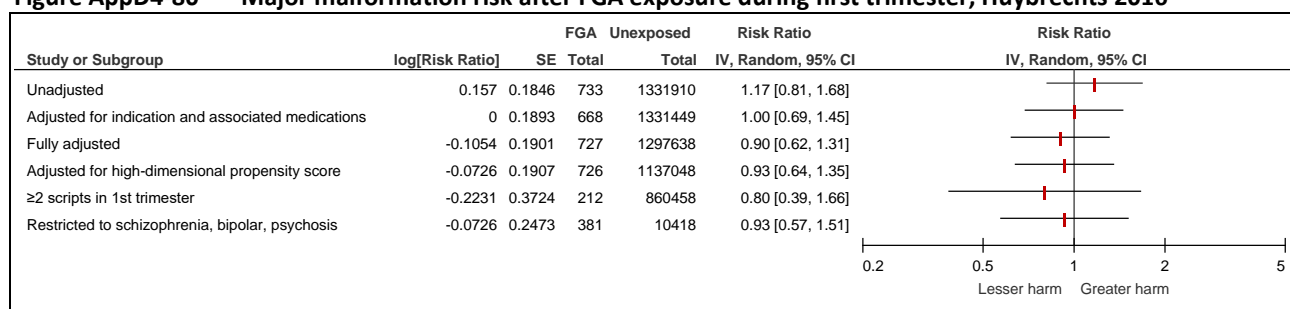
Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; SGA, second generation antipsychotic.

Two analyses from Huybrechts 2016 – the fully adjusted main analysis and the analysis restricted by indication – will be included in the body of evidence for SGAs. In light of the difference in study size and design compared to Huybrechts 2016 (risk of selection bias introduced by TIS) and the lack of any adjustment for indication), the Habermann 2013 comparison of SGA and unexposed cohorts will not be considered in the body of evidence for SGAs. However, the Habermann 2013 comparison of SGAs and FGAs, which carries a lower risk of bias due to increased comparability of groups, will be considered.

FGAs

Two studies report adjusted risk estimates for FGAs as a group; Huybrechts 2016 and Habermann 2013. None of the Huybrechts 2016 analyses found statistically significant risk of major malformations in infants exposed to FGAs (**Figure AppD4-80**). Adjusting for indication-related confounders shifts the risk estimate to the null effect, and reduces it further when other covariates are taken into account in each of the other analyses. It should be noted that FGAs are less-commonly used, and the FGA cohorts are smaller, by an order of magnitude, than SGA cohorts derived from the same population.

The Huybrechts 2016 fully adjusted main analysis and the analysis restricted by indication will be included in the body of evidence for FGAs. The Habermann 2013 comparison of FGAs with unexposed infants will not be considered in the body of evidence for SGAs, due to the difference in study size and design compared to Huybrechts 2016 (i.e. the lack of any adjustment for indication).

Figure AppD4-80 Major malformation risk after FGA exposure during first trimester, Huybrechts 2016

Note: Confidence intervals may differ slightly to reported results due to rounding. Restricted analysis: both exposed and unexposed groups were restricted to women with schizophrenia, bipolar disorder or psychosis.

Abbreviations: CI, confidence interval; FGA, first generation antipsychotic; IV, inverse variance; SE, standard error.

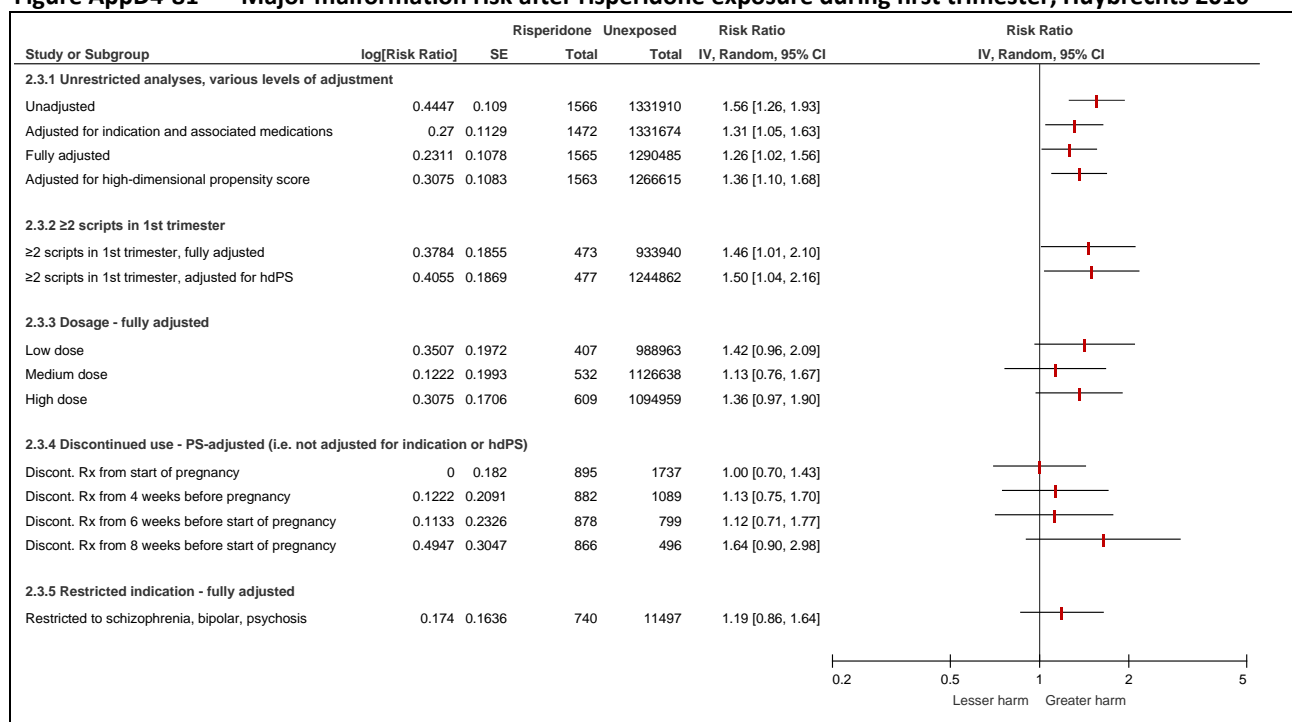
Specific antipsychotics

Huybrechts 2016 analysed the following, frequently used antipsychotics individually: aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. In unadjusted analyses, a statistically significant increase in the risk of malformations was found for all except ziprasidone (**Table AppD4-43**). With the exception of risperidone, adjustment for indication-related confounders both reduced the risk estimates and led to a loss of statistical significance without loss of precision.

The risk of major malformations in the risperidone-exposed cohort remained significant after adjusting for indication-related confounders, and in the fully adjusted estimate (**Figure AppD4-81**). Restricting the analysis to women filling at least two scripts in the first trimester, either fully adjusted or high-dimensional-propensity-score-adjusted, increased the point estimates over the unrestricted analyses without loss of significance. The risk estimates from other restricted analyses were not statistically significant (**Figure AppD4-81**), including restricting the populations of both comparison groups to women with schizophrenia, bipolar or psychosis diagnoses. It should be noted that for this latter comparison, the size of the cohorts is substantially smaller than in the analyses of unrestricted populations achieving significance.

Fully adjusted estimates for both the unrestricted and indication-restricted populations from Huybrechts 2016 will be included in the body of evidence for the risk of major malformation after exposure to individual antipsychotics.

Figure AppD4-81 Major malformation risk after risperidone exposure during first trimester, Huybrechts 2016



Abbreviations: CI, confidence interval; hdPS, high-dimensional propensity score; IV, inverse variance; Rx, prescription; SE, standard error.

Källén et al 2013 provided risk estimates for individual interventions where at least 100 infants were exposed: olanzapine, flupenthixol and haloperidol.⁴³³ A large risk increase was found for flupenthixol, which almost reached statistical significance (RR 1.94; 95% CI 1.00, 3.4). The authors make the following conclusion regarding individual interventions: “Among neuroleptics, flupenthixol appears to be associated with an increased malformation risk, perhaps notably for urogenital malformations. This association has been indicated in previous studies from the Swedish Medical Birth Register but not by other studies”. This is the only study providing evidence for major malformations after flupenthixol and haloperidol, but the body of evidence for malformations after olanzapine exposure will be derived from the Huybrechts 2016 study.

⁴³³ For these analyses, as the expected number of events in the exposed group was less than 10, a RR was calculated instead of an OR, analysing the observed over expected number with a 95% CI from exact Poisson distributions. More than 100 infants were exposed to perphenazine but fewer than two events in the exposed group were reported, so risk was not estimated.

AppD4.1.2.4 Cardiac malformations – antipsychotics**AppD4.1.2.4.1 Results based on systematic reviews**

The systematic review reporting quantitative results for cardiac malformations (Coughlin 2015) was not eligible for inclusion in the Technical Report as it did not restrict analyses to adjusted data. Furthermore, Coughlin 2015 included data incorrectly extracted from an original study.⁴³⁴ *Therefore, these published SR findings will not be used to generate recommendations and an examination of the results of individual studies has been undertaken for the current Guideline.*

AppD4.1.2.4.2 Results based on individual studies

Table AppD4-44 presents adjusted data from a selection of the most relevant analyses extracted in Section AppD3.1.2.2.1 regarding the association between antipsychotic use and cardiac malformations. Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

Table AppD4-44 Antipsychotics – cardiac malformation outcomes from observational studies

Study ID	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotics						
Källén 2013 <i>Moderate</i>	Any cardiac defects	Antipsychotics or lithium ⁴²⁴ (early pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Infant exposure instances: 1,344 Total: 1,575,847	OR 0.83 (0.48, 1.41)
Källén 2013 <i>Moderate</i>	Septal cardiac defects	Antipsychotics or lithium ⁴²⁴ (early pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Infant exposure instances: 1,344 Total: 1,575,847	OR 0.83 (0.44, 1.59)
SGAs						
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	SGAs (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 9,258 Unexposed: 1,331,910	RR 1.40 (1.19, 1.64)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	SGAs (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 9,240 Unexposed: 1,331,896	RR 1.15 (0.98, 1.35)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	SGAs (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 9,237 Unexposed: 1,289,826	RR 1.06 (0.90, 1.24)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	SGAs, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 3,995 Unexposed: 11,606	RR 1.21 (0.93, 1.57)
FGAs						
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	FGAs (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 733 Unexposed: 1,331,910	RR 1.18 (0.64, 2.18)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	FGAs (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 668 Unexposed: 1,331,449	RR 0.94 (0.49, 1.80)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	FGAs (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 727 Unexposed: 1,297,638	RR 0.75 (0.39, 1.43)

⁴³⁴ Data for Källén 2013 incorrectly extracted for cardiac malformations: the numerator of 13 events relates to exposure early in pregnancy while the 592 denominator relates to late exposure. The correct denominator was not reported but was calculated post hoc to range from 1,201 and 1,344. The pooled estimate remained statistically significant at the lower end of the range (13/1,201; OR 1.72 (95% CI 1.01, 2.94)) but at the upper end of the range this pooled estimate is no longer statistically significant (13/1,344; OR 1.68 (95% CI 0.93, 3.06)).

Study ID	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	FGAs, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to psychosis, schizophrenia, bipolar disorder</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 381 Unexposed: 10,418	RR 0.91 (0.43, 1.91)
Aripiprazole						
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Aripiprazole (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 1,756 Unexposed: 1,331,910	RR 1.33 (0.91, 1.93)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Aripiprazole (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 1,750 Unexposed: 1,325,710	RR 1.06 (0.72, 1.55)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Aripiprazole (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 1,752 Unexposed: 957,012	RR 0.93 (0.64, 1.37)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Aripiprazole, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 949 Unexposed: 10,174	RR 1.13 (0.71, 1.80)
Olanzapine						
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Olanzapine (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 1,394 Unexposed: 1,331,910	RR 1.24 (0.80, 1.92)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Olanzapine (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 1,335 Unexposed: 1,329,948	RR 0.96 (0.61, 1.52)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Olanzapine (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 1,392 Unexposed: 1,231,441	RR 0.99 (0.64, 1.53)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Olanzapine, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 648 Unexposed: 10,949	RR 1.23 (0.69, 2.19)
Quetiapine						
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Quetiapine (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 4,221 Unexposed: 1,331,910	RR 1.43 (1.14, 1.81)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Quetiapine (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 4,213 Unexposed: 1,331,557	RR 1.18 (0.94, 1.49)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Quetiapine (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 4,213 Unexposed: 1,161,955	RR 1.07 (0.85, 1.35)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Quetiapine, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 1,747 Unexposed: 11,440	RR 1.17 (0.81, 1.67)
Risperidone						
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Risperidone (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 1,566 Unexposed: 1,331,910	RR 1.60 (1.12, 2.30)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Risperidone (1 st trimester)	Unexposed – adjusted for indication and medication	Retrospective, Medicaid cohort	Exposed: 1,472 Unexposed: 1,331,674	RR 1.39 (0.96, 2.01)

Study ID	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Risperidone (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 1,565 Unexposed: 1,290,485	RR 1.26 (0.88, 1.81)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Risperidone, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 740 Unexposed: 11,497	RR 1.64 (1.03, 2.62)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Risperidone, <u>continued use from 3 months prior</u> (1 st trimester)	Discontinued: <u>no Rx from 8 weeks before pregnancy</u> – no further adjustment for indication (PS-adjusted) ⁴³⁵	Retrospective, Medicaid cohort	Exposed: 866 Unexposed: 496	RR 2.46 (0.77, 7.87)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Risperidone, <u>low dose</u> (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 407 Unexposed: 988,963	RR 0.95 (0.43, 2.10)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Risperidone, <u>medium dose</u> (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 532 Unexposed: 1,126,638	RR 0.67 (0.28, 1.60)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Risperidone, <u>high dose</u> (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 609 Unexposed: 1,094,959	RR 2.08 (1.32, 3.28)
Ziprasidone						
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Ziprasidone (1 st trimester)	Unexposed – no adjustment for indication	Retrospective, Medicaid cohort	Exposed: 697 Unexposed: 1,331,910	RR 1.12 (0.58, 2.14)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Ziprasidone (1 st trimester)	Unexposed – adjusted for hdPS	Retrospective, Medicaid cohort	Exposed: 695 Unexposed: 1,270,722	RR 0.88 (0.46, 1.69)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Ziprasidone (1 st trimester)	Unexposed – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 696 Unexposed: 979,614	RR 0.85 (0.44, 1.63)
Huybrechts 2016 <i>Moderate</i>	Cardiac malformations	Ziprasidone, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> (1 st trimester)	Unexposed, <u>restricted to schizophrenia, bipolar disorder, psychosis</u> – fully adjusted (indication, medication, propensity score)	Retrospective, Medicaid cohort	Exposed: 425 Unexposed: 10,971	RR 0.75 (0.31, 1.81)

Abbreviations: CI, confidence interval; FGAs, first generation antipsychotics; hdPS, high-dimensional propensity score; OR, odds ratio; PS, propensity score; RE, risk estimate; RR, risk ratio; Rx, prescription; SGA, second generation antipsychotic.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

AppD4.1.2.5 Neonatal mortality – antipsychotics

AppD4.1.2.5.1 Results based on systematic reviews

Neither of the two systematic reviews reporting quantitative results for neonatal mortality (Coughlin 2015; Terrana 2015) were eligible for inclusion in the Technical Report as they did not restrict their analyses to adjusted data. *Therefore, these published SR findings will not be used to generate recommendations and an examination of the results of individual studies has been undertaken for the current Guideline.*

⁴³⁵ This analysis was adjusted for propensity score only. It is assumed the propensity score does not include indication variables as for other outcomes, indication was adjusted for separately prior to adjusting for propensity score. Therefore, it is assumed this PS-adjusted analysis does not adjusted for indication.

AppD4.1.2.5.2 Results based on individual studies

Table AppD4-45 presents all adjusted data extracted in Section AppD3.1.2.2.2 regarding the association between antipsychotic use and neonatal mortality. Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

Two low risk-of-bias studies report adjusted results for neonatal mortality after exposure to any antipsychotic, each reporting imprecise estimates. The Reis 2008 Swedish population-based database study compared stillbirth after exposure during early pregnancy with no exposure in the overall population, without adjusting for indication.

Vigod 2015 is a Canadian population-based study of women covered under the provincial drug plan of Ontario that investigated antipsychotics use during pregnancy (at least two scripts filled during pregnancy, with at least one filled during the first or second trimester). Results were reported for any antipsychotic use (for other outcomes, this study also reports for each of SGAs, quetiapine, olanzapine and risperidone).

Starting with a cohort of 41,523 single live births or stillbirth of known antipsychotics-exposure status, a comparator cohort of unexposed women was identified by matching 1:1 with exposed women using a high-dimensional propensity algorithm derived from 500 covariates (hdPS-matched). Covariate selection was based on exposure status-covariate relations (baseline characteristics) rather than covariate outcomes, allowing the generation of a single matched cohort for all outcomes (N = 1,021 per matched cohort). This matching process reduces the potential impact of both identified and unidentified confounders.

Adjustment was performed for exposure to other psychotropic drugs during the index pregnancy (SSRIs, non-SSRIs, mood stabilisers or benzodiazepines), as these key prognostic variables showed residual imbalance even after matching. To illustrate the degree and direction of confounding, results are reported for all three analyses; unadjusted, matched and matched plus adjusted.

Table AppD4-45 shows risk estimates for neonatal mortality and stillbirth from unmatched and matched cohort comparisons (for these outcomes, additional adjusting for other psychoactive drugs was not reportable because of non-convergence of the adjusted model). For neonatal death, both the unmatched and matched cohorts report imprecise estimates, with the matched cohort comparison reporting a reduced point estimate.

For stillbirth, unmatched cohorts show an increased risk with exposure, but when indication-related confounders are accounted for with matched cohorts, the estimate is reduced to the point of indicating less risk of stillbirth after exposure to antipsychotics. Neither of these estimates is statistically significant, and the matched cohort estimate is imprecise.

Reis 208 also reported the risk of stillbirth after exposure to any antipsychotic, although no indication-related adjustment was performed. Opposing estimates of risk are reported by these two studies, although both are imprecise.

As the Vigod 2016 study adjusted for a wide range of confounders, including indication, results from this study were used as the body of evidence for stillbirth and neonatal mortality after exposure to any antipsychotic.

Table AppD4-45 Antipsychotics – neonatal mortality outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotics – neonatal mortality						
Vigod 2015 <i>Low</i>	Neonatal mortality (<90 days)	Any antipsychotic (≥ 2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 1,209 Unexposed: 40,314	RR 1.64 (0.84, 3.20)

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Vigod 2015 <i>Low</i>	Neonatal mortality (<90 days)	Any antipsychotic (≥ 2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS- matched (includes indication)	Population- based cohort	Exposed: 1,021 Unexposed: 1,021	RR 1.50 (0.53, 4.21)
Any antipsychotics – stillbirth						
Vigod 2015 <i>Low</i>	Stillbirth	Any antipsychotic (≥ 2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 1,209 Unexposed: 40,314	RR 1.15 (0.64, 2.05)
Vigod 2015 <i>Low</i>	Stillbirth	Any antipsychotic (≥ 2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS- matched (includes indication)	Population- based cohort	Exposed: 1,021 Unexposed: 1,021	RR 0.56 (0.25, 1.27)
Reis 2008 <i>Low</i>	Stillbirth	Antipsychotics (early pregnancy)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 576 Total: 973,767	RR 1.48 (0.48, 3.47)

Abbreviations: CI, confidence interval; hdPS, high-dimensional propensity score; RE, risk estimate; RR, risk ratio.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

AppD4.1.2.6 Miscarriage – antipsychotics

AppD4.1.2.6.1 Results based on systematic reviews

Neither of the two systematic reviews reporting quantitative results for miscarriage (Coughlin 2015; Terrana 2015) were eligible for inclusion in the Technical Report as they did not restrict their analyses to adjusted data. *Therefore, these published SR findings will not be used to generate recommendations and an examination of the results of individual studies has been undertaken for the current Guideline.*

AppD4.1.2.6.2 Results based on individual studies

Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

The Danish population-based registry cohort study by Sorensen et al 2015 is the only study of antipsychotics reporting adjusted results for miscarriage. The comparator population is not limited to women with a mental health disorder, and the analyses are not adjusted for indication, but concomitant medication was an included covariate. This study was considered to be at low risk of bias. Exposure cohorts analysed included any antipsychotics and a range of individual drugs.

Most of the analyses in this study found exposure significantly increased the risk of miscarriage. However, without adjustment for indication, these results should be interpreted cautiously. Two analyses of any antipsychotics exposure attempted to address the imbalance in indication between the groups, by restricting the comparator cohort to women who discontinued treatment at least 30 days prior to pregnancy, or to women with a severe mental disorder diagnosis recorded in the Danish Psychiatric Central Register. In both cases this led to more precise estimate of risk that was closer to unity, and a loss of statistical significance. Only these two analyses are included in the body of evidence for any antipsychotics exposure.

The population with a severe mental disorder diagnosis was further stratified by dose, finding a substantial and significant increase in risk is seen for the high-dose population. However, only crude results are reported so they are not included in the body of evidence.

For the analyses of specific antipsychotics, as no higher quality evidence was available, results from this study were included in the body of evidence.

Table AppD4-46 Antipsychotics – miscarriage outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotics						
Sorensen 2015 <i>Low</i>	Spontaneous abortion	Any antipsychotics (any time from 30 days before, to end of pregnancy)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 1,881 Unexposed: 841,183	RR 1.34 (1.22, 1.46)
Sorensen 2015 <i>Low</i>	Spontaneous abortion	Any antipsychotics (any time from 30 days before, to end of pregnancy)	Discontinued ⁴³⁶ – no further adjustment for indication	Population- based cohort	Exposed: 1,181 Unexposed: 2,745	RR 1.04 (0.93; 1.17)
Sorensen 2015 <i>Low</i>	Miscarriage	Any antipsychotics, <u>hospital diagnosis of severe mental disorder</u> (any time from 30 days before, to end of pregnancy)	Unexposed, <u>hospital diagnosis of severe mental disorder</u> ⁴³⁷ – no further adjustment for indication	Population- based cohort	Exposed: 461 Unexposed: 1,337	RR 1.14 (0.94, 1.39)
Sorensen 2015 <i>Low</i>	Miscarriage	Any antipsychotics, <u>hospital diagnosis of severe mental disorder and high dose</u> (any time from 30 days before, to end of pregnancy)	Unexposed, <u>hospital diagnosis of severe mental disorder</u> – no further adjustment for indication	Population- based cohort	Exposed: NR Unexposed: 839,846	RR 2.22 (1.67, 2.95)
Sorensen 2015 <i>Low</i>	Miscarriage	Any antipsychotics, <u>hospital diagnosis of severe mental disorder and low dose</u> (any time from 30 days before, to end of pregnancy)	Unexposed, <u>hospital diagnosis of severe mental disorder</u> – no further adjustment for indication	Population- based cohort	Exposed: NR Unexposed: 839,846	RR 2.95 (0.73, 1.26)
Specific antipsychotics						
Sorensen 2015 <i>Low</i>	Spontaneous abortion	Chlorprothixene ⁴³⁸ (any time from 30 days before, to end of pregnancy)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 365 Unexposed: 841,183	RR 1.65 (1.39, 1.95)
Sorensen 2015 <i>Low</i>	Spontaneous abortion	Flupenthixol (any time from 30 days before, to end of pregnancy)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 233 Unexposed: 841,183	RR 1.55 (1.22, 1.97)
Sorensen 2015 <i>Low</i>	Spontaneous abortion	Levomepromazine ⁴³⁸ (any time from 30 days before, to end of pregnancy)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 200 Unexposed: 841,183	RR 1.32 (1.01, 1.72)
Sorensen 2015 <i>Low</i>	Spontaneous abortion	Olanzapine (any time from 30 days before, to end of pregnancy)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 223 Unexposed: 841,183	RR 1.10 (0.83, 1.46)
Sorensen 2015 <i>Low</i>	Spontaneous abortion	Perphenazine (any time from 30 days before, to end of pregnancy)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 229 Unexposed: 841,183	RR 1.25 (0.95, 1.64)
Sorensen 2015 <i>Low</i>	Spontaneous abortion	Quetiapine (any time from 30 days before, to end of pregnancy)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 174 Unexposed: 841,183	RR 1.65 (1.28, 2.15)
Sorensen 2015 <i>Low</i>	Spontaneous abortion	Zuclopenthixol (any time from 30 days before, to end of pregnancy)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 229 Unexposed: 841,183	RR 1.26 (0.95, 1.66)

Abbreviations: CI, confidence interval; NR, not reported; RE, risk estimate; RR, risk ratio.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

AppD4.1.2.7 Preterm birth – antipsychotics

AppD4.1.2.7.1 Results based on systematic reviews

Neither of the two systematic reviews reporting quantitative results for preterm birth (Coughlin 2015; Terrana 2015) were eligible for inclusion in the Technical Report as they did not restrict their analyses to adjusted data. *Therefore, these published SR findings will not be used to generate recommendations and an examination of the results of individual studies has been undertaken for the current Guideline.*

⁴³⁶ Used during preceding year but not from 30 days prior.

⁴³⁷ "The Danish Psychiatric Central Register contains information on treatment at psychiatric hospital-based units in Denmark. However, data on diagnoses made by general practitioners or private psychiatrists are not included in the register. Only diagnoses recorded in the register can be adjusted for."

⁴³⁸ This intervention is not currently listed on the Australian Register of Therapeutic Goods, so while data is extracted here, it is not taken through to evidence profile tables.

AppD4.1.2.7.2 Results based on individual studies

Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

Five population-based studies reported adjusted risk estimates for preterm birth; one Canadian study (Vigod 2015), one Taiwanese study (Lin 2010) and three studies of the same Swedish national databases (Källén et al 2013, Reis et al 2008, Bodén et al 2012b). Results for preterm birth, defined as birth earlier than week 37, are shown in **Table AppD4-47**.

The design of the Vigod 2015 study described in detail in Section AppD4.1.2.5 – results for preterm birth (<37 weeks) were reported for unadjusted estimates, for estimates from comparisons of hdPS-matched cohorts, and also for estimates adjusted further for other psychotropic medications. The impact of accounting for a large array of potential confounders, including indication-related confounders, is illustrated by the shift from a substantial and significant increase in risk in the unadjusted results, to estimates close to a null effect in the matched cohort comparisons. Restricting populations by trimester showed similar results, with the exception of the third trimester, for which the risk estimate is lower in the exposure group, although this is not statistically significant.

Estimates from the adjusted analyses of each of these matched cohorts are included in the body of evidence for preterm birth (<37 weeks).

Källén 2013, Bodén 2012b and Reis 2008 are studies of the same Swedish databases, and none adjusted for indication or concomitant medication. Their risk estimates are similar to the unadjusted results reported by Vigod 2015, so are not included in the body of evidence for preterm birth after exposure to any antipsychotic.

The Lin 2010 Taiwanese, population-based study limited the exposure group and a comparator group to women with schizophrenia, and reported results for exposure to SGAs or FGAs. Results were adjusted for a range of covariates and a significant and large increase in risk was observed for FGA exposure during pregnancy. These results constitute the body of evidence for preterm birth after exposure to either SGAs or FGAs.

Bodén 2012b reported risk of preterm birth for exposure to either olanzapine or clozapine. Adjustment for indication was not performed, and as the one individual treatment cannot be separated from the other, this evidence will not be considered further in the current Review.

Vigod 2015 presented forest plots (but not risk estimate or 95% CIs) for the risk of preterm birth (<37 weeks) after exposure to each of quetiapine, olanzapine and risperidone (**Figure AppD4-82**). They are not included in the body of evidence for these interventions as risk estimates are not reported. However, none show a statistically significant result, and none appear to be imprecise.

Table AppD4-47 Antipsychotics – preterm birth (<37 weeks) outcomes from observational studies

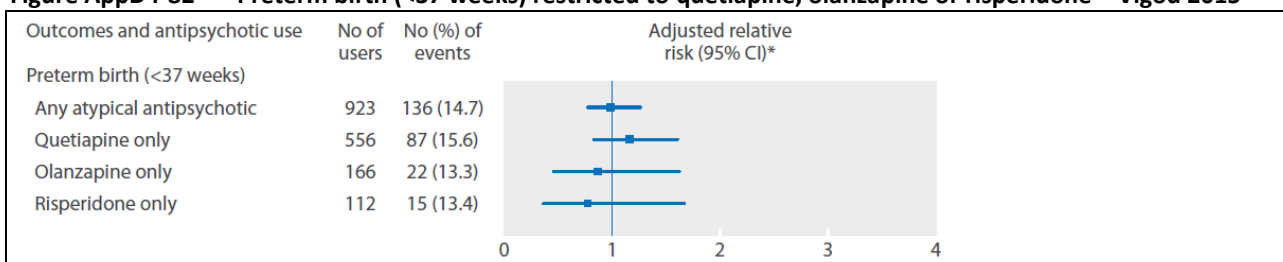
Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotics						
Vigod 2015 <i>Low</i>	Preterm birth (<37 weeks)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 1,209 Unexposed: 40,314	RR 1.51 (1.29, 1.78)
Vigod 2015 <i>Low</i>	Preterm birth (<37 weeks)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication)	Population- based cohort	Exposed: 1,021 Unexposed: 1,021	RR 1.01 (0.81, 1.27)
Vigod 2015 <i>Low</i>	Preterm birth (<37 weeks)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population- based cohort	Exposed: 1,021 Unexposed: 1,021	RR 0.99 (0.78, 1.26)

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Vigod 2015 <i>Low</i>	Preterm birth (<37 weeks)	Any antipsychotic (1 st trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 893 Unexposed: 893	RR 0.99 (0.77, 1.27)
Vigod 2015 <i>Low</i>	Preterm birth (<37 weeks)	Any antipsychotic (2 nd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 758 Unexposed: 758	RR 1.00 (0.75, 1.35)
Vigod 2015 <i>Low</i>	Preterm birth (<37 weeks)	Any antipsychotic (3 rd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 614 Unexposed: 614	RR 0.83 (0.59, 1.16)
Källén 2013 <i>Low</i>	Preterm birth (<37 weeks) ⁴³⁹	Antipsychotics or lithium ⁴⁴⁰ (2 nd or 3 rd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Infant exposure instances: 1,344 Total: 1,575,847	OR 1.02 (0.69, 1.51)
Bodén 2012b <i>Low</i>	Preterm birth singletons (<37 weeks)	Antipsychotics other than olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 338 Unexposed: 357,696	OR 1.94 (1.37, 2.77)
Reis 2008 <i>Low</i>	Preterm birth singletons (< 37 weeks)	Antipsychotics (early pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 563 Total: 942,780	OR 1.73 (1.31, 2.29)
SGAs						
Lin 2010 <i>Low</i>	Preterm birth singletons (<37 weeks)	SGAs for schizophrenia (pregnancy)	Unexposed to FGAs or SGAs, schizophrenia ⁴⁴¹	Population-based cohort	Exposed: 48 Unexposed: 454	OR 1.61 (0.63, 4.12)
FGAs						
Lin 2010 <i>Low</i>	Preterm birth singletons (<37 weeks)	FGAs for schizophrenia (pregnancy)	Unexposed to FGAs or SGAs, schizophrenia ⁴⁴¹	Population-based cohort	Exposed: 194 Unexposed: 454	OR 2.46 (1.50, 4.11)
Specific antipsychotics						
Bodén 2012b <i>Low</i>	Preterm birth singletons (<37 weeks)	Olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 169 Unexposed: 357,696	OR 1.58 (0.91, 2.73)

Abbreviations: CI, confidence interval; FGA, first generation antipsychotics; hdPS, high-dimensional propensity score; OR, odds ratio; RE, risk estimate; RR, risk ratio; SGA, second generation antipsychotic.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

Figure AppD4-82 Preterm birth (<37 weeks) restricted to quetiapine, olanzapine or risperidone – Vigod 2015



Source: Vigod et al (2015) Figure 2 p6

Abbreviations: CI, confidence interval.

⁴³⁹ Not indicated in study publication whether this outcome is for singleton births only.

⁴⁴⁰ Lithium is the most commonly used (17% of neuroleptic-exposed women in the database), confounding the data for antipsychotics.

⁴⁴¹ Smoking was not adjusted for in this study, but this confounder will be largely accounted for by the use of a comparator group of women with schizophrenia.

AppD4.1.2.8 Small for gestational age – antipsychotics**AppD4.1.2.8.1 Results based on systematic reviews**

Neither of the two systematic reviews reporting quantitative results for the outcome ‘small for gestational age’ (Coughlin 2015; Terrana 2015) were eligible for inclusion in the Technical Report as they did not restrict their analyses to adjusted data. *Therefore, these published SR findings will not be used to generate recommendations and an examination of the results of individual studies has been undertaken for the current Guideline.*

AppD4.1.2.8.2 Results based on individual studies

Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

All studies reporting small for gestational age were for singleton infants (with the exception of Källén 2013 which did not specify restriction to singletons for this outcome).

Vigod 2015 reported the risk of infants being born small for gestational age (birth weight <3rd centile) to mothers exposed to at least two consecutive scripts for any antipsychotics, with one being dispensed in either the first or second trimester. Risk was elevated in the exposed groups but were not statistically significant in either the unmatched/unadjusted or hdPS-matched/adjusted analyses (**Table AppD4-48**). Using a less stringent definition of ‘small for gestational age’ (birth weight <10th centile) also showed an increase in risk after exposure, which was statistically significant for the unmatched/unadjusted analysis only.

When restricted by trimester, the hdPS-matched/adjusted estimates and degree of precision remain similar to that for the overall population. Adjusted results for the more stringent definition of this outcome (<3rd centile) were included in the body of evidence, as a threshold beyond two standard deviations (<2.3rd centile) is frequently used to define this outcome.

The Källén 2013, Bodén 2012b and Reis 2008 Swedish database studies also report increased risk of newborns being small for gestational age after exposure to any antipsychotic (other than olanzapine or clozapine in the case of Bodén 2012b). However, these estimates will not be included in the body of evidence for this outcome as adjustment for indication was not performed.

The Lin 2010 population-based study limited the exposure group and a comparator group to women with schizophrenia, and reported results for the less stringent definition of this outcome (<10th centile) after exposure to SGAs or FGAs. Results were adjusted for a range of covariates and a large but non-significant increase in risk was observed for FGA exposure during pregnancy. These results constitute the body of evidence for the risk of being born small for gestational age after exposure to either SGAs or FGAs.

Bodén 2012b reported risk of newborns being small for gestation age after exposure to either olanzapine or clozapine. Adjustment for indication was not performed, so this evidence will not be considered further in the current Review.

Vigod 2015 presented forest plots (but not risk estimate or 95% CIs) for the risk of newborns being small for gestation age (<3rd centile weight) after exposure to each of quetiapine and olanzapine (**Figure AppD4-83**; event rates were too low for risperidone to include in this plot). These results are not included in the body of evidence for these interventions as risk estimates are not reported. None show a statistically significant result, and all are imprecise.

Table AppD4-48 Antipsychotics – small for gestational age (by weight) from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotics						
Vigod 2015 <i>Low</i>	Small for gestational age (<3 rd centile)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 1,209 Unexposed: 40,314	RR 1.20 (0.95, 1.53)
Vigod 2015 <i>Low</i>	Small for gestational age (<3 rd centile)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 1,021 Unexposed: 1,021	RR 1.21 (0.81, 1.82)
Vigod 2015 <i>Low</i>	Small for gestational age (<10 th centile)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 1,209 Unexposed: 40,314	RR 1.33 (1.15, 1.54)
Vigod 2015 <i>Low</i>	Small for gestational age (<10 th centile)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 1,021 Unexposed: 1,021	RR 1.20 (0.97, 1.50)
Vigod 2015 <i>Low</i>	Small for gestational age (<3 rd centile)	Any antipsychotic (<u>1st trimester</u>)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 893 Unexposed: 893	RR 1.33 (0.88, 2.02)
Vigod 2015 <i>Low</i>	Small for gestational age (<3 rd centile)	Any antipsychotic (<u>2nd trimester</u>)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 758 Unexposed: 758	RR 1.21 (0.74, 1.96)
Vigod 2015 <i>Low</i>	Small for gestational age (<3 rd centile)	Any antipsychotic (<u>3rd trimester</u>)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 614 Unexposed: 614	RR 1.24 (0.73, 2.10)
Källén 2013 <i>Low</i>	Small for gestational age (≤2.3 rd centile) ⁴⁴²	Antipsychotics or lithium ⁴⁴³ (2 nd or 3 rd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 592 Unexposed: 1,575,255	OR 1.72 (1.13, 2.95)
Bodén 2012b <i>Low</i>	Small for gestational age (≤2.3 rd centile) singletons	Antipsychotic other than olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 338 Unexposed: 357,696	OR 1.24 (0.72, 2.15)
Reis 2008 <i>Low</i>	Small for gestational age (<2.3 rd centile), singletons	Antipsychotics (early pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 561 Total: 938,318	OR 1.46 (0.99, 2.15)
SGAs						
Lin 2010 <i>Low</i>	Small for gestational age (<10 th centile), singletons	SGAs for schizophrenia (pregnancy)	Unexposed to FGAs or SGAs, schizophrenia ⁴⁴⁴	Population-based cohort	Exposed: 48 Unexposed: 454	OR 1.15 (0.55, 2.41)
FGAs						
Lin 2010 <i>Low</i>	Small for gestational age (<10 th centile), singletons	FGAs for schizophrenia (pregnancy)	Unexposed to FGAs or SGAs, schizophrenia ⁴⁴⁴	Population-based cohort	Exposed: 194 Unexposed: 454	OR 1.39 (0.93, 2.08)

⁴⁴² Not indicated in study publication whether this outcome is for singleton births only. Definition of small for gestational age was ≤2 standard deviations, which is equivalent to ≤2.3rd centile.

⁴⁴³ Lithium is the most commonly used (17% of neuroleptic-exposed women in the database), confounding the data for antipsychotics.

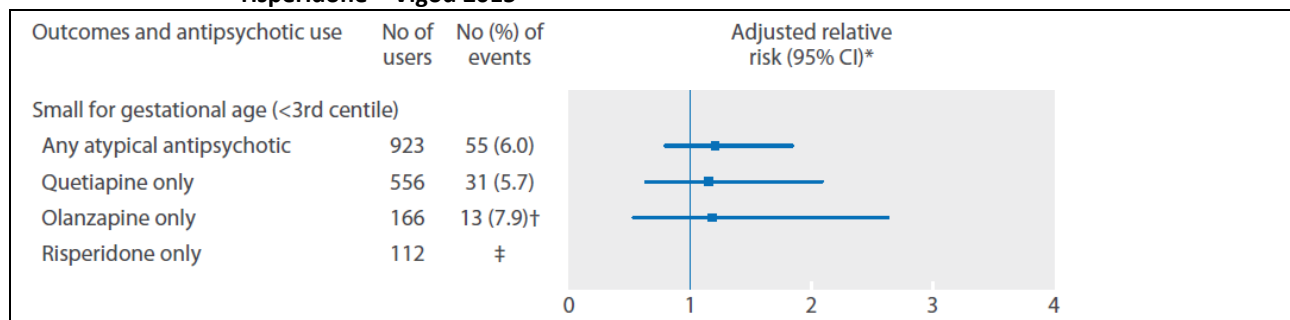
⁴⁴⁴ Smoking was not adjusted for in this study, but this confounder will be largely accounted for by the use of a comparator group of women with schizophrenia.

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Specific antipsychotics						
Bodén 2012b <i>Low</i>	Small for gestational age ($\leq 2.3^{\text{rd}}$ percentile) singletons	Olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 169 Unexposed: 357,696	OR 1.82 (0.91, 3.61)

Abbreviations: CI, confidence interval; FGA, first generation antipsychotics; hdPS, high-dimensional propensity score; OR, odds ratio; RE, risk estimate; RR, risk ratio; SGA, second generation antipsychotic.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

Figure AppD4-83 Small for gestational age ($<3^{\text{rd}}$ centile weight) restricted to quetiapine, olanzapine or risperidone – Vigod 2015



Source: Vigod et al (2015) Figure 2 p6

† Event rates and/or relative risks are too low to report.

Abbreviations: CI, confidence interval.

Table AppD4-49 Antipsychotics – small for gestational age (by length and by head circumference) from observational studies

Study ID	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotics						
Bodén 2012b <i>High</i>	Small for gestational age, singletons (by birth length)	Antipsychotic other than olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 338 Unexposed: 357,696	OR 1.35 (0.79, 2.28)
Bodén 2012b <i>High</i>	Small for gestational age, singletons (by head circumference)	Antipsychotic other than olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 338 Unexposed: 357,696	OR 1.64 (0.97, 2.77)
Olanzapine or clozapine						
Bodén 2012b <i>High</i>	Small for gestational age, singletons (by birth length)	Olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 169 Unexposed: 357,696	OR 1.17 (0.54, 2.55)
Bodén 2012b <i>High</i>	Small for gestational age, singletons (by head circumference)	Olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 169 Unexposed: 357,696	OR 0.62 (0.19, 2.01)

Abbreviations: CI, confidence interval; OR, odds ratio; RE, risk estimate.

Note: Data for these alternative measures of this outcome are not assessed as part of the primary evidence in this Review and so do not appear in the Evidence Profile Tables in the Technical Report.

AppD4.1.2.9 Large for gestational age – antipsychotics

AppD4.1.2.9.1 Results based on systematic reviews

Neither of the two systematic reviews reporting quantitative results for the outcome ‘large for gestational age’ (Coughlin 2015; Terrana 2015) were eligible for inclusion in the Technical Report as they did not restrict their analyses to adjusted data. *Therefore, these published SR findings will not be used to generate*

recommendations and an examination of the results of individual studies has been undertaken for the current Guideline.

AppD4.1.2.9.2 Results based on individual studies

Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

All studies reporting large for gestational age were for singleton infants (with the exception of Källén 2013 which did not specify restriction to singletons for this outcome).

Vigod 2015 reported the risk of infants being born large for gestational age (birth weight >97th centile) to mothers exposed to at least two consecutive scripts for any antipsychotics, with one being dispensed in either the first or second trimester. Unadjusted risk was statistically higher in the exposed group, but when compared between hdPS-matched cohorts and adjusted for other psychotropic medications, the risk estimate is reduced and significance is lost (**Table AppD4-50**). Using a less stringent definition of 'large for gestational age' (birth weight >90th centile), no significant exposure risk was seen.

Exposure in the later stages of pregnancy was associated with a greater risk of infants being born large for gestational age, with third trimester exposure having a 2.39-fold increased risk that almost reached statistical significance (hdPS-matched cohorts and adjusted). The adjusted results for the more stringent definition of this outcome were included in the body of evidence.

The Källén 2013, Bodén 2012b and Reis 2008 Swedish database studies also report the risk of newborns being large for gestational age after exposure to any antipsychotic. A statistically significant increase in risk was reported by Källén 2013 after exposure to any antipsychotic or lithium, and Bodén 2012b reported a non-significant risk increase after exposure to any antipsychotic other than olanzapine or clozapine. None of these estimates, however, will be included in the body of evidence for this outcome as adjustment for indication was not performed.

The Lin 2010 population-based study limited the exposure group and a comparator group to women with schizophrenia, and reported results for the less stringent definition of this outcome (>90th centile) after exposure to SGAs or FGAs. Results were adjusted for a range of covariates and no increase in risk was observed for either SGA or FGA exposure during pregnancy. These results constitute the body of evidence for the risk of being born large for gestational age after exposure to either SGAs or FGAs.

Bodén 2012b reported risk of newborns being large for gestation age after exposure to either olanzapine or clozapine. No increase in risk was observed, and as adjustment for indication was not performed, this evidence will not be considered further in the current Review.

Vigod 2015 restricted analyses to specific antipsychotics for quetiapine, olanzapine and risperidone but as the event rates for the latter two were too low, risk was reported for quetiapine only. Results were reported only as a forest plot (i.e. no risk estimate or 95% CI). An increase in risk similar to that after any antipsychotic exposure was observed, but the estimate was less precise (**Figure AppD4-84**).

Table AppD4-50 Antipsychotics – large for gestational age (by birth weight) from observational studies

Study ID	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotics						
Vigod 2015	Large for gestational age, (>97 th centile)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 1,209 Unexposed: 40,314	RR 1.44 (1.06, 1.96)
Vigod 2015	Large for gestational age (>97 th centile)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 1,021 Unexposed: 1,021	RR 1.26 (0.69, 2.29)

Study ID	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Vigod 2015	Large for gestational age (>90 th centile)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 1,209 Unexposed: 40,314	RR 1.18 (0.97, 1.45)
Vigod 2015	Large for gestational age (>90 th centile)	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 1,021 Unexposed: 1,021	RR 1.07 (0.76, 1.51)
Vigod 2015	Large for gestational age (>97 th centile)	Any antipsychotic (1 st trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 893 Unexposed: 893	RR 0.94 (0.46, 1.93)
Vigod 2015	Large for gestational age (>97 th centile)	Any antipsychotic (2 nd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 758 Unexposed: 758	RR 1.83 (0.89, 3.77)
Vigod 2015	Large for gestational age (>97 th centile)	Any antipsychotic (3 rd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 614 Unexposed: 614	RR 2.39 (1.00, 5.75)
Källén 2013 <i>High</i>	Large for gestational age (≥97.7 th centile) ⁴⁴⁵	Antipsychotics or lithium ⁴⁴³ (2 nd or 3 rd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 592 Unexposed: 1,575,255	OR 2.03 (1.39, 2.95)
Bodén 2012b <i>High</i>	Large for gestational age (≥97.7 th centile)	Antipsychotic other than olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 338 Unexposed: 357,696	OR 1.37 (0.69, 2.75)
Reis 2008 <i>High</i>	Large for gestational age (≥97.7 th centile) ⁴⁴⁶	Antipsychotics (early pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 561 Total: 938,318	OR 1.04 (0.70, 1.55)
SGAs						
Lin 2010 <i>Moderate</i>	Large for gestational age (>90 th centile) ⁴⁴⁷	SGAs for schizophrenia (pregnancy)	Unexposed, schizophrenia	Population-based cohort	Exposed: 48 Unexposed: 454	OR 0.55 (0.16, 1.85)
FGAs						
Lin 2010 <i>Moderate</i>	Large for gestational age (>90 th centile) ⁴⁴⁷	FGAs for schizophrenia (pregnancy)	Unexposed, schizophrenia	Population-based cohort	Exposed: 194 Unexposed: 454	OR 0.72 (0.39, 1.34)
Specific antipsychotics						
Bodén 2012b <i>High</i>	Large for gestational age (≥97.7 th centile)	Olanzapine or clozapine (pregnancy)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 338 Unexposed: 357,696	OR 0.55 (0.14, 2.11)

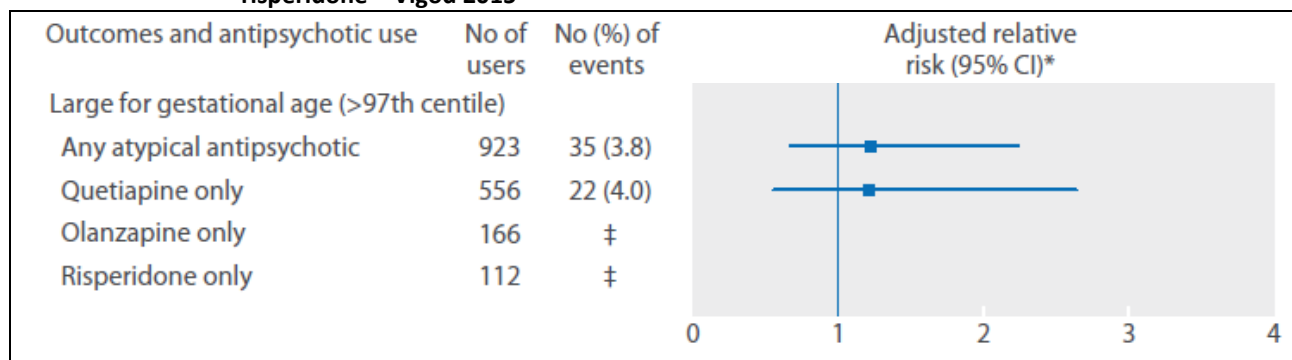
Abbreviations: CI, confidence interval; FGA, first generation antipsychotics; hdPS, high-dimensional propensity score; OR, odds ratio; RE, risk estimate; RR, risk ratio; SGA, second generation antipsychotic.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

⁴⁴⁵ Not indicated in study publication whether this outcome is for singleton births only. Definition of large for gestational age was ≥2 standard deviations, which is equivalent to ≥97.7th centile.

⁴⁴⁶ Definition of large for gestational age was >2 standard deviations, which is equivalent to ≥97.7th centile.

⁴⁴⁷ Lin 2010 reported definition of large for gestational age as ‘above the tenth percentile for gestational age’, which is interpreted here as above the 90th percentile (within the top 10%).

Figure AppD4-84 Large for gestational age (>97th centile weight) restricted to quetiapine, olanzapine or risperidone – Vigod 2015

Source: Vigod et al (2015) Figure 2 p6

‡ Event rates and/or relative risks are too low to report.

Abbreviations: CI, confidence interval.

AppD4.1.2.10 Seizures – antipsychotics

AppD4.1.2.10.1 Results based on systematic reviews

No systematic reviews reported quantitative results for seizures in newborns. *Therefore, an examination of the results of individual studies has been undertaken for the current Guideline.*

AppD4.1.2.10.2 Results based on individual studies

Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

Vigod 2015 is the only study reporting adjusted data for seizures (**Table AppD4-51**). Both unmatched and hdPS-matched estimates are shown to illustrate the impact of confounders. Statistical limitations prevented this analysis from being adjusted further for other psychotropic medications. Risk remains elevated in the matched analysis, although the estimate is imprecise.

Table AppD4-51 Antipsychotics – seizure outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotics						
Vigod 2015 <i>Low</i>	Seizure	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population- based cohort	Exposed: 1,209 Unexposed: 40,314	RR 4.30 (2.22, 8.33)
Vigod 2015 <i>Low</i>	Seizure	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS- matched (includes indication)	Population- based cohort	Exposed: 1,021 Unexposed: 1,021	RR 1.29 (0.48, 3.45)

Abbreviations: CI, confidence interval; hdPS, high-dimensional propensity score; RE, risk estimate; RR, risk ratio.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

AppD4.1.2.11 Respiratory distress – antipsychotics

AppD4.1.2.11.1 Results based on systematic reviews

No systematic reviews reported quantitative results for respiratory distress in newborns. *Therefore, an examination of the results of individual studies has been undertaken for the current Guideline.*

AppD4.1.2.11.2 Results based on individual studies

Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

The unadjusted risk estimates for respiratory distress syndrome after exposure to any antipsychotics reported by Vigod 2015 are similar to the estimates reported by Källén 2013 for a composite outcome of respiratory distress and birth asphyxia (**Table AppD4-52**). The Källén 2013 estimate was not adjusted for indication or related confounders, only for year of birth, maternal age (5-year class), parity, smoking in early pregnancy and BMI).

The majority of the confounding in the Vigod 2015 comparison was addressed by matching cohorts, which shifted the risk from a statistically significant 1.87 to a non-significant 0.87. The estimate from the matched and adjusted analysis forms the body of evidence for respiratory distress.

Table AppD4-52 Antipsychotics – respiratory distress outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotics						
Vigod 2015 <i>Low</i>	Respiratory distress syndrome ⁴⁴⁸	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 1,209 Unexposed: 40,314	RR 1.87 (1.31, 2.66)
Vigod 2015 <i>Low</i>	Respiratory distress syndrome	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication)	Population-based cohort	Exposed: 1,021 Unexposed: 1,021	RR 0.87 (0.51, 1.47)
Vigod 2015 <i>Low</i>	Respiratory distress syndrome	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 1,021 Unexposed: 1,021	RR 0.82 (0.46, 1.43)
Källén 2013 <i>Low</i>	Respiratory diagnosis ⁴⁴⁹	Antipsychotics or lithium ⁴⁵⁰ (2 nd or 3 rd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 592 Unexposed: 1,575,255	OR 1.73 (1.24, 2.40)

Abbreviations: CI, confidence interval; hdPS, high-dimensional propensity score; OR, odds ratio; RE, risk estimate; RR, risk ratio.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

AppD4.1.2.12 Poor neonatal adaptation syndrome – antipsychotics

AppD4.1.2.12.1 Results based on systematic reviews

No systematic reviews reported quantitative results for poor neonatal adaptation syndrome. *Therefore, an examination of the results of individual studies has been undertaken for the current Guideline.*

AppD4.1.2.12.2 Results based on individual studies

Studies shown in dark shading represent primary evidence, and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report (full quality assessment is limited to these studies).

Only Vigod 2015 reported adjusted results for poor neonatal adaptation syndrome (**Table AppD4-53**). Estimates from unmatched, matched and matched plus adjusted analyses are all shown to illustrate the impact of confounding that arises when cohorts are selected based solely on exposure, and the direction

⁴⁴⁸ No outcomes were observed in either group for acute respiratory distress syndrome.

⁴⁴⁹ ICD-10 (P21-P28): 66% respiratory distress, 20% birth asphyxia.

⁴⁵⁰ Lithium is the most commonly used (17% of neuroleptic-exposed women in the database), confounding the data for antipsychotics.

and magnitude of the bias that can be created when these confounders are not adjusted for. For example, exposure to any antipsychotic during pregnancy appears to be associated with a substantial and significant increased risk of poor neonatal adaptation syndrome of 7.06 (95% CI 5.91, 8.45), which, upon matching cohorts for a high-dimensional propensity score, is reduced to a far lower and non-significant risk increase (RR 1.19; 95% CI 0.92, 1.53). The matched and adjusted estimate of 1.15 (95% CI 0.88, 1.50) for this period of exposure, along with the estimates from analyses restricted by trimester, form the body of the evidence for poor neonatal adaptation syndrome.

Table AppD4-53 Antipsychotics – PNAS outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotic						
Vigod 2015 <i>Low</i>	Poor neonatal adaptation syndrome	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 1,209 Unexposed: 40,314	RR 7.06 (5.91, 8.45)
Vigod 2015 <i>Low</i>	Poor neonatal adaptation syndrome	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication)	Population-based cohort	Exposed: 1,021 Unexposed: 1,021	RR 1.19 (0.92, 1.53)
Vigod 2015 <i>Low</i>	Poor neonatal adaptation syndrome	Any antipsychotic (≥2 consecutive scripts, one in 1 st or 2 nd trimester)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 1,021 Unexposed: 1,021	RR 1.15 (0.88, 1.50)
Vigod 2015 <i>Low</i>	Poor neonatal adaptation syndrome	Any antipsychotic (<u>only in 1st or 2nd trimester</u>)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 180 Unexposed: 40,314	RR 5.49 (3.56, 8.46)
Vigod 2015 <i>Low</i>	Poor neonatal adaptation syndrome	Any antipsychotic (<u>only in 1st or 2nd trimester</u>)	Unexposed – hdPS-matched (includes indication)	Population-based cohort	Exposed: 151 Unexposed: 151	RR 1.50 (0.72, 3.11)
Vigod 2015 <i>Low</i>	Poor neonatal adaptation syndrome	Any antipsychotic (<u>only in 3rd trimester</u>)	Unexposed – no adjustment for indication	Population-based cohort	Exposed: 747 Unexposed: 40,314	RR 6.29 (5.11, 7.74)
Vigod 2015 <i>Low</i>	Poor neonatal adaptation syndrome	Any antipsychotic (<u>only in 3rd trimester</u>)	Unexposed – hdPS-matched (includes indication)	Population-based cohort	Exposed: 614 Unexposed: 614	RR 1.25 (0.89, 1.75)
Vigod 2015 <i>Low</i>	Poor neonatal adaptation syndrome	Any antipsychotic (<u>only in 3rd trimester</u>)	Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication	Population-based cohort	Exposed: 614 Unexposed: 614	RR 1.31 (0.91, 1.90)

Abbreviations: CI, confidence interval; hdPS, high-dimensional propensity score; PNAS, poor neonatal adaptation syndrome; RE, risk estimate; RR, risk ratio.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

AppD4.1.2.13 Neurodevelopmental outcomes – antipsychotics

AppD4.1.2.13.1 Results based on systematic reviews

No systematic reviews reported quantitative results for neurodevelopmental outcomes. *Therefore, an examination of the results of individual studies has been undertaken for the current Guideline.*

AppD4.1.2.13.2 Results based on individual studies

Clements 2015 is a case-control study that identified two sets of patients (2 to 19 years of age) with one of the two following outcomes of interest; autism spectrum disorder (ASD) or an attention-deficit disorder (ADHD). Each group was matched with healthy controls from the same overall cohort of children born at

one of three hospitals. The risk of having been exposed to any antipsychotic was assessed by period of exposure. The study reported pre-pregnancy exposure, but the results for each trimester and for exposure during pregnancy (including up to 30 days prior to conception) are shown here.

Results are adjusted for gender, race, birth year, insurance type, maternal age, median income tertile, and presence or absence of maternal major depressive disorder (antidepressants were the intervention of interest in this study, and major depression was, consequently, the only indication used as a covariate). The number of cases or controls exposed to antipsychotics is not reported, but is calculated post hoc for each period of exposure from the reported percentages.

The authors noted that for antipsychotics, “the modest number of exposures led to wide confidence intervals”. As fewer than 10 exposures to antipsychotics were included in any group, this study was considered underpowered for an analysis of this intervention, and for this reason, was not selected to provide a body of evidence for these outcomes (nor was a quality assessment performed).

Two other studies reported adjusted estimates for neurodevelopmental outcomes; a retrospective primary care database study in the UK (Petersen 2016a) and a prospective study at the Infant Development Laboratory of the Emory Psychological Center in the US (Johnson 2012).

Petersen 2016a ascertained neurodevelopment and behavioural outcomes from codes used by practice staff to record diagnoses and symptoms. Codes were identified for neurodevelopmental and behavioural disorders relating to conditions listed as neurodevelopmental or behavioural disorders in Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition. This form of assessment is not a validated tool for measuring neurodevelopmental outcomes, which increases the risk of bias for this outcome.

Cohorts were defined by exposure and indication was not adjusted for, although the analyses did adjust for alcohol and illicit drug problems and concomitant prescriptions (antidepressants and anticonvulsant mood stabilisers). However, an important confounder for neurodevelopmental outcomes is maternal disease severity, which was not taken into account in these analyses. So, despite restricting some analyses to women who discontinued use prior to pregnancy, the lack of adjustment for disease severity increases the risk of bias in all comparisons for this outcome. Consequently, the overall risk of bias for neurodevelopmental outcomes in this study was considered high.

After exposure to any antipsychotic, risk of neurodevelopment/ behavioural disorders was seen to be increased compared to the unrestricted, unexposed population, and decreased compared to the population that discontinued use, although both estimates are statistically non-significant.

Johnson 2012 used the Infant Neurological International Battery (INFANIB), consisting of twenty items that assess infant posture, muscle tone, reflexes, and motor abilities (neuromotor performance). Standardized scores are not available but clinically informative cutoff scores are available for three age groups, including 4 to 8 months old (infants were tested at 6 months). Accordingly, results were categorized as abnormal (54 or less), transiently abnormal, (55 to 71), or normal (72 or more), but the authors condensed the categories into normal versus not normal ‘to maximize power and simplify interpretation’. The authors of the current Review consider this may impact on any validity of the outcome measure⁴⁵¹.

Cohorts were defined by exposure to any antipsychotic but a proportion of the comparator group had a psychiatric history (32/85). Analyses adjusted for a lifetime diagnosis of a major psychotic disorder, and a lifetime history of at least 1 major depressive episode or dysthymia. Psychiatric diagnosis during pregnancy was not significantly associated with INFANIB scores, so was not adjusted for. However, postnatal diagnoses were not assessed or accounted for, which may be the more relevant confounder. This outcome was considered to have a high risk of bias due to lack of adjustment for maternal disease severity and using a non-validated derivative of the assessment tool.

⁴⁵¹ Between-group difference in adjusted mean scores was significant ($p < 0.01$) but continuous outcomes are not extracted for the current Review.

Each of the estimates reported for this outcome are included in the body of evidence for neurodevelopmental outcomes.

Table AppD4-54 Antipsychotics – neurodevelopmental outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Any antipsychotic						
Clements 2015	ASD (2-19 years)	Any antipsychotics (1 st trimester)	Unexposed – adjusted for major depression	Case control ⁴⁵²	Cases: 1,377 (0.3% exposed; n = 4) Controls: 4,022 (0.0% exposed; n = 0-1) ⁴⁵³	OR 3.66 (0.70, 26.82)
Clements 2015	ASD (2-19 years)	Any antipsychotics (2 nd trimester)	Unexposed – adjusted for major depression	Case control	Cases: 1,377 (0.3% exposed; n = 4) Controls: 4,022 (0.0% exposed; n = 0-1)	NA
Clements 2015	ASD (2-19 years)	Any antipsychotics (3 rd trimester)	Unexposed – adjusted for major depression	Case control	Cases: 1,377 (0.1% exposed; n = 1-2) Controls: 4,022 (0.1% exposed; n = 3-6)	OR 1.23 (0.15, 7.93)
Clements 2015	ASD (2-19 years)	Any antipsychotics (pregnancy)	Unexposed – adjusted for major depression	Case control	Cases: 1,377 (0.5% exposed; n = 7) Controls: 4,022 (0.1% exposed; n = 3-6)	OR 2.23 (0.65, 8.01)
Clements 2015	ADHD (2-19 years)	Any antipsychotics (1 st trimester)	Unexposed – adjusted for major depression	Case control ⁴⁵⁴	Cases: 2,243 (0.0% exposed; n = 0-1) ⁴⁵³ Controls: 5,631 (0.0% exposed; n = 0-3)	OR 0.72 (0.03, 7.80)
Clements 2015	ADHD (2-19 years)	Any antipsychotics (2 nd trimester)	Unexposed – adjusted for major depression	Case control	Cases: 2,243 (0.0% exposed; n = 0-1) Controls: 5,631 (0.0% exposed; n = 0-3)	NA
Clements 2015	ADHD (2-19 years)	Any antipsychotics (3 rd trimester)	Unexposed – adjusted for major depression	Case control	Cases: 2,243 (0.2% exposed; n = 4-5) Controls: 5,631 (0.1% exposed; n = 3-8)	OR 0.60 (0.08, 3.18)
Clements 2015	ADHD (2-19 years)	Any antipsychotics (pregnancy)	Unexposed – adjusted for major depression	Case control	Cases: 2,243 (0.2% exposed; n = 4-5) Controls: 5,631 (0.1% exposed; n = 3-8)	OR 0.61 (0.13, 2.40)
Petersen 2016a <i>High risk</i>	Neurodevelopment / behavioural disorders ⁴⁵⁵	Any antipsychotics (early; 31-105 days)	Unexposed – no adjustment for indication	Retrospective primary care database	Exposed: 290 Unexposed: 210,966	RR 1.22 (0.80, 1.84)
Petersen 2016a <i>High risk</i>	Neurodevelopment / behavioural disorders	Any antipsychotics (early; 31-105 days)	Discontinued – no further accounting for indication	Retrospective primary care database	Exposed: 290 Unexposed: 492	RR 0.83 (0.49, 1.39)

⁴⁵² Delivered at the MGH, BWH or NWH and matched 1:3 on birth year, hospital, sex, insurance type (as proxy for socioeconomic status), race/ethnicity and preterm/full-term status (for 81 of the 1,377 ASD cases, only 1 or 2 matched controls were found).

⁴⁵³ As % only reported, estimates of n were calculated post hoc (ranges reported where rounding of % results in more than one possible integer).

⁴⁵⁴ Delivered at the MGH, BWH or NWH and matched 1:3 on birth year, hospital, sex, insurance type (as proxy for socioeconomic status), race/ethnicity and preterm/full-term status (for 726 of the 2,243 ADHD cases, only 1 or 2 matched controls were found).

⁴⁵⁵ This outcome includes a broad range of Read codes describing developmental delay as well as behavioural problems recorded within the first five years of life. Read codes for neurodevelopmental and behavioural disorders were identified as those relating to conditions listed as neurodevelopmental or behavioural disorders in Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition.

Study ID <i>Risk of bias</i>	Outcome	Exposure (Timing)	Comparator	Study design	N	Adjusted RE (95% CI)
Johnson 2012 <i>High risk</i>	Neuromotor performance (INFANIB score at 6 months postpartum, condensed to 'normal vs abnormal') ⁴⁵⁶	Any antipsychotic (pregnancy)	Unexposed ⁴⁵⁷ – adjusted for lifetime history of a major depressive episode, dysthymia or psychotic disorder	Prospective cohort	Exposed: 22 Unexposed: 85	OR 5.41 ⁴⁵⁸ (1.22, 24.09)
Johnson 2012	INFANIB score at 6 months postpartum	Any antipsychotic (pregnancy)	Any antidepressant – adjusted for lifetime history of a major depressive episode, dysthymia or psychotic disorder	Prospective cohort	Exposed to antipsychotics: 22 Exposed to antidepressants: 202	OR 4.11 ⁴⁵⁹ (1.05, 15.99)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; INFANIB, Infant Neurological International Battery; OR, odds ratio; RE, risk estimate; RR, risk ratio.

Note: Data shown in dark shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.2** of the Technical Report.

AppD4.1.3 Anticonvulsants

AppD4.1.3.1 Included systematic reviews – anticonvulsants

Five SRs were identified that provided evidence relating to the assessment of anticonvulsant harms. It should be noted that none of the SRs met the higher quality criteria defined for antidepressants, because all were based on analysis of raw data from the included observational studies. A summary of the characteristics of the identified SRs is presented in **Table AppD2-13**.

Table AppD4-55 Characteristics of the included systematic reviews of anticonvulsant harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Quantitative review					
Weston 2016	SR (50 prospective cohort or registry studies)	Pregnant women with epilepsy	Sodium valproate Carbamazepine Lamotrigine ⁴⁶⁰	Unexposed/no epilepsy Unexposed/epilepsy Other AED/epilepsy	Major congenital malformations Specific major congenital malformations Minor congenital malformations
NICE 2015	SR (21 prospective cohort studies, 10 retrospective cohort studies and 4 retrospective case-control studies)	Pregnant women	Sodium valproate Carbamazepine Lamotrigine	Unexposed	Teratogenic harms Pregnancy, obstetric and neonatal complications Neurodevelopmental outcomes

⁴⁵⁶ Categories based on published clinical cutoffs. Between-group difference in adjusted mean scores was significant ($p < 0.01$) but continuous outcomes are not extracted for the current Review.

⁴⁵⁷ No data reported regarding psychiatric status at pregnancy or at infant assessment, but 62% of comparator group had experienced psychiatric illness in their lifetime.

⁴⁵⁸ Likelihood of a normal score in unexposed vs exposed group. Between-group difference in adjusted mean scores was significant ($p < 0.01$) but continuous outcomes are not extracted for the current Review.

⁴⁵⁹ Likelihood of a normal score in the group exposed to antidepressants vs the group exposed to antipsychotics. Between-group difference in adjusted mean scores was significant ($p < 0.01$) but continuous outcomes are not extracted for the current Review.

⁴⁶⁰ Also included phenobarbitone, phenytoin, oxcarbazepine, topiramate, gabapentin, vigabatrin, tiagabine, zonisamide, levetiracetam, ethosuximide, clobazam, clonazepam, zonisamide, pregabalin, lacosamide, retigabine, rufinamide or sulthiame.

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Tanoshima 2015	SR 59 OBS (44 prospective cohort studies and 15 retrospective cohort studies)	Pregnant women with epilepsy	Sodium valproate	Carbamazepine/epilepsy Lamotrigine/epilepsy	Major congenital malformations Congenital heart defects Clef lip and/or palate Genitourinary anomalies Musculoskeletal anomalies
Bromley 2014	SR 28 OBS (22 were prospective cohort studies)	Pregnant women with epilepsy	Sodium valproate Carbamazepine Lamotrigine ⁴⁶¹	Unexposed/no epilepsy Unexposed/epilepsy Other AED/epilepsy	Global cognitive functioning or ability/IQ ASD ADHD Dyspraxia Cognitive function
Banach 2010	SR 11 cohort studies	Pregnant women with epilepsy	Sodium valproate Carbamazepine	Unexposed/epilepsy Unexposed/any	IQ

Abbreviations: ADHD, attention-deficit hyperactivity disorder; AED, antiepileptic drug; ASD, autism spectrum disorder; IQ, intelligence quotient; OBS, observational studies; SR, systematic review.

AppD4.1.3.2 Included individual studies – anticonvulsants

The assessment of anticonvulsants was limited to SRs.

AppD4.1.3.3 Major malformations – anticonvulsants

AppD4.1.3.3.1 Results based on systematic reviews

A summary of the results regarding the association between anticonvulsant use and major malformations is presented in **Table AppD4-4**. Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of major malformations in the depressed/unexposed population (2.8% in Ban 2014a), it is assumed that odds ratios (ORs) approximate the relative risks (RRs) and where applicable, they will be interpreted as such.

Three SRs provided data for this outcome: a Cochrane review by Weston 2016 and SRs by NICE 2015 and Tanoshima 2015. There are a number of methodological differences between these SRs. Weston 2016 limited inclusion of studies to RCTs, prospective cohort studies and registry studies; retrospective studies/registers were excluded. For NICE 2015, both prospective and retrospective studies were included, but analyses were grouped by type (i.e. cohort or case control). Tanoshima limited to RCTs and cohort studies, and only included those which compared sodium valproate with another anticonvulsant in pregnant women with epilepsy. All SRs based their findings on a meta-analysis of raw data from the included observational studies.

The data shown below represents a subset of that extracted from the studies and presented in the data extraction tables in **Section AppD3.1.3.1**, and is limited to analyses based on a comparator group with epilepsy, in order to reduce the impact of confounding by indication.

⁴⁶¹ Also included phenobarbitone, phenytoin, oxcarbazepine, topiramate, gabapentin, vigabatrin, tiagabine, zonisamide, levetiracetam, ethosuximide, clobazam, clonazepam, zonisamide, pregabalin, lacosamide, retigabine, rufinamide, and sulthiame.

Table AppD4-56 Anticonvulsants – major malformation outcomes from systematic reviews

Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Unadjusted RE (95% CI)	Heterogeneity I ² (P value)
Sodium valproate							
Weston 2016 <i>Moderate</i>	Major malformations	Sodium valproate (monotherapy – any time)	Unexposed – epilepsy (no medication)	14 (OBS) ⁴⁶²	3,182	RR 3.13 (2.16, 4.54)	0% (0.71)
NICE 2015	Major malformations	Sodium valproate (any time)	Unexposed – epilepsy	8 (cohort) ⁴⁶³	3,526	OR 2.60 (1.7, 3.97)	0% (0.64)
Tanoshima 2015 <i>Moderate</i>	Major congenital malformations	Sodium valproate (any time)	Carbamazepine – epilepsy	23 (OBS) ⁴⁶⁴	10,509	RR 2.21 (1.88, 2.59)	0% (NR)
Weston 2016 <i>Moderate</i>	Major malformations	Sodium valproate (monotherapy – any time)	Lamotrigine – epilepsy	7 (OBS) ⁴⁶⁵	6,185	RR 3.56 (2.77, 4.58)	0% (0.44)
Tanoshima 2015 <i>Moderate</i>	Major congenital malformations	Sodium valproate (any time)	Lamotrigine – epilepsy	7 (OBS) ⁴⁶⁶	8,074	RR 3.23 (2.59, 4.03)	0% (NR)
Carbamazepine							
Weston 2016 <i>Moderate</i>	Major malformations	Carbamazepine (monotherapy – any time)	Unexposed – epilepsy (no medication)	17 (OBS) ⁴⁶⁷	4,345	RR 1.50 (1.03, 2.19)	0% (0.95)
NICE 2015	Major congenital malformations	Carbamazepine (any time)	Unexposed – epilepsy	12 (cohort) ⁴⁶⁸	6,669	OR 1.43 (1.04, 1.96)	0% (0.44)
Weston 2016 <i>Moderate</i>	Major malformations	Carbamazepine (monotherapy – any time)	Lamotrigine	7 (OBS) ⁴⁶⁹	7,549	RR 1.34 (1.01, 1.76)	0% (0.74)
Weston 2016 <i>Moderate</i>	Major malformations	Carbamazepine (monotherapy – any time)	Sodium valproate	25 (OBS) ⁴⁷⁰	7,078	<i>RR 0.41</i> <i>(0.34, 0.50)</i>	0% (0.94)
Lamotrigine							
Weston 2016 <i>Moderate</i>	Major malformations	Lamotrigine (monotherapy – any time)	Unexposed – epilepsy (no medication)	3 (OBS) ⁴⁷¹	3,181	RR 1.07 (0.64, 1.77)	0% (0.81)
NICE 2015	Major malformations	Lamotrigine (any time)	Unexposed – epilepsy	5 (cohort) ⁴⁷²	3,008	OR 1.41 (0.62, 3.21)	51% (0.09)

Abbreviations: CI, confidence interval; OBS, observational studies; OR, odds ratio; RE, risk estimate; RR, relative risk; SR, systematic review.

Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report

Figure AppD4-1 summarises the findings of the association between anticonvulsant use and major malformations as determined in the SR by Weston 2016. A strong association was seen with sodium valproate use (RR 3.13; 95% CI 2.16, 4.54), while a weaker association was seen with carbamazepine (RR 1.50; 95% CI 1.03, 2.19); no association was seen with lamotrigine (RR 1.07; 95% CI 0.64, 1.77). Similar findings were seen in the NICE 2015 review.

⁴⁶² Includes Al Bunyan 1999, Campbell 2014, Canger 1999, Fairgrieve 2000, Garza-Morales 1996, Kaaja 2003, Kaneko 1999, Kelly 1984, Koch 1992, Lindhout 1992, Mawer 2010, Oguni 1992, Thomas 2008 and Vajda 2012.

⁴⁶³ Includes Bodén 2012, Canger 1998, Charlton 2011, Kaaja 2003, Kaneko 1999, Kini 2007, Morrow 2006 and Vajda 2012.

⁴⁶⁴ Included studies not reported.

⁴⁶⁵ Includes Campbell 2014, Cassina 2013, Hernandez-Diaz 2012, Matrinez Ferri 2009, Mawer 2010, Meador 2006 and Vajda 2012.

⁴⁶⁶ Included studies not reported.

⁴⁶⁷ Includes Al Bunyan 1999, Campbell 2014, Canger 1999, D'Souza 1990, Delmis 1991, Fairgrieve 2000, Garza-Morales 1996, Kaaja 2003, Kaneko 1999, Koch 1992, Lindhout 1992, Mawer 2010, Oguni 1992, Thomas 2008, Vajda 2012, Waters 1994.

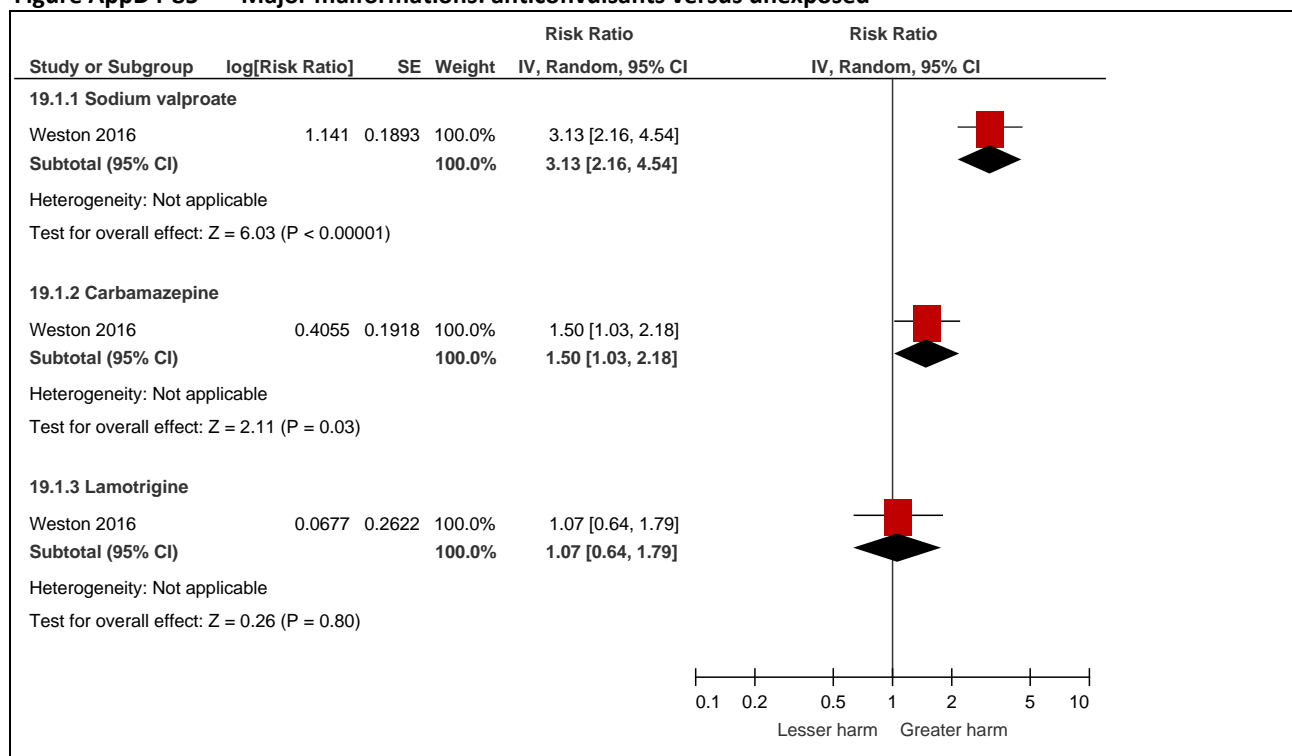
⁴⁶⁸ Includes Artama 2005, Bodén 2012, Burja 2006, Canger 1998, Charlton 2011, Diav-Citrin 2001, Holmes 2001, Kaaja 2003, Kaneko 1999, Kini 2007, Morrow 2006 and Vajda 2012.

⁴⁶⁹ Includes Campbell 2014, Cassina 2013, Hernandez-Diaz 2012, Martinez Ferri 2009, Mawer 2010, Meador 2006 and Vajda 2012.

⁴⁷⁰ Includes Al Bunyan 1999, Arulmozhi 2006, Campbell 2014, Canger 1999, Cassina 2013, Eroglu 2008, Fairgrieve 2000, Froscher 1991, Garza-Morales 1996, Hernandez-Diaz 2012, Kaaja 2003, Kaneko 1999, Koch 1992, Lindhout 1992, Martinez Ferri 2009, Mawer 2010, Meador 2006, Meischenguiser 2004, Ogani 1992, Omtzigt 1992, Pardi 1982, Steegers-Theunissen 1994, Tanganelli 1992, Thomas 2008 and Vajda 2012.

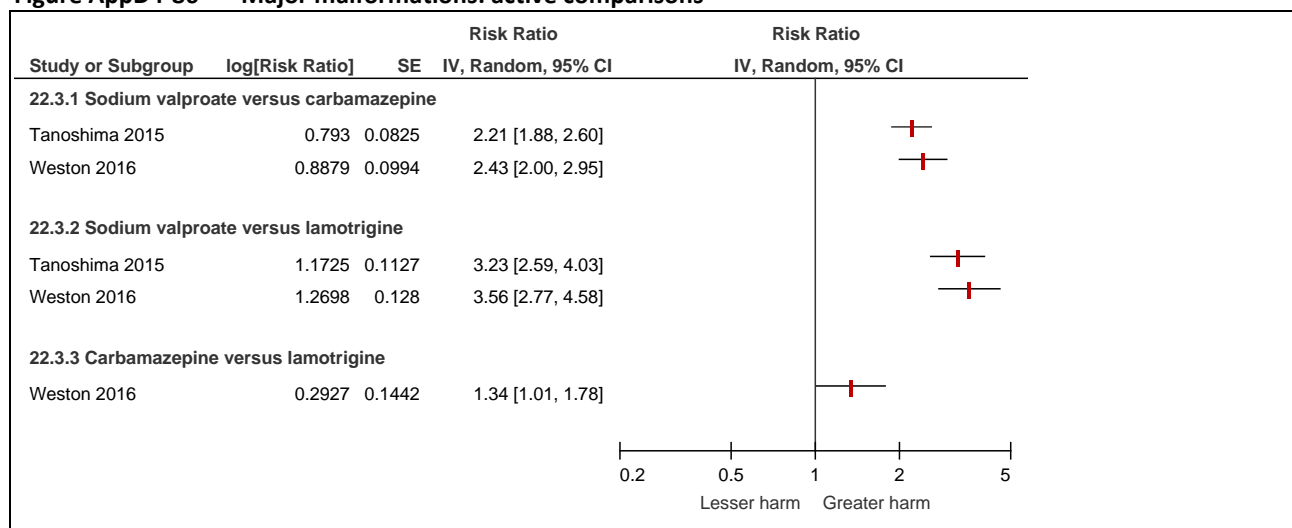
⁴⁷¹ Includes Campbell 2013, Mawer 2010 and Vajda 2012.

⁴⁷² Includes Bodén 2012, Borthen 2011, Charlton 2011, Morrow 2006 and Vajda 2012.

Figure AppD4-85 Major malformations: anticonvulsants versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

The Weston 2016 and Tanoshima 2015 SRs included comparisons between the three anticonvulsants shown in **Figure AppD4-86**. The analyses of sodium valproate were consistent between the two studies and showed that the risk of major congenital malformations is significantly higher for sodium valproate compared with either carbamazepine or lamotrigine. The comparison between carbamazepine and lamotrigine showed a higher risk associated with carbamazepine; however, this risk was much lower than that seen with sodium valproate.

Figure AppD4-86 Major malformations: active comparisons

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The comparison between sodium valproate versus carbamazepine was converted from the analysis of carbamazepine versus sodium valproate.

AppD4.1.3.4 Cardiac malformations – anticonvulsants**AppD4.1.3.4.1 Results based on systematic reviews**

A summary of the results regarding the association between anticonvulsant use and cardiac malformations is presented in **Table AppD4-57**. Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of cardiac malformations in the depressed/unexposed population (0.6% based on weighted pooled estimates from Petersen 2016, Ban 2014a, Huybrechts 2014a and Margulis 2013), it is assumed that ORs closely approximate the RRs, and will be interpreted as such.

As noted previously, Weston 2016 limited inclusion of studies to RCTs, prospective cohort studies and registry studies (retrospective studies/registers were excluded), while Tanoshima limited inclusion to RCTs and cohort studies. The data shown below represents a subset of that extracted from Weston 2016 and presented in the data extraction table in **Section AppD3.1.3.1**, and is limited to analyses based on a comparator group with epilepsy, in order to reduce the impact of confounding by indication.

Table AppD4-57 Anticonvulsants – cardiac malformation outcomes from systematic reviews

Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Unadjusted RE (95% CI)	Heterogeneity I ² (P value)
Sodium valproate							
Weston 2016 <i>Moderate</i>	Cardiac malformations	Sodium valproate (monotherapy – any time)	Unexposed – epilepsy (no medication)	6 (OBS) ⁴⁷³	768	RR 4.85 (1.28, 18.47)	0% (0.95)
Tanoshima 2015	Congenital heart defects	Sodium valproate (any time)	Carbamazepine – epilepsy	15 (OBS) ⁴⁷⁴	9,998	RR 1.82 (1.30, 2.54)	0% (NR)
Weston 2016 <i>Moderate</i>	Cardiac malformations	Sodium valproate (monotherapy – any time)	Lamotrigine	6 (OBS) ⁴⁷⁵	6,151	RR 4.07 (2.33, 7.09)	0% (0.54)
Tanoshima 2015	Congenital heart defects	Sodium valproate (any time)	Lamotrigine – epilepsy	5 (OBS) ⁴⁷⁶	7,651	RR 3.75 (2.27, 6.18)	0% (NR)
Carbamazepine							
Weston 2016 <i>Moderate</i>	Cardiac malformations	Carbamazepine (monotherapy – any time)	Unexposed – epilepsy (no medication)	7 (OBS) ⁴⁷⁷	1,026	RR 1.84 (0.32, 10.71)	0% (0.62)
Weston 2016 <i>Moderate</i>	Cardiac malformations	Carbamazepine (monotherapy – any time)	Lamotrigine	6 (OBS) ⁴⁷⁸	7,509	RR 1.57 (0.85, 2.89)	0% (0.85)
Weston 2016 <i>Moderate</i>	Cardiac malformations	Carbamazepine (monotherapy – any time)	Sodium valproate	16 (OBS) ⁴⁷⁹	6,476	RR 0.45 (0.31, 0.68)	12% (0.33)

⁴⁷³ Includes Canger 1999, Fairgrieve 2000, Garza-Morales 1996, Koch 1992, Mawer 2010 and Vajda 2012.

⁴⁷⁴ Included studies not reported.

⁴⁷⁵ Includes Campbell 2014, Cassina 2013, Hernandez-Diaz 2012, Matrinez Ferri 2009, Meador 2006 and Vajda 2012.

⁴⁷⁶ Included studies not reported.

⁴⁷⁷ Includes Al Bunyan 1999, Barqawi 2005, Canger 1999, Fairgrieve 2000, Koch 1992 and Mawer 2010 and Vajda 2012.

⁴⁷⁸ Includes Campbell 2014, Cassina 2013, Hernandez-Diaz 2012, Martinez Ferri 2009, Meador 2006, and Vajda 2012.

⁴⁷⁹ Includes Campbell 2014, Canger 1999, Cassina 2013, Eroglu 2008, Fairgrieve 2000, Froscher 1991, Hernandez-Diaz 2012, Kaaja 2003, Koch 1992, Martinez Ferri 2009, Meador 2006, Meischenguiser 2004, Omtzigt 1992, Pardi 1982, Thomas 2008 and Vajda 2012.

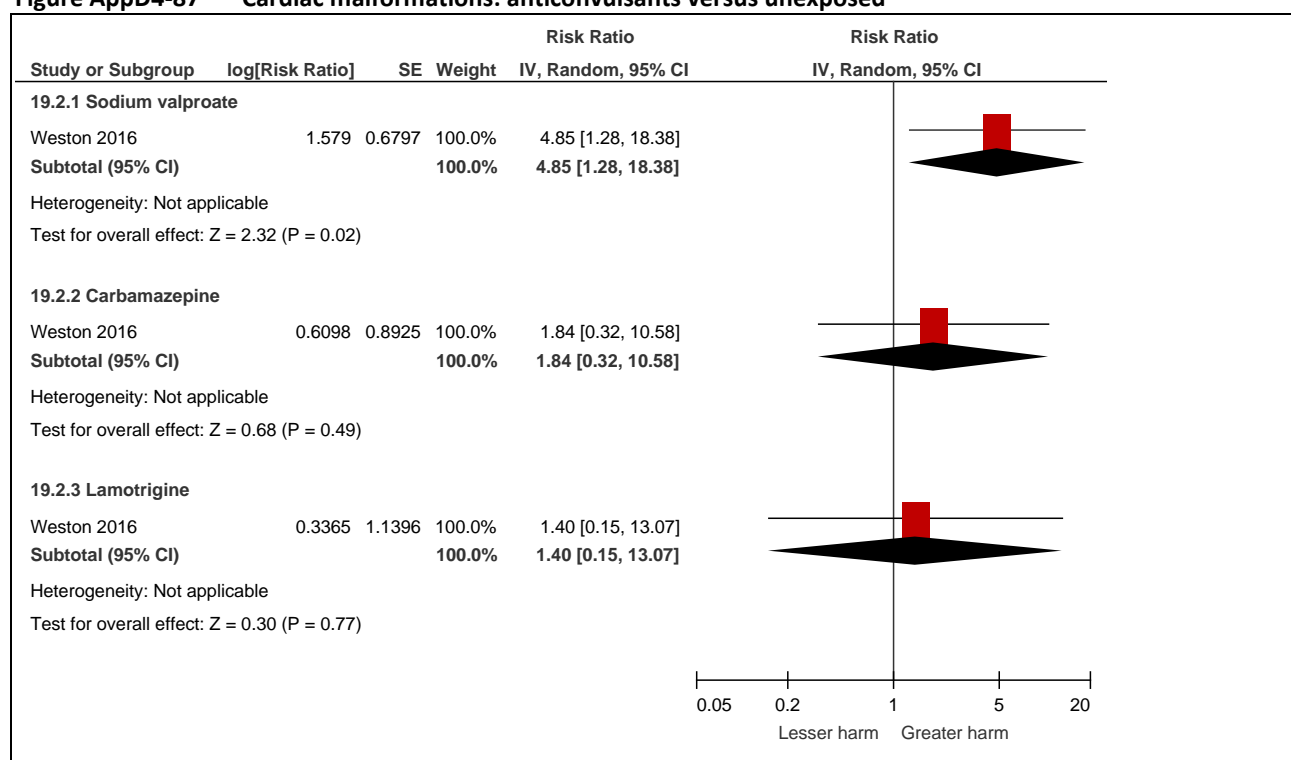
Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Unadjusted RE (95% CI)	Heterogeneity I ² (P value)
Lamotrigine							
Weston 2016 <i>Moderate</i>	Cardiac malformations	Lamotrigine (monotherapy – any time)	Unexposed – epilepsy (no medication)	2 (OBS) ⁴⁸⁰	542	RR 1.40 (0.15, 13.35)	NA

Abbreviations: CI, confidence interval; NA, not applicable; OBS, observational studies; OR, odds ratio; RE, risk estimate; RR, relative risk; SR, systematic review.

Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report.

Figure AppD4-87 summarises the findings of the association between anticonvulsant use and cardiac malformations as determined in the SR by Weston 2016. A strong association was seen with sodium valproate use (RR 4.85; 95% CI 1.28, 18.47), while there was no association for carbamazepine and lamotrigine. Both of these comparisons were subject to imprecision because the 95% CI included a measure of both appreciable benefit and harm (RR 0.75/1.25).

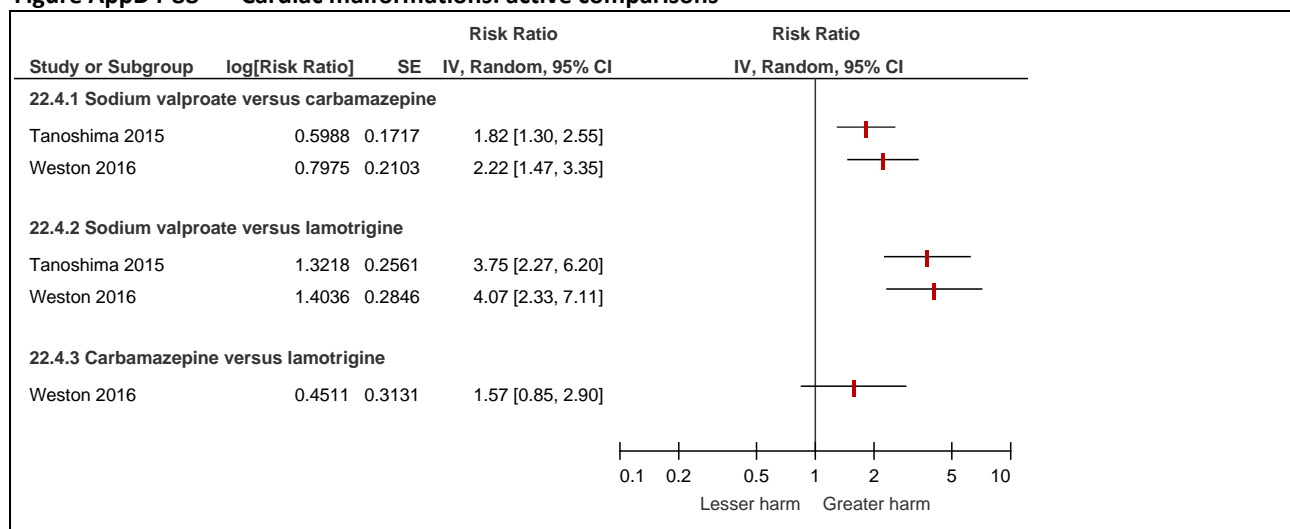
Figure AppD4-87 Cardiac malformations: anticonvulsants versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

The Weston 2016 and Tanoshima 2015 SRs included comparisons between the three anticonvulsants shown in **Figure AppD4-88**. The analyses of sodium valproate were consistent between the two studies and showed that the risk of major congenital malformations is significantly higher for sodium valproate compared with both carbamazepine and lamotrigine. The comparison between carbamazepine and lamotrigine showed no significant difference in risk.

⁴⁸⁰ Includes Mawer 2010 and Vajda 2012.

Figure AppD4-88 Cardiac malformations: active comparisons

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The comparison between sodium valproate versus carbamazepine was converted from the analysis of carbamazepine versus sodium valproate.

AppD4.1.3.5 Neonatal mortality – anticonvulsants

AppD4.1.3.5.1 Results based on systematic reviews

A summary of the results regarding the association between anticonvulsant use and neonatal mortality is presented in **Table AppD4-58**. Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of cardiac malformations in the depressed/unexposed population (0.5% based on Ban 2012), it is assumed that ORs closely approximate the RRs, and will be interpreted as such.

Table AppD4-58 Anticonvulsants – neonatal mortality outcomes from systematic reviews

Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity I^2 (P value)
Sodium valproate							
NICE 2015 <i>Moderate</i>	Still birth/perinatal death	Sodium valproate (any time)	Unexposed – any	2 (cohort) ⁴⁸¹	3,975	OR 1.93 (0.79, 4.7)	0% (0.71)
Carbamazepine							
NICE 2015 <i>Moderate</i>	Still birth/perinatal death	Carbamazepine (any time)	Unexposed – any	2 (cohort) ⁴⁸²	3,202	OR 0.79 (0.12, 5.31)	67% (0.08)
Lamotrigine							
NICE 2015 <i>Moderate</i>	Still birth/perinatal death	Lamotrigine (any time)	Unexposed – any	1 (cohort) ⁴⁸³	1,973	OR 0.49 (0.03, 8.42)	NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RE, risk estimate; SR, systematic review.

Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report.

Figure AppD4-89 summarises the findings of the association between anticonvulsant use and neonatal mortality as determined in the SR by NICE 2016. There was no significant association between any of the anticonvulsants examined and neonatal mortality; however, all of these comparisons were subject to

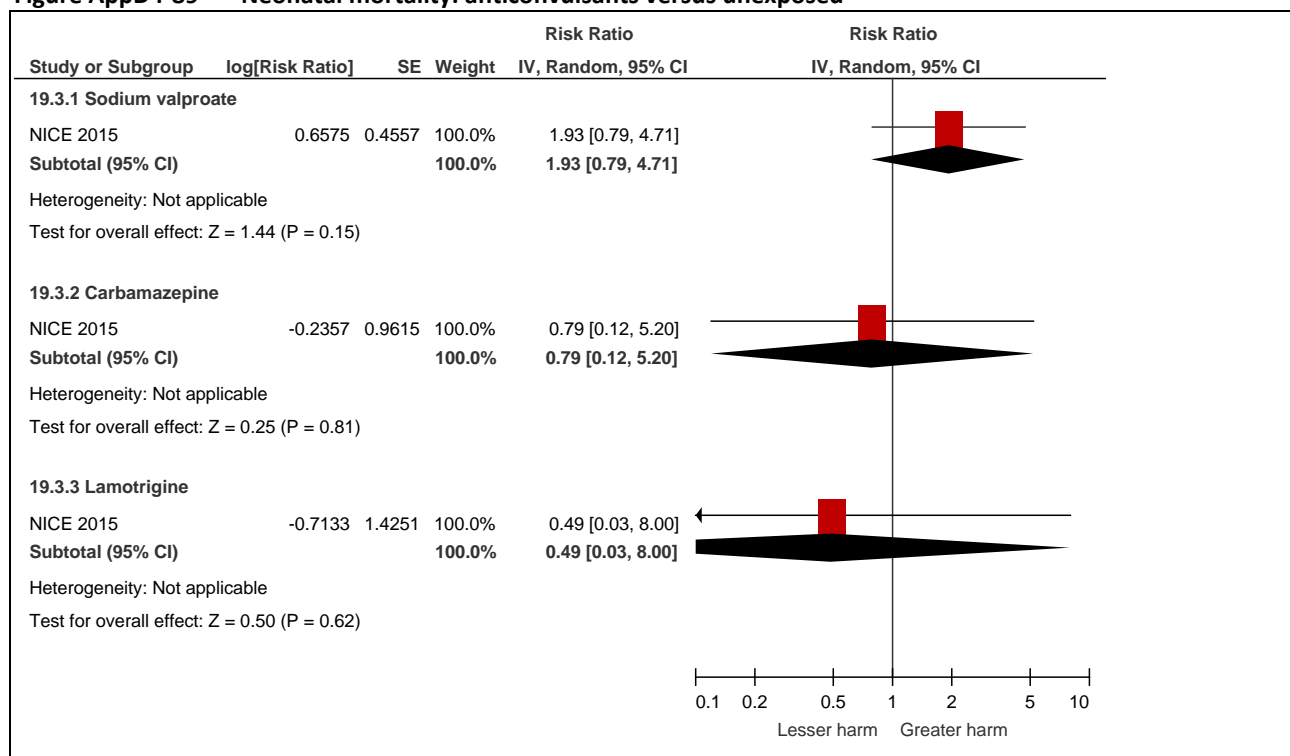
⁴⁸¹ Includes Artama 2013 and Diav-Citrin 2001.

⁴⁸² Includes Artama 2013 and Diav-Citrin 2001.

⁴⁸³ Includes Artama 2013.

imprecision because the 95% CI included a measure of appreciable benefit and/or harm (RR 0.75/1.25). In addition, the comparator group in these analyses was a general population, which may have given rise to confounding by indication.

Figure AppD4-89 Neonatal mortality: anticonvulsants versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

AppD4.1.3.6 Preterm birth – anticonvulsants

AppD4.1.3.6.1 Results based on systematic reviews

A summary of the results regarding the association between anticonvulsant use and preterm birth is presented in **Table AppD4-59**. Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of preterm birth in the depressed or psychiatric diagnosis/unexposed population (1% for < 32 weeks and 5% for 32-36 weeks),⁴⁸⁴ it is assumed that ORs approximate the RR, and will be interpreted as such.

⁴⁸⁴ Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

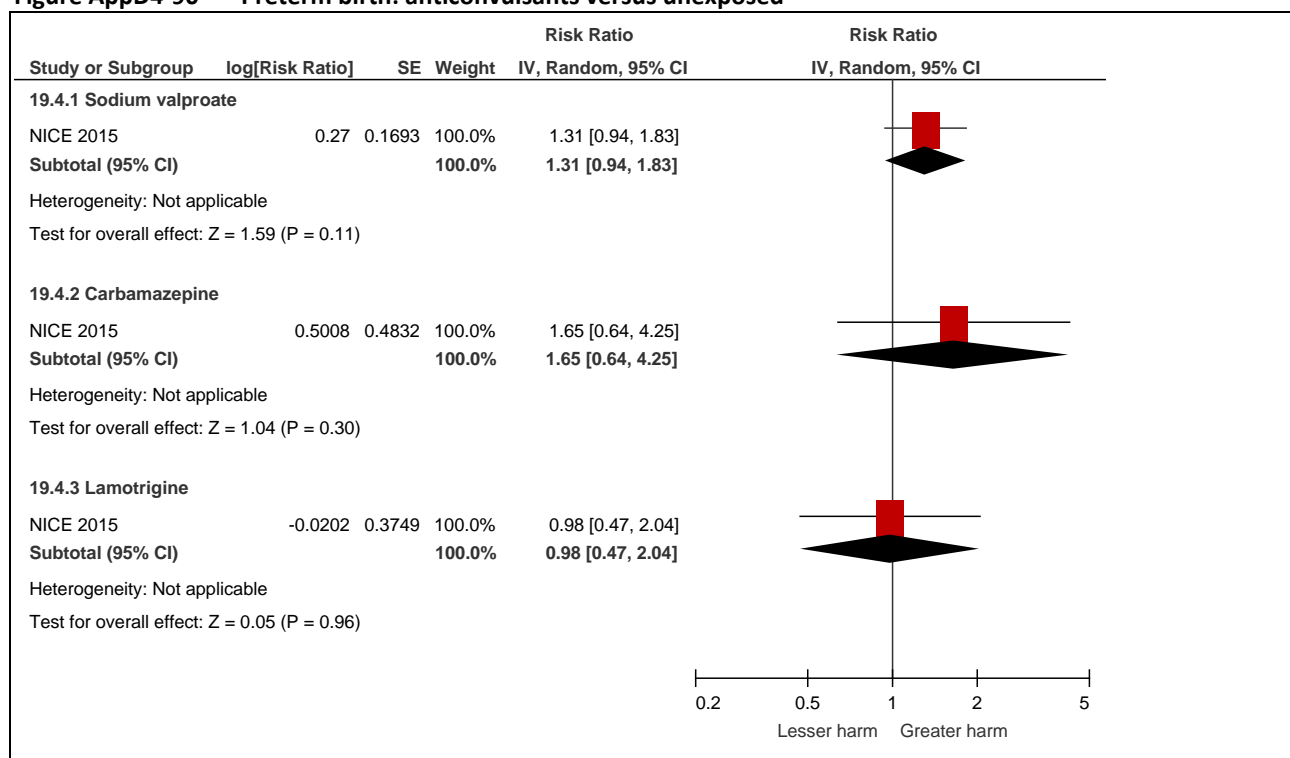
Table AppD4-59 Anticonvulsants – preterm birth outcomes from systematic reviews

Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity I^2 (P value)
Sodium valproate							
NICE 2015 <i>Moderate</i>	Preterm birth	Sodium valproate (any time)	Unexposed – any	2 (cohort) ⁴⁸⁵	3,804	OR 1.31 (0.94, 1.83)	0% (0.44)
Carbamazepine							
NICE 2015 <i>Moderate</i>	Preterm birth	Carbamazepine (any time)	Unexposed – any	2 (cohort) ⁴⁸⁶	3,202	OR 1.65 (0.64, 4.22)	67% (0.08)
Lamotrigine							
NICE 2015 <i>Moderate</i>	Preterm birth	Lamotrigine (any time)	Unexposed – any	1 (cohort) ⁴⁸⁷	1,973	OR 0.98 (0.47, 2.05)	NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RE, risk estimate; SR, systematic review.

Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report.

Figure AppD4-90 summarises the findings of the association between anticonvulsant use and preterm birth as determined in the SR by NICE 2016. There was no significant association between any of the anticonvulsants examined and neonatal mortality; however, all of these comparisons were subject to imprecision because the 95% CI included a measure of appreciable benefit and/or harm (RR 0.75/1.25). In addition, the comparator group in these analyses was a general population, which may have given rise to confounding by indication.

Figure AppD4-90 Preterm birth: anticonvulsants versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

⁴⁸⁵ Includes Artama 2013 and Diav-Citrin 2001.

⁴⁸⁶ Includes Artama 2013 and Diav-Citrin 2001.

⁴⁸⁷ Includes Artama 2013.

AppD4.1.3.7 Autism spectrum disorder – anticonvulsants**AppD4.1.3.7.1 Results based on systematic reviews**

A summary of the results regarding the association between anticonvulsant use and autism spectrum disorder is presented in **Table AppD4-60**. Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of ASD in the depressed or psychiatric diagnosis/unexposed population (0.9%),⁴⁸⁸ it is assumed that the OR approximates the RR, and will be interpreted as such.

Table AppD4-60 Anticonvulsants – autism spectrum disorder outcomes from systematic reviews

Study ID SR quality	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity I ² (P value)
Sodium valproate							
NICE 2015 Moderate	ASD (ICD-10) (9 years)	Sodium valproate (any time)	Unexposed – any	1 (cohort) ⁴⁸⁹	655,495	OR 3.82 (2.15, 6.80)	NA
Carbamazepine							
NICE 2015 Moderate	ASD (ICD-10) (9 years)	Carbamazepine (any time)	Unexposed – any	1 (cohort) ⁴⁸⁹	655,539	OR 1.25 (0.47, 3.35)	NA
Lamotrigine							
NICE 2015 Moderate	ASD (ICD-10) (9 years)	Lamotrigine (any time)	Unexposed – any	1 (cohort) ⁴⁸⁹	655,394	OR 1.5 (0.75, 3.01)	NA

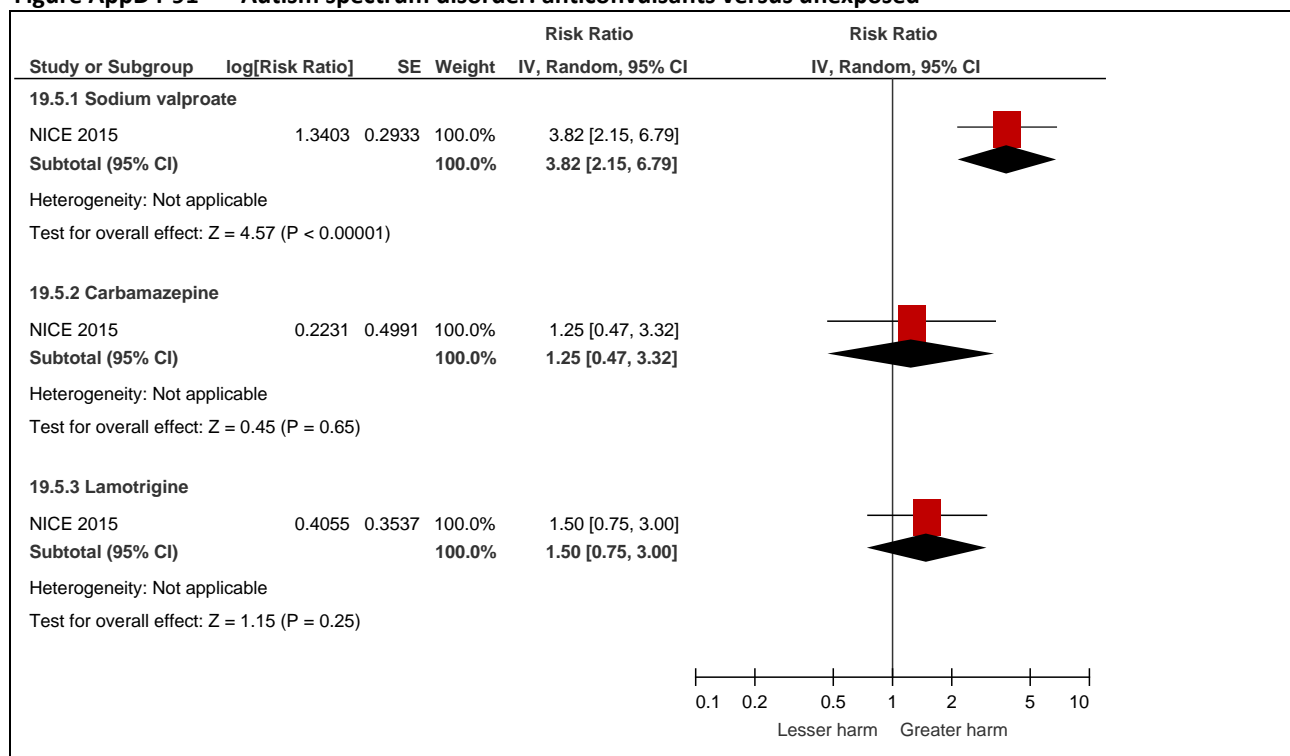
Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; NA, not applicable; OR, odds ratio; RE, risk estimate; SR, systematic review.

Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report.

Figure AppD4-91 summarises the findings of the association between anticonvulsant use and autism spectrum disorder as determined in the SR by NICE 2016. There was no significant association between carbamazepine or lamotrigine and autism spectrum disorder; however, both of these comparisons were subject to imprecision because the 95% CI included a measure of appreciable benefit and/or harm (RR 0.75/1.25). There was a significant association between sodium valproate and autism spectrum disorder (RR 3.82; 95% CI 2.15, 6.80). For all analyses, the comparator group was a general population, which may have given rise to confounding by indication.

⁴⁸⁸ Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

⁴⁸⁹ Includes Christensen 2013.

Figure AppD4-91 Autism spectrum disorder: anticonvulsants versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

AppD4.1.3.8 Autism checklist – anticonvulsants

AppD4.1.3.8.1 Results based on systematic reviews

A summary of the results regarding the association between anticonvulsant use and the autism checklist is presented in **Table AppD4-61**. Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of autism (as measured using the Modified Checklist for Autism in Toddlers) in the depressed or psychiatric diagnosis/unexposed population,⁴⁹⁰ it is assumed that the OR approximates the RR, and will be interpreted as such.

⁴⁹⁰ There was no data available specifically regarding the prevalence of autism (as measured using the Modified Checklist for Autism in Toddlers) in offspring of the population of interest; however, it is likely to be very low based on the on the pooled prevalence from Sørensen 2013 and Malm 2016 of ASD in depressed/psychiatric diagnosis population (0.9%).

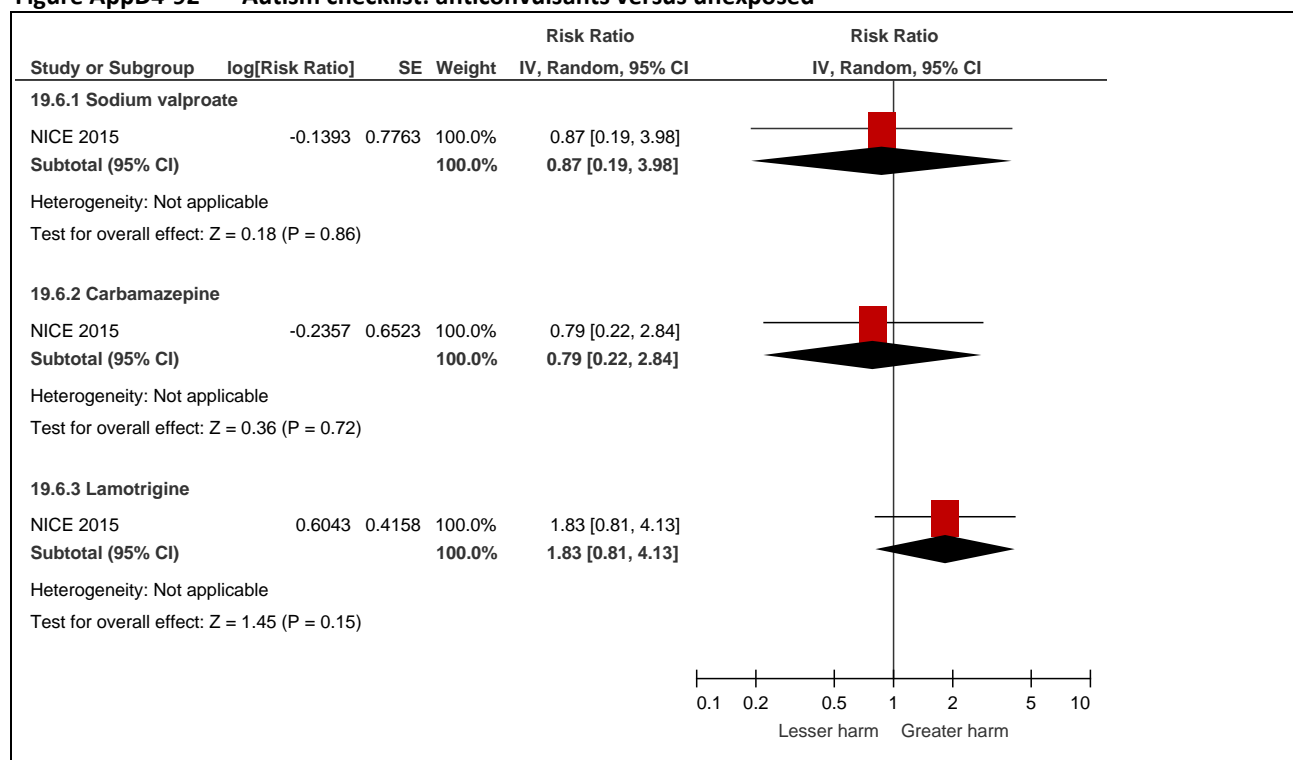
Table AppD4-61 Anticonvulsants – autism checklist outcomes from systematic reviews

Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity I^2 (P value)
Sodium valproate							
NICE 2015 <i>Moderate</i>	Autism checklist ⁴⁹¹ (78 week)	Sodium valproate (any time)	Unexposed – any	1 (cohort) ⁴⁹²	246	OR 0.87 (0.19, 3.98)	NA
Carbamazepine							
NICE 2015 <i>Moderate</i>	Autism checklist (78 week)	Carbamazepine (any time)	Unexposed – any	1 (cohort) ⁴⁹²	262	OR 0.79 (0.22, 2.8)	NA
Lamotrigine							
NICE 2015 <i>Moderate</i>	Autism checklist (78 week)	Lamotrigine (any time)	Unexposed – any	1 (cohort) ⁴⁹²	286	OR 1.83 (0.81, 4.13)	NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RE, risk estimate; SR, systematic review.

Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report.

Figure AppD4-92 summarises the findings of the association between anticonvulsant use and the autism checklist as determined in the SR by NICE 2016. There was no significant association for any of the anticonvulsants examined; however, all of these comparisons were subject to imprecision because the 95% CI included a measure of appreciable benefit and/or harm (RR 0.75/1.25). In addition, for all analyses, the comparator group was a general population, which may have given rise to confounding by indication.

Figure AppD4-92 Autism checklist: anticonvulsants versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

AppD4.1.3.9 Intelligence quotient – anticonvulsants

AppD4.1.3.9.1 Results based on systematic reviews

A summary of the results regarding the association between anticonvulsant use and intelligence quotient (IQ) is presented in **Table AppD4-62**. Data shown in dark shading represent primary evidence and are

⁴⁹¹ Modified Checklist for Autism in Toddlers.

⁴⁹² Includes Veiby 2013.

presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Three SRs provided data for this outcome: a Cochrane review by Bromley 2014 and a SR by NICE 2015. There are a number of methodological differences between these SRs. Bromley 2014 limited inclusion of studies to RCTs, prospective cohort studies and registry studies; retrospective studies/registers were excluded. For NICE 2015, both prospective and retrospective studies were included, but analyses were grouped by type (i.e. cohort or case control). The data shown below represents a subset of that extracted from the SRs and presented in the data extraction tables in **Section AppD3.1.3.1**, and is limited to analyses based on a comparator group with epilepsy, in order to reduce the impact of confounding by indication. The additional study by Banach 2010 examined sodium valproate and carbamazepine only; however only the results for the comparison between carbamazepine and the unexposed/epilepsy group are shown below. There was very little detail included in this study regarding the individual studies included in each analysis and the heterogeneity of the analyses.

Table AppD4-62 Anticonvulsants – IQ outcomes from systematic reviews

Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity I ² (P value)
Sodium valproate							
<i>Full scale IQ – dichotomous</i>							
Bromley 2014 <i>Moderate</i>	Full scale IQ – <1SD	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	2 (OBS) ⁴⁹³	76	RR 10.33 (2.05, 52.01)	0% (0.96)
Bromley 2014 <i>Moderate</i>	Full scale IQ – <1SD	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	1 (p-cohort)	50	RR 10.0 (1.38, 72.39)	NA
Bromley 2014 <i>Moderate</i>	Full scale IQ – <1SD	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	1 (registry)	26	RR 11.0 (0.67, 180.65)	NA
Bromley 2014 <i>Moderate</i>	Full scale IQ – >2SD	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	1 (registry)	58	MD 1.73 (0.17, 17.61)	NA
Bromley 2014 <i>Moderate</i>	Full scale IQ – >1SD	Sodium valproate (any time)	Lamotrigine	2 (p-cohort) ⁴⁹⁴	157	RR 4.87 (1.50, 15.78)	0% (0.68)
<i>Full scale IQ – continuous</i>							
NICE 2015 <i>Moderate</i>	Full scale IQ	Sodium valproate (any time)	Unexposed – epilepsy	4 (cohort) ⁴⁹⁵	286	MD -5.06 (-8.42, -1.70) ⁴⁹⁶	0% (0.51)
Bromley 2014 <i>Moderate</i>	Full scale IQ	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	4 (OBS) ⁴⁹⁷	176	MD -8.17 (-12.80, -3.55)	27% (0.25)
Bromley 2014 <i>Moderate</i>	Full scale IQ	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	1 (p-cohort)	76	MD -9.30 (-15.34, -3.26)	NA
Bromley 2014 <i>Moderate</i>	Full scale IQ	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	3 (registry)	100	MD -6.58 (-13.77, 0.62)	47% (0.15)
Bromley 2014 <i>Moderate</i>	Full scale IQ	Sodium valproate (any time)	Lamotrigine	2 (p-cohort) ⁴⁹⁸	158	MD -10.80 (-14.42, -7.17)	0% (0.43)

⁴⁹³ Includes Bromley 2010 and Eriksson 2005.

⁴⁹⁴ Includes Bromley 2010 and Meador 2013.

⁴⁹⁵ Includes Rihtman 2013, Eriksson 2005, Adab 2004/Viten 2005 and Gaily 2004.

⁴⁹⁶ Reported as mean difference in the Guideline document (NICE 2015) and standardised mean difference in Appendix 19.

⁴⁹⁷ Includes Bromley 2010, Thomas 2007, Eriksson 2005 and Gaily 2004.

⁴⁹⁸ Includes Bromley 2010 and Meador 2013.

Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity I ² (P value)
<i>Verbal IQ – continuous</i>							
NICE 2015 <i>Moderate</i>	Verbal IQ	Sodium valproate (any time)	Unexposed – epilepsy	4 (cohort) ⁴⁹⁹	286	MD -6.83 (-10.51, 2.15) ⁵⁰⁰	0% (0.83)
Bromley 2014 <i>Moderate</i>	Verbal IQ	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	3 (OBS) ⁵⁰¹	160	-MD -8.81 (-13.32, -4.30)	0% (0.69)
Bromley 2014 <i>Moderate</i>	Verbal IQ	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	1 (p-cohort)	76	MD -7.45 (-13.02, -1.88)	NA
Bromley 2014 <i>Moderate</i>	Verbal IQ	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	2 (registry)	84	MD -11.42 (-19.13, -3.72)	0% (0.79)
<i>Performance IQ - continuous</i>							
NICE 2015 <i>Moderate</i>	Performance IQ	Sodium valproate (any time)	Unexposed – epilepsy	4 (cohort) ⁵⁰²	286	MD -3.54 (-10.06, 2.98) ⁵⁰³	60% (0.06)
Bromley 2014 <i>Moderate</i>	Performance IQ	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	3 (OBS) ⁵⁰⁴	160	MD -7.20 (-12.44, -1.96)	12% (0.32)
Bromley 2014 <i>Moderate</i>	Performance IQ	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	1 (p-cohort)	76	MD -7.30 (-13.71, -0.89)	NA
Bromley 2014 <i>Moderate</i>	Performance IQ	Sodium valproate (any time)	Unexposed – epilepsy (no medication)	2 (registry)	84	MD -7.01 (-16.13, 2.11)	56% (0.13)
Carbamazepine							
<i>Full scale IQ – dichotomous</i>							
Bromley 2014 <i>Moderate</i>	Full scale IQ – >2SD	Carbamazepine (any time)	Unexposed – epilepsy (no medication)	1 (registry)	131	RR 0.26 (0.02, 2.81)	NA
Bromley 2014 <i>Moderate</i>	Full scale IQ – >1SD	Carbamazepine (any time)	Sodium valproate	3 (OBS) ⁵⁰⁵	178	<i>RR 0.40</i> <i>(0.19, 0.83)</i>	0% (0.83)
Bromley 2014 <i>Moderate</i>	Full scale IQ – >1SD	Carbamazepine (any time)	Sodium valproate	2 (p-cohort)	152	<i>RR 0.40</i> <i>(0.17, 0.93)</i>	0% (0.55)
Bromley 2014 <i>Moderate</i>	Full scale IQ – >1SD	Carbamazepine (any time)	Sodium valproate	1 (registry)	26	<i>RR 0.40</i> <i>(0.09, 1.70)</i>	NA
Bromley 2014 <i>Moderate</i>	Full scale IQ – >2SD	Carbamazepine (any time)	Sodium valproate	4 (OBS)	277	RR 0.26 (0.05, 1.19)	0% (0.86)
Bromley 2014 <i>Moderate</i>	Full scale IQ – >2SD	Carbamazepine (any time)	Sodium valproate	2 (p-cohort)	152	RR 0.40 (0.04, 4.30)	NA
Bromley 2014	Full scale IQ – >2SD	Carbamazepine (any time)	Sodium valproate	2 (registry)	125	RR 0.18 (0.02, 1.46)	0% (0.89)
Bromley 2014 <i>Moderate</i>	Full scale IQ – >1SD	Carbamazepine (any time)	Lamotrigine	2 (p-cohort) ⁵⁰⁶	159	RR 2.28 (0.63, 8.22)	0% (0.51)
<i>Full scale IQ – continuous</i>							
NICE 2015 <i>Moderate</i>	Full scale IQ	Carbamazepine (any time)	Unexposed – epilepsy	4 (cohort) ⁵⁰⁷	377	MD -3.80 (-16.81, 0.80)	87% (<0.001) ⁵⁰⁸

⁴⁹⁹ Includes Rihtman 2013, Eriksson 2005, Adab 2004/Viten 2005 and Gaily 2004.

⁵⁰⁰ Reported as mean difference in the Guideline document (NICE 2015) and standardised mean difference in Appendix 19.

⁵⁰¹ Includes Bromley 2010, Eriksson 2005 and Gaily 2004.

⁵⁰² Includes Rihtman 2013, Eriksson 2005, Adab 2004/Viten 2005 and Gaily 2004.

⁵⁰³ Reported as standardised mean difference in the Guideline document (NICE 2015) and Appendix 19. Recalculated as mean difference for this review.

⁵⁰⁴ Includes Bromley 2010, Eriksson 2005 and Gaily 2004.

⁵⁰⁵ Includes Bromley 2010, Eriksson 2005 and Meador 2013.

⁵⁰⁶ Includes Bromley 2010 and Meador 2013.

⁵⁰⁷ Includes Eriksson 2005, Adab 2004/Viten 2005, Gaily 2004 and Ornoy 1996.

⁵⁰⁸ Heterogeneity values relate to meta-analysis of SMD as presented in NICE 2015, Appendix 19.

Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity I ² (P value)
Bromley 2014 <i>Moderate</i>	Full scale IQ	Carbamazepine (any time)	Unexposed – epilepsy no medication)	4 (OBS) ⁵⁰⁹	250	MD 1.84 (-2.13, 5.80)	0% (0.81)
Bromley 2014 <i>Moderate</i>	Full scale IQ	Carbamazepine (any time)	Unexposed – epilepsy no medication)	2 (p-cohort)	93	MD 1.27 (-5.08, 7.63)	0% (0.75)
Bromley 2014 <i>Moderate</i>	Full scale IQ	Carbamazepine (any time)	Unexposed – epilepsy (no medication)	2 (registry)	157	MD 2.20 (-2.87, 7.28)	0% (0.36)
Banach 2010	Full scale IQ (Weschler)	Carbamazepine	Unexposed – epilepsy	NR	NR	NR P=0.41	NR
Bromley 2014 <i>Moderate</i>	Full scale IQ	Carbamazepine (any time)	Lamotrigine	2 (p-cohort) ⁵¹⁰	162	MD -1.62 (-5.44, 2.21)	0% (0.65)
Bromley 2014 <i>Moderate</i>	Full scale IQ	Carbamazepine (any time)	Sodium valproate	5 (OBS) ⁵¹¹	303	MD 8.69 (5.51, 11.87)	43% (0.13)
Bromley 2014 <i>Moderate</i>	Full scale IQ	Carbamazepine (any time)	Sodium valproate	2 (p-cohort)	152	MD 9.19 (5.49, 12.88)	36% (0.21)
Bromley 2014 <i>Moderate</i>	Full scale IQ	Carbamazepine (any time)	Sodium valproate	3 (registry)	151	MD 7.29 (1.06, 13.53)	62% (0.07)
<i>Verbal IQ – continuous</i>							
NICE 2015 <i>Moderate</i>	Verbal IQ	Carbamazepine (any time)	Unexposed – epilepsy	3 (cohort) ⁵¹²	289	MD 1.47 (-2.42, 5.36)	0% (0.85)
Bromley 2014 <i>Moderate</i>	Verbal IQ	Carbamazepine (any time)	Unexposed – epilepsy (no medication)	3 (OBS) ⁵¹³	232	MD 0.13 (-3.98, 4.23)	0% (0.76)
Bromley 2014 <i>Moderate</i>	Verbal IQ	Carbamazepine (any time)	Unexposed – epilepsy (no medication)	1 (p-cohort)	75	MD -1.0 (-7.28, 5.28)	NA
Bromley 2014 <i>Moderate</i>	Verbal IQ	Carbamazepine (any time)	Unexposed – epilepsy (no medication)	2 (registry)	157	MD 0.97 (-4.47, 6.40)	0% (0.57)
Banach 2010	Verbal IQ (Weschler)	Carbamazepine	Unexposed – epilepsy	NR	NR	NR P=0.39	NR
Bromley 2014 <i>Moderate</i>	Verbal IQ	Carbamazepine (any time)	Sodium valproate	3 (OBS) ⁵¹⁴	226	MD 8.44 (4.21, 12.66)	0% (0.43)
<i>Performance IQ</i>							
NICE 2015 <i>Moderate</i>	Performance IQ	Carbamazepine (any time)	Unexposed – epilepsy	3 (cohort) ⁵¹⁵	289	MD 0.92 (3.29, 5.13)	16% (0.31)
Bromley 2014 <i>Moderate</i>	Performance IQ	Carbamazepine (any time)	Unexposed – epilepsy (no medication)	3 (OBS) ⁵¹⁶	232	MD 3.65 (-0.60, 7.90)	0% (0.81)
Bromley 2014 <i>Moderate</i>	Performance IQ	Carbamazepine (any time)	Unexposed – epilepsy (no medication)	1 (p-cohort)	75	MD 4.0 (-2.72, 10.72)	NA
Bromley 2014 <i>Moderate</i>	Performance IQ	Carbamazepine (any time)	Unexposed – epilepsy (no medication)	2 (registry)	157	MD 3.42 (-2.07, 8.91)	0% (0.52)
Banach 2010	Performance IQ (Weschler)	Carbamazepine	Unexposed – epilepsy	NR	NR	NR P=0.19	NR
Bromley 2014 <i>Moderate</i>	Performance IQ	Carbamazepine (any time)	Sodium valproate	3 (OBS)	226	MD 10.48 (6.02, 14.94)	0% (0.52)

⁵⁰⁹ Includes Bromley 2010, Thomas 2007, Eriksson 2005 and Gaily 2004.⁵¹⁰ Includes Bromley 2010 and Meador 2013.⁵¹¹ Includes Bromley 2010, Eriksson 2005, Gaily 2014, Meador 2013 and Thomas 2007.⁵¹² Includes Eriksson 2005, Adab 2004/Viten 2005 and Gaily 2004.⁵¹³ Includes Bromley 2001, Eriksson 2005 and Gaily 2004.⁵¹⁴ Includes Bromley 2010, Eriksson 2005 and Gaily 2004.⁵¹⁵ Includes Eriksson 2005, Adab 2004/Viten 2005 and Gaily 2004.⁵¹⁶ Includes Bromley 2010, Eriksson 2005 and Gaily 2004.

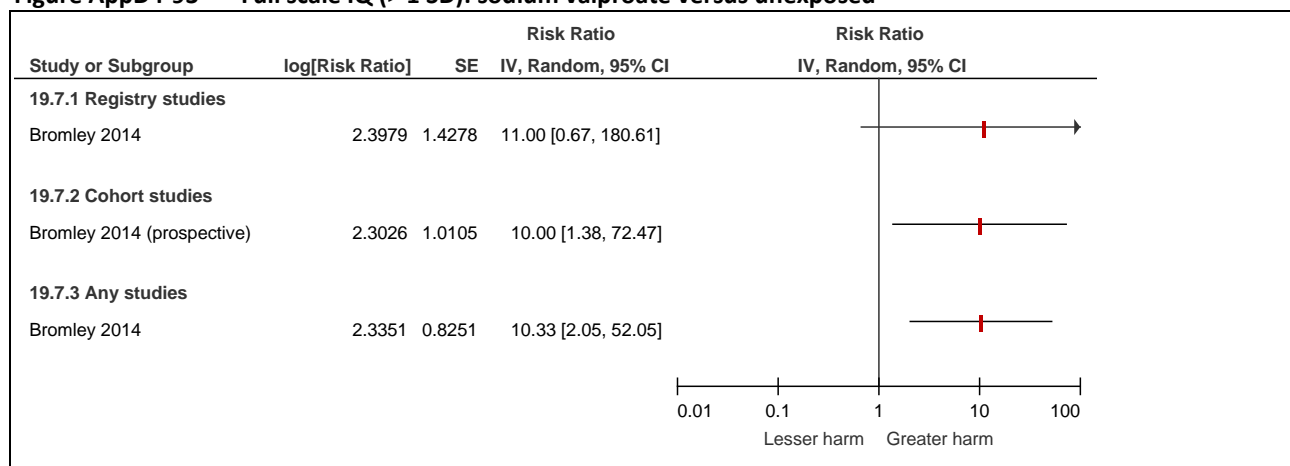
Study ID <i>SR quality</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity I ² (P value)
Lamotrigine							
<i>Full scale IQ</i>							
Bromley 2014 <i>Moderate</i>	Full scale IQ	Lamotrigine (any time)	Unexposed – epilepsy (no medication)	1 (p-cohort) ⁵¹⁷	54	MD -1.0 (-7.48, 5.48)	NA

Abbreviations: CI, confidence interval; IQ, intelligence quotient; MD, mean difference; NA, not applicable; NR, not reported; p, prospective; RE, risk estimate; RR, relative risk; SD, standard deviation; SR, systematic review.

Data shown in dark shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.1.3** of the Technical Report.

Figure AppD4-93 presents the findings for the association between sodium valproate and full scale IQ based on the proportion of children with a reduction in score of 1 SD from the mean. There was a significantly greater harm associated with sodium valproate. Bromley 2014 also assessed full scale IQ dichotomised based on a definition of a reduction in score of 2 SDs from the mean and found no significant difference; however, this finding is imprecise as the 95% CI includes measures of both appreciable benefit and harm.

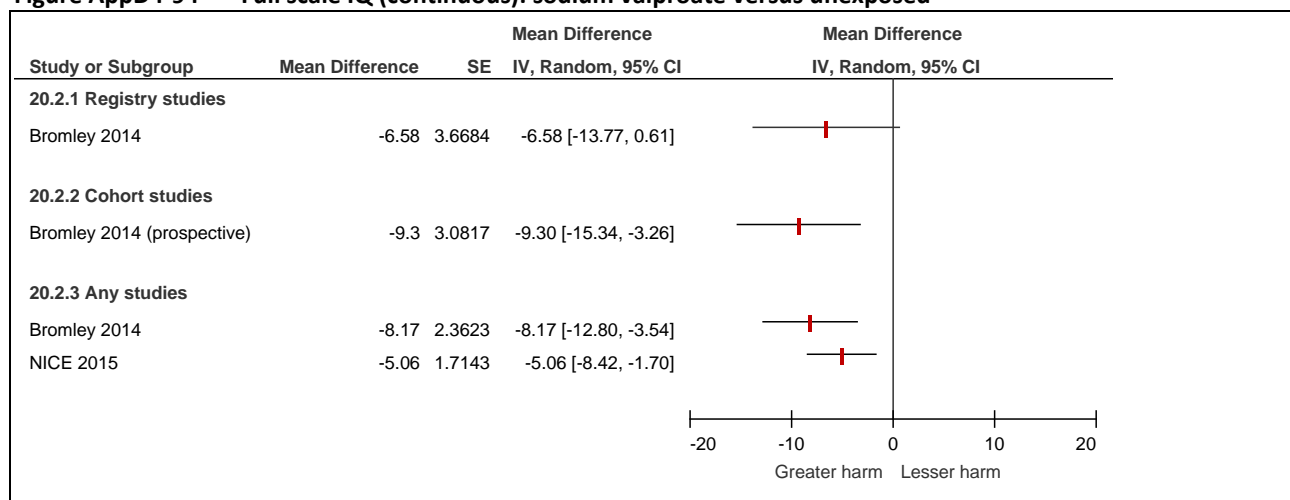
Figure AppD4-93 Full scale IQ (> 1 SD): sodium valproate versus unexposed



Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SD, standard deviation; SE, standard error.

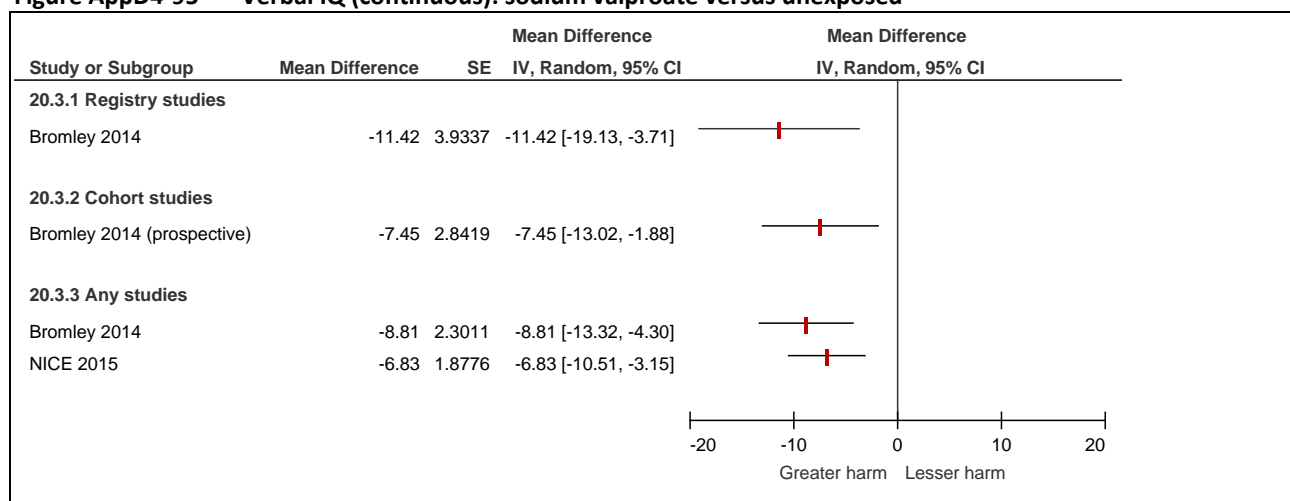
Figure AppD4-94 presents the findings for the association between sodium valproate and full scale IQ based on mean difference (continuous scale). As for the previous outcome, there was a significantly greater harm associated with sodium valproate. The findings for the Bromley 2014 and NICE 2015 review were similar, and the difference in magnitude may be explained by the different studies included in each analysis.

⁵¹⁷ Includes Bromley 2010.

Figure AppD4-94 Full scale IQ (continuous): sodium valproate versus unexposed

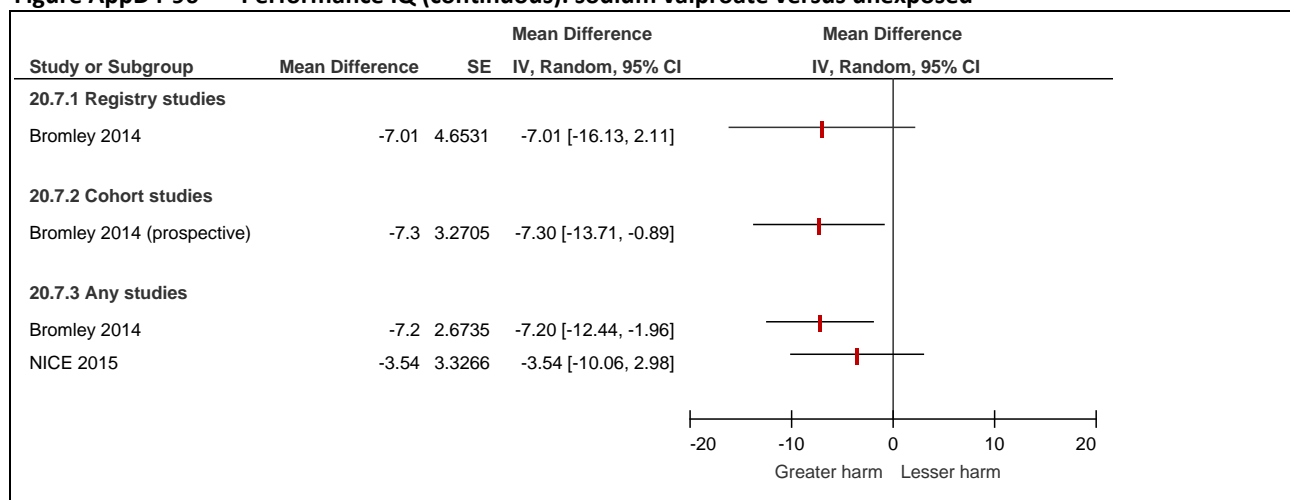
Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SD, standard deviation; SE, standard error.

Figure AppD4-95 presents the findings for the association between sodium valproate and verbal IQ on a continuous scale (mean difference). The findings of the NICE 2015 and Bromley 2014 reviews SRs were consistent and the results suggest that sodium valproate is significantly associated with a reduction in verbal IQ.

Figure AppD4-95 Verbal IQ (continuous): sodium valproate versus unexposed

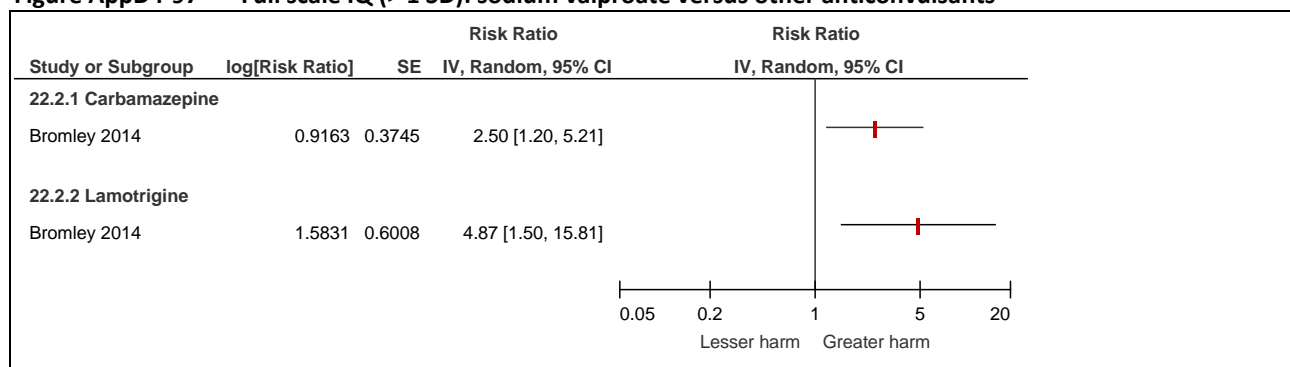
Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SD, standard deviation; SE, standard error.

Figure AppD4-96 presents the findings for the association between sodium valproate and performance IQ on a continuous scale (mean difference). The findings of the Bromley 2014 review SRs suggest that sodium valproate is significantly associated with a reduction in performance IQ. The NICE 2015 review suggests a reduction in performance IQ; however, this finding was significantly heterogeneous ($I^2=60\%$).

Figure AppD4-96 Performance IQ (continuous): sodium valproate versus unexposed

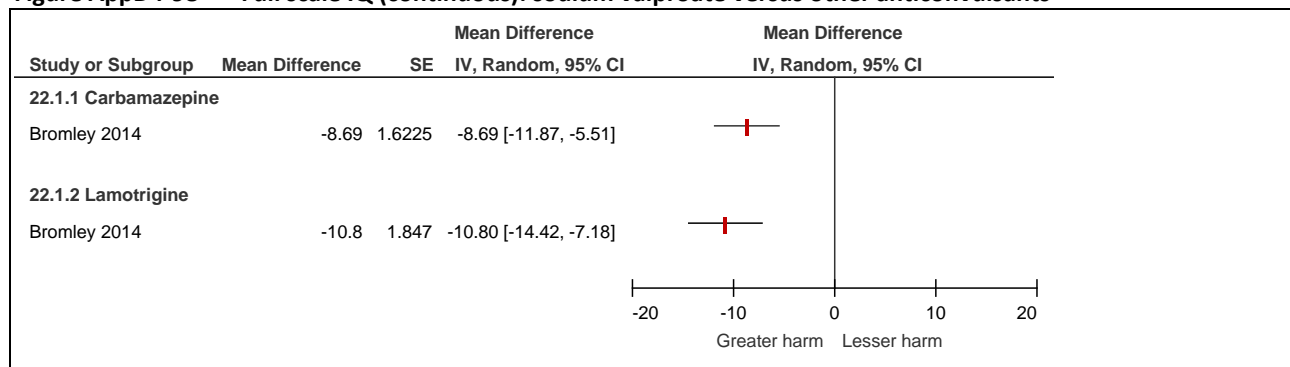
Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SD, standard deviation; SE, standard error.

Bromley 2014 also carried out comparisons between sodium valproate and carbamazepine or lamotrigine and found that sodium valproate was associated with a large and statistically significant increased risk of having a reduction in full scale IQ of > 1 SD compared with carbamazepine or lamotrigine (**Figure AppD4-97**), and a reduction in mean full scale IQ compared with carbamazepine or lamotrigine (**Figure AppD4-98**).

Figure AppD4-97 Full scale IQ (> 1 SD): sodium valproate versus other anticonvulsants

Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SD, standard deviation; SE, standard error.

Note: Data for sodium valproate versus carbamazepine recalculated from comparison of carbamazepine versus sodium valproate.

Figure AppD4-98 Full scale IQ (continuous): sodium valproate versus other anticonvulsants

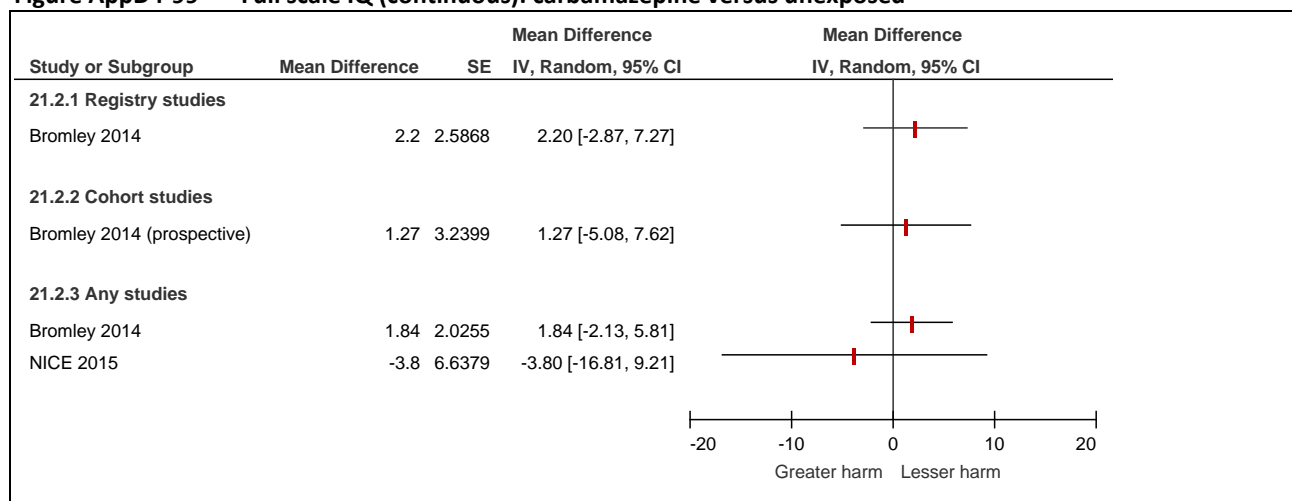
Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SE, standard error.

Note: Data for sodium valproate versus carbamazepine recalculated from comparison of carbamazepine versus sodium valproate.

A significantly greater reduction in mean verbal IQ score was also seen for sodium valproate compared with carbamazepine (MD -8.44; 95% CI -12.66, -4.21),⁵¹⁸ while there was no significant difference in mean performance IQ score (MD 1.0; 95% CI -5.48, 7.48).⁵¹⁹

Figure AppD4-99 presents the findings for the association between carbamazepine and full scale IQ on a continuous scale (mean difference). The findings of the NICE 2015 and Bromley 2014 SRs were relatively consistent, with both suggesting that carbamazepine is not associated with a reduction in full scale IQ. However, there was some difference between the two results, probably because of different included studies. The only dichotomised outcome for full scale IQ was defined as a reduction in score of > 2 SDs. In this analysis, there was an increased risk associated with carbamazepine (RR 0.26); however, this was highly imprecise (95% CI 0.02, 2.81).

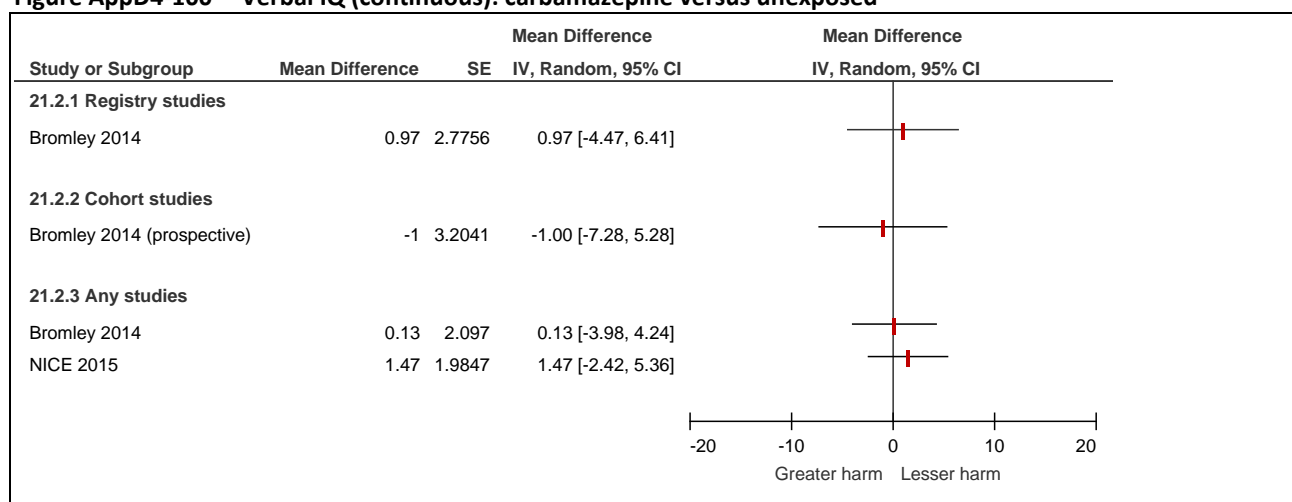
Figure AppD4-99 Full scale IQ (continuous): carbamazepine versus unexposed



Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SE, standard error.

Figure AppD4-100 presents the findings for the association between carbamazepine and verbal IQ on a continuous scale (mean difference). The findings of the NICE 2015 and Bromley 2014 SRs were consistent and the results suggest that carbamazepine is not associated with a reduction in verbal IQ.

Figure AppD4-100 Verbal IQ (continuous): carbamazepine versus unexposed



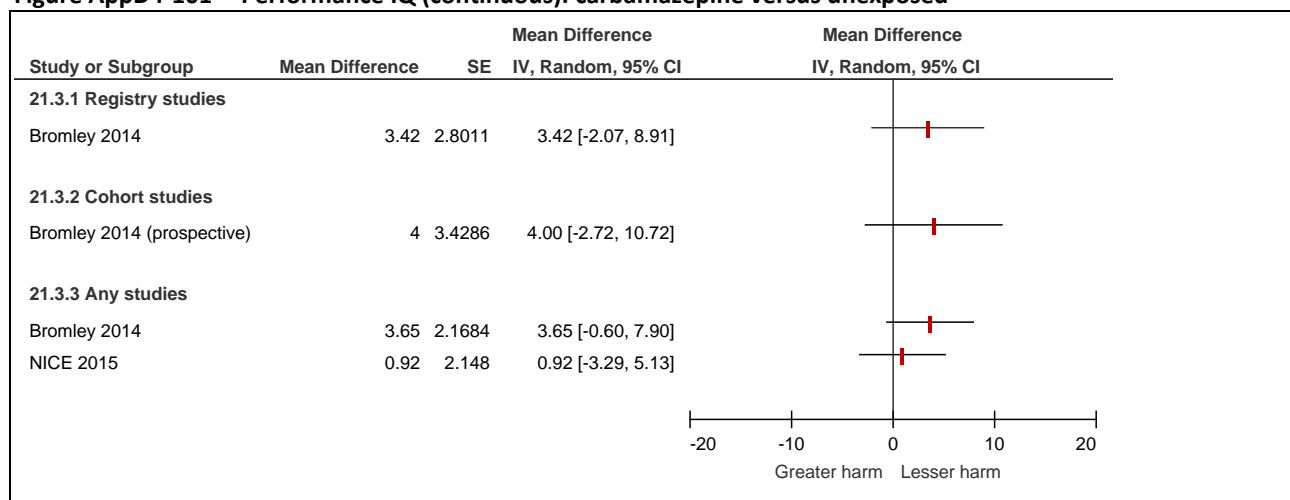
Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SE, standard error.

⁵¹⁸ Data for sodium valproate versus carbamazepine recalculated from comparison of carbamazepine versus sodium valproate presented in Bromley 2014 (RR 8.44; 95% CI 4.21, 12.66).

⁵¹⁹ Data for sodium valproate versus carbamazepine recalculated from comparison of carbamazepine versus sodium valproate presented in Bromley 2014 (RR -1.0; 95% CI -7.48, 5.48).

Figure AppD4-101 presents the findings for the association between carbamazepine and performance IQ on a continuous scale (mean difference). The findings of the Bromley 2014 SRs suggest carbamazepine is not associated with a reduction in performance IQ. The findings of the NICE review were similar.

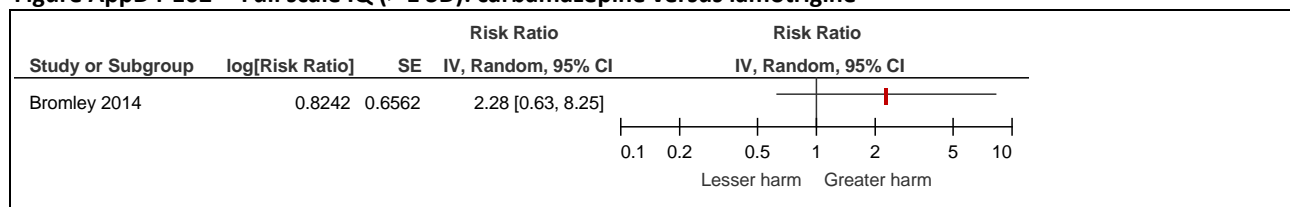
Figure AppD4-101 Performance IQ (continuous): carbamazepine versus unexposed



Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SE, standard error.

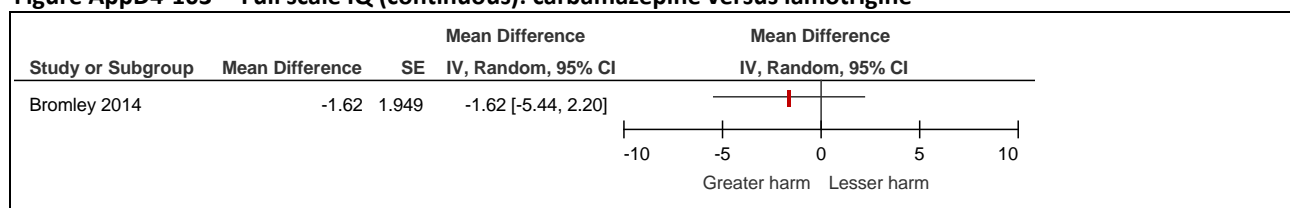
Bromley 2014 also carried out comparisons between carbamazepine and lamotrigine and found that there was no significant difference in the proportion of children with a reduction in IQ of > 1 SD with carbamazepine compared to lamotrigine (**Figure AppD4-97**), and no significant difference in mean full scale IQ with carbamazepine compared to lamotrigine (**Figure AppD4-98**).

Figure AppD4-102 Full scale IQ (> 1 SD): carbamazepine versus lamotrigine



Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SD, standard deviation; SE, standard error.

Figure AppD4-103 Full scale IQ (continuous): carbamazepine versus lamotrigine



Abbreviations: CI, confidence interval; IQ, intelligence quotient; IV, inverse variance; SD, standard deviation; SE, standard error.

Only one SR assessed the association between lamotrigine and full scale IQ on a continuous scale (mean difference) using an untreated cohort with epilepsy as a comparator. Bromley 2014 found there was no significant association between lamotrigine and full scale IQ (MD -1.00; -7.47, 5.48).

AppD4.1.4 Benzodiazepines and z-drugs

AppD4.1.4.1 Included systematic reviews – benzodiazepines and z-drugs

Two SRs were identified that provided evidence relating to the assessment of benzodiazepine harms. A summary of the characteristics of the identified SRs is presented in **Table AppD4-63**.

Table AppD4-63 Characteristics of the included systematic reviews of benzodiazepine harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
NICE 2015	SR 18 observational studies	Pregnant women	Benzodiazepines and related drugs ⁵²⁰	Unexposed	Congenital malformations Major congenital malformations Cleft lip/palate Cardiac abnormalities Septal heart defects Gestational age at delivery Birth weight Caesarean delivery Miscarriage Instrumental delivery Respiratory disorder
Enato 2011	SR 9 observational studies	Pregnant women	Benzodiazepines	Unexposed	Major malformations Cardiac malformations

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: SR, systematic review.

AppD4.1.4.2 Included individual studies – benzodiazepines and z-drugs

Ten publications representing data from nine individual populations were identified that provided evidence relating to the assessment of benzodiazepine and z-drug harms. A summary of the characteristics of the identified SRs is presented in **Table AppD4-64**.

Table AppD4-64 Characteristics of the included comparative observational studies of benzodiazepine and z-drug harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Odsbu 2015	Prospective cohort study Norway 1999-2008	Pregnant women and their offspring age 3 (N=51,748 singleton pregnancies)	Benzodiazepines Z-drugs	Unexposed/adjusted for anxiety and depression	Lower language competence
Ban 2014b	Retrospective primary care-based cohort study THIN, UK 1990–2010	Singleton live births (N=20,137)	Diazepam Temazepam Zopiclone	Unexposed/no depression or anxiety Unexposed/depression or anxiety	Major congenital malformations Heart malformations Limb malformations Genital system malformations
Wikner 2011	Retrospective population-based cohort study Sweden 1995-2007	Live-born infants (N=1,127,075)	Z-drugs (zolpidem, zopiclone and zaleplon)	Unexposed	Relatively severe congenital malformations Any cardiovascular defect Hypospadias Other intestinal malformations than atresia/stenosis

⁵²⁰ Identified one study that examined zopiclone also (Ban 2014) but results not included in analyses.

drugs

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Wikner 2007	Retrospective population-based cohort study Sweden 1995-2004	Infants born (N=873, 879)	Benzodiazepines and z-drugs	Unexposed	Preterm birth Low birth weight Small for gestational age Low Apgar score Respiratory problems Neonatal jaundice Hypoglycaemia Convulsions CNS problems Any malformations Major malformations Individual malformations (including cardiovascular defects)
Wang 2010	Retrospective population-based cohort study Taiwan 2005	Singleton live births (N=14,982)	Zolpidem	Unexposed	Low birth weight Preterm birth Small for gestational age Congenital abnormalities (major) Caesarean delivery
Juric 2009	Prospective cohort study US NR	Women enrolled in a study of pharmacokinetics of psychotropic medications during pregnancy (N=90)	Zolpidem	Unexposed/psychiatric disorders	Preterm delivery EGA at delivery Low birth weight Birth weight NICU admission Respiratory difficulty Lethargy Hypotonia APGAR 1 and 5 HTN/pre-eclampsia
Oberlander 2008a	Retrospective, population-based cohort study British Colombia Linked Health Database, Canada 1998–2001	Women who had registered live births (N=20,188)	SSRIs Benzodiazepines SSRIs + benzodiazepines	Unexposed Adjusted/matched on psychiatric variables	Major congenital anomalies Cardiovascular congenital defects Ventricular septal defects Atrial septal defects
Kjær 2007	Retrospective population-based cohort study Hungary 1980-1996	<u>Cases</u> Identified within 3 months of birth via HCAR <u>Controls</u> 2:1 identified via the National Birth Registry (3:1 during 1986-1992)	Diazepam	Unexposed	Individual congenital abnormalities (including cardiovascular congenital abnormalities)
Eros 2002	Retrospective population-based case-control study Hungary 1980-1996	<u>Cases</u> Identified within 3 months of birth via HCAR <u>Controls</u> 2:1 identified via the National Birth Registry	Benzodiazepines (including nitrazepam, medazepam, tofisopam, alprazolam and clonazepam)	Unexposed/adjusted for chronic maternal disease (included psychiatric disorders)	Isolated congenital abnormalities (including cardiovascular congenital abnormalities)

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Diav-Citrin 1999	Prospective cohort study Canada 1993-1997	Women contacting the Motherisk program (i) exposed to zopiclone and (ii) matched non-teratogen-exposed (N=80)	Zopiclone	Unexposed	Live birth Spontaneous abortion Therapeutic abortion Major birth defects Minor birth defects Delivery method Gestational age Preterm delivery Birth weight/ small for gestational age Meconium Fetal distress NICU admission

Abbreviations: HCAR, Hungarian Congenital Abnormality Registry; NICU, neonatal intensive care unit.

AppD4.1.4.3 Major malformations – benzodiazepines and z-drugs

AppD4.1.4.3.1 Results based on systematic reviews

The results of the analyses of the association between benzodiazepines and major malformations presented in the two included SRs, NICE 2015 and Enato 2011, are presented in **Table AppD4-65**. It should be noted that these analyses were neither adjusted for potential confounding, nor limited to or adjusted for a mental health disorder. *As such, these findings have not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-65 Benzodiazepines and/or z-drugs – major malformation outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any benzodiazepines								
NICE 2015	Major malformations	Benzodiazepines and z-drugs	Unexposed - any	5 (cohort) ⁵²¹	130,429	-	OR 1.01 (0.81, 1.25) ⁵²²	0% (0.88)
NICE 2015	Major malformations	Benzodiazepines and z-drugs	Unexposed - any	1 (CC) ⁵²³	78	-	OR 19.95 (4.17, 95.45) ⁵²⁴	NA
Enato 2011	Major malformations	Benzodiazepines	Unexposed - any	9 (OBS)	1,055,020	-	OR 1.07 (0.91, 1.25)	0.95 (0%)

Abbreviations: CC, case-control study; CI, confidence interval; OR, odds ratio; NA, not applicable; RE, risk estimate.

AppD4.1.4.3.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and major malformations is presented in **Table AppD4-4**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.4** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

⁵²¹ Includes Ban 2014, Laegreid 1992, Oberlander 2008, Ornoy 1998 and Pastuszak 1996.

⁵²² Peto odds ratio.

⁵²³ Includes Laegreid 1990.

⁵²⁴ Peto odds ratio.

Due to the low prevalence of major malformations in the depressed/unexposed population (2.8% in a depressed/anxious population),⁵²⁵ it is assumed that odds ratios (ORs) approximate the relative risks (RRs), and has been interpreted as such.

Table AppD4-66 Benzodiazepines and/or z-drugs – major malformation outcomes from observational studies

Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Any benzodiazepines ± z-drugs						
Oberlander 2008a <i>Moderate</i>	Major congenital anomalies	Benzodiazepines ⁵²⁶ (first trimester)	Unexposed – adjusted for depression in first trimester	1 (r-cohort)	108,288	RD –0.0041 (-0.0151, 0.0069)
Wikner 2007 <i>Moderate</i>	Malformations excluding mild and variable ⁵²⁷	Benzodiazepines and z-drugs ⁵²⁸ –excluding anticonvulsants (any time)	Unexposed - any	1 (r-cohort)	NR	OR 1.22 (0.97, 1.52)
Wikner 2007 <i>High</i>	Malformations excluding mild and variable ⁵²⁹	Benzodiazepines (any time)	Unexposed - any	1 (r-cohort)	NR	OR 1.37 (1.07, 1.76)
Diazepam						
Ban 2014b <i>Moderate</i>	Major congenital anomalies	Diazepam (first trimester)	Unexposed - depression or anxiety	1 (cohort)	20,352	OR 0.99 (0.61, 1.61)
Temazepam						
Ban 2014b <i>Moderate</i>	Major congenital anomalies	Temazepam (first trimester)	Unexposed - depression or anxiety	1 (cohort)	19,572	OR 1.04 (0.47, 2.32)
Z-drugs						
Wikner 2011 <i>High</i>	Relatively severe malformations ⁵³⁰	Z-drugs (any time)	Unexposed - any	1 (r-cohort)	36,321	OR 0.95 (0.69, 1.30)
Wikner 2007 <i>High</i>	Malformations excluding mild and variable ⁵³¹	Z-drugs (any time)	Unexposed - any	1 (r-cohort)	NR	OR 1.09 (0.68, 1.75)
Zopiclone						
Ban 2014b <i>Moderate</i>	Major congenital anomalies	Zopiclone (first trimester)	Unexposed - depression or anxiety	1 (cohort)	19,599	OR 0.93 (0.40, 2.15)
Diav-Citrin 1999	Major birth defects	Zopiclone (any time)	Unexposed - any	1 (p-cohort)	68	NR 0% vs. 2.7%; 1.00
Zolpidem						
Wang 2010	Major congenital abnormalities ⁵³²	Zolpidem (any time)	Unexposed - any	1 (r-cohort)	14,982	OR 0.70 (0.38, 1.28)
Wang 2010	Major congenital abnormalities ⁵³²	Zolpidem (first trimester)	Unexposed - any	1 (r-cohort)	13,020	Not estimable

⁵²⁵ Ban 2014.

⁵²⁶ Includes lorazepam (44.0%), clonazepam (21.4%), oxazepam (15.0%), alprazolam (6.8%), temazepam (5.1%), diazepam (5.0%) and others.

⁵²⁷ Mild and variable malformations include the following diagnoses: preauricular appendix, undescended testicle, hip (sub)luxation, patent ductus arteriosus at preterm birth, tongue tie, single umbilical artery and nevus.

⁵²⁸ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs. Of the 415 infant exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

⁵²⁹ Mild and variable malformations include the following diagnoses: preauricular appendix, undescended testicle, hip (sub)luxation, patent ductus arteriosus at preterm birth, tongue tie, single umbilical artery and nevus.

⁵³⁰ Excludes preauricular appendix, undescended testicle, unstable hip, patent ductus arteriosus in preterm infants, single umbilical artery, tongue tie and nevus.

⁵³¹ Mild and variable malformations include the following diagnoses: preauricular appendix, undescended testicle, hip (sub)luxation, patent ductus arteriosus at preterm birth, tongue tie, single umbilical artery and nevus.

⁵³² Limited to hydrocephaly, anencephaly, microcephaly, meningomyelocele, encephalocele and spina bifida.

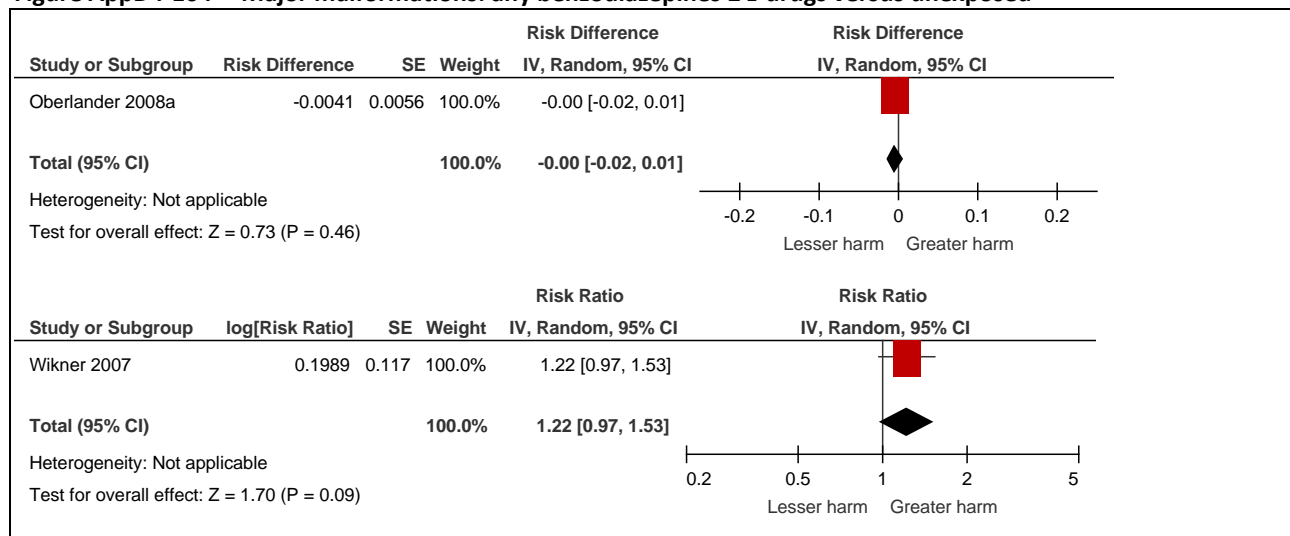
Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Wang 2010	Major congenital abnormalities ⁵³²	Zolpidem (second or third trimester)	Unexposed - any	1 (r-cohort)	14,447	OR 0.74 (0.38, 1.44)
Wang 2010	Major congenital abnormalities ⁵³²	Zolpidem (30-90 days)	Unexposed - any	1 (r-cohort)	13,946	OR 0.60 (0.26, 1.38)
Wang 2010	Major congenital abnormalities ⁵³²	Zolpidem (90-180 days)	Unexposed - any	1 (r-cohort)	13,016	Not estimable
Wang 2010	Major congenital abnormalities ⁵³²	Zolpidem (> 180 days)	Unexposed - any	1 (r-cohort)	12,990	Not estimable

Abbreviations: CI, confidence interval; NR, not reported; OR, odds ratio; RD, risk difference; RE, risk estimate.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

Figure AppD4-104 summarises the findings of the association between exposure to any benzodiazepines and major malformations. Oberlander 2008a examined first-trimester exposure to any benzodiazepines after adjusting for depression in first trimester and found that there was no significant association (RD – 0.0041; 95% CI –0.0151, 0.0069). Wikner 2007 examined the association between any benzodiazepines or z-drugs at any time during pregnancy with no limiting/adjustment for mental health and found no significant association, although there was a trend suggesting increased risk (RR 1.22; 95% CI 0.97, 1.53). This is also subject to imprecision because the upper 95% CI includes a measure of appreciable harm (RR 1.25).

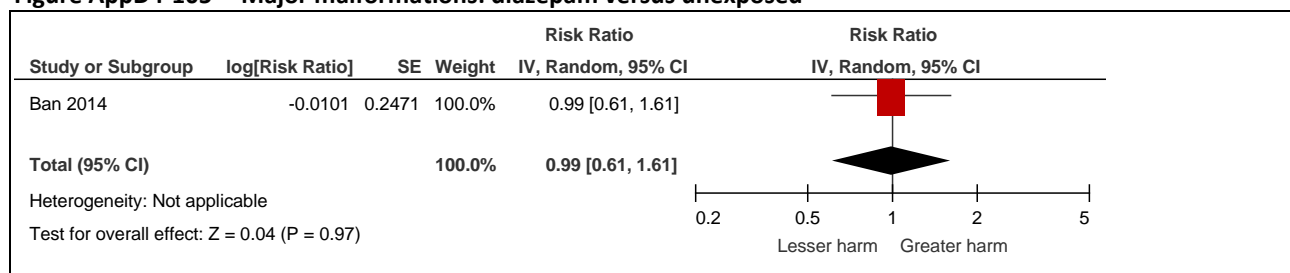
Figure AppD4-104 Major malformations: any benzodiazepines ± z-drugs versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

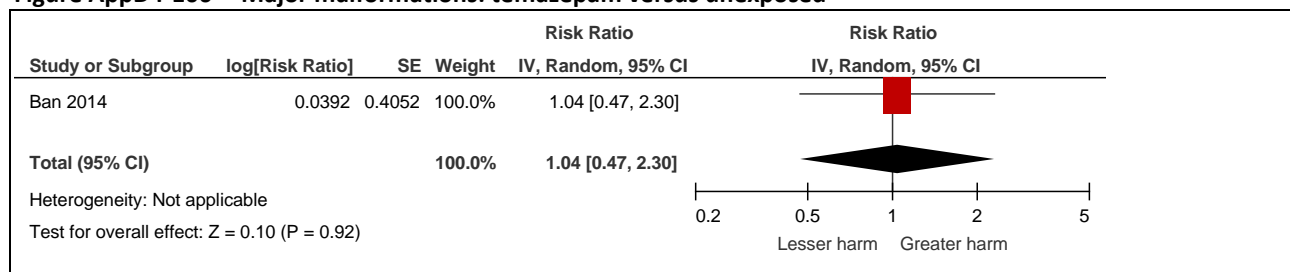
Figure AppD4-1 summarises the findings of the association between diazepam use and major malformations. Ban 2014b examined first-trimester exposure with diazepam and found that there was no significant association (RR 0.99; 95% CI 0.61, 1.61). This result is imprecise because the 95% confidence interval (CI) includes a measure of appreciable benefit and harm (RR 0.75/1.25).

Figure AppD4-105 Major malformations: diazepam versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

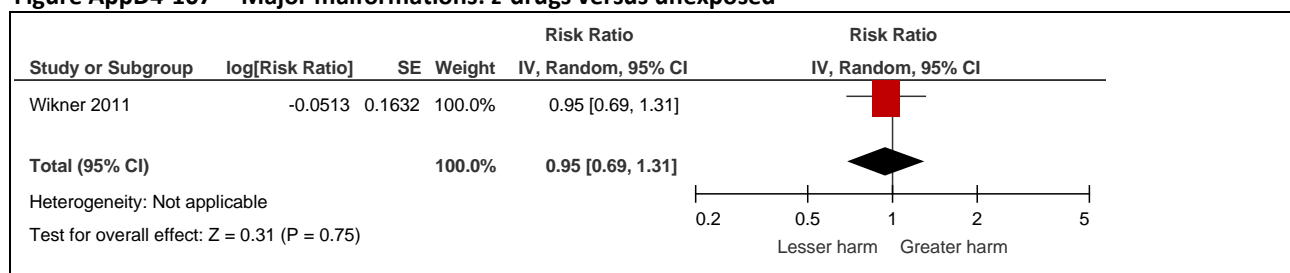
Figure AppD4-106 summarises the findings of the association between temazepam use and major malformations. Ban 2014b examined first-trimester exposure with diazepam and found that there was no significant association (RR 1.04; 95% CI 0.47, 2.32). This result is imprecise because the 95% CI includes a measure of appreciable benefit and harm (RR 0.75/1.25).

Figure AppD4-106 Major malformations: temazepam versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-107 summarises the findings of the association between exposure to z-drugs as a group and major malformations. Wikner 2011 examined first-trimester exposure with z-drugs⁵³³ and found that there was no significant association (RR 0.95; 95% CI 0.69, 1.30). This result is imprecise because the 95% CI includes a measure of appreciable benefit and harm (RR 0.75/1.25).

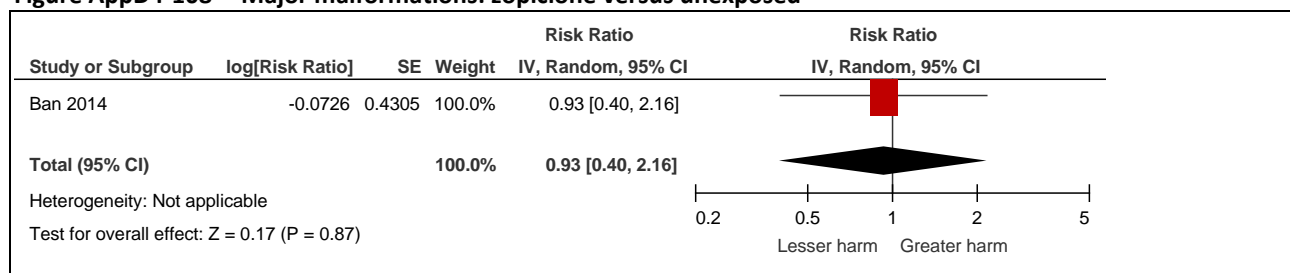
Figure AppD4-107 Major malformations: z-drugs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-108 summarises the findings of the association between exposure to zopiclone and major malformations. Ban 2014b examined first-trimester exposure with zopiclone and found that there was no significant association (RR 0.93; 95% CI 0.40, 2.15). This result is imprecise because the 95% CI includes a measure of appreciable benefit and harm (RR 0.75/1.25).

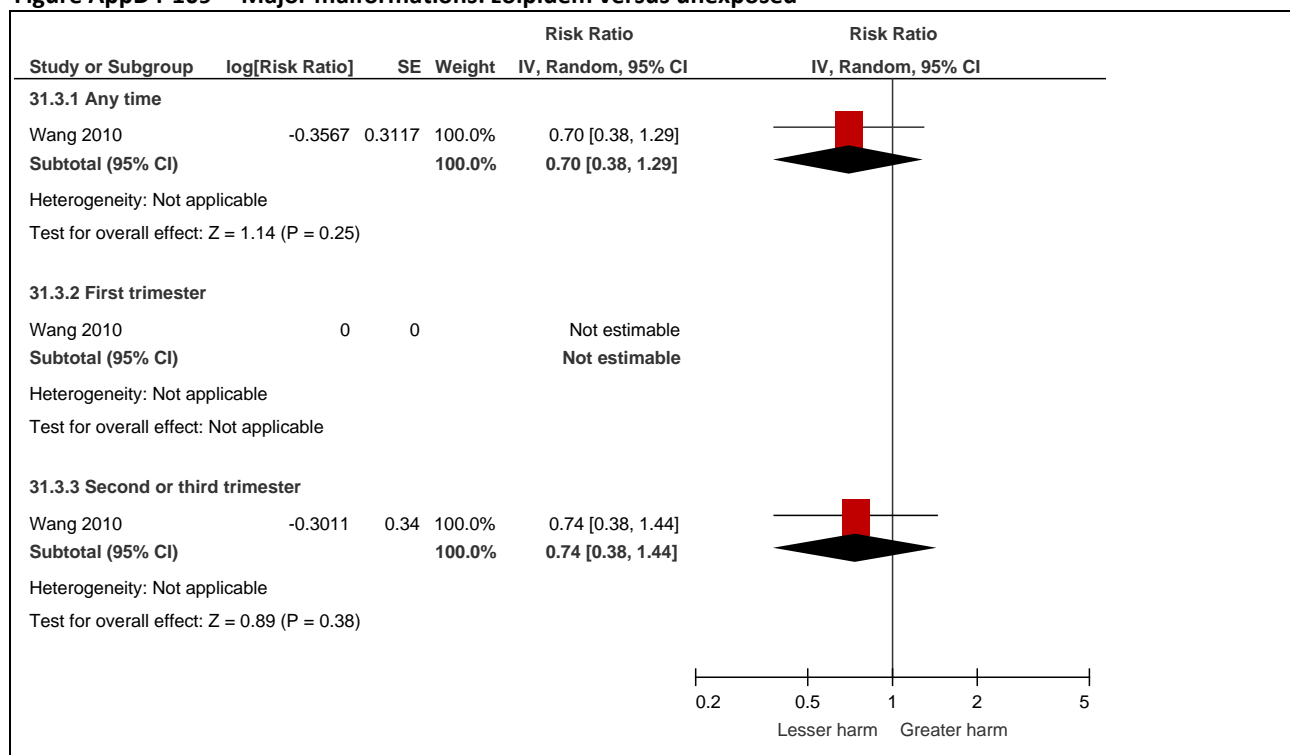
⁵³³ Of 1341 infants, 51.6% were exposed to zopiclone, 50.0% were exposed to zolpidem and 2.4% were exposed to zaleplon; 1.9% were exposed to two z-drugs.

Figure AppD4-108 Major malformations: zopiclone versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-110 summarises the findings of the association between exposure to zolpidem and major malformations. Wang 2010 examined exposure to zolpidem at various timepoints and durations of exposure found that there was no significant association following exposure at any time, or in second or third trimester (the findings for first-trimester-only exposure were not estimable due to too few events, and no significant association for exposure of 30-90 days (the findings for 90-180 and > 180 were also not estimable due to too few events).

Figure AppD4-109 Major malformations: zolpidem versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.4.4 Cardiac malformations – benzodiazepines and z-drugs

AppD4.1.4.4.1 Results based on systematic reviews

The results of the analyses of the association between benzodiazepines and cardiac malformations presented in the two included SRs, NICE 2015 and Enato 2011, are presented in **Table AppD4-67**. It should be noted that these analyses were neither adjusted for potential confounding, nor limited to or adjusted for a mental health disorder. *As such, these findings have not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-67 Benzodiazepines and/or z-drugs – cardiac malformation outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any benzodiazepines								
NICE 2015	Cardiac abnormalities	Benzodiazepines	Unexposed - any	5 (cohort) ⁵³⁴	1,007,764	-	OR 1.04 (0.56, 1.90)	66% (0.02)
Enato 2011	Cardiac malformations	Benzodiazepines	Unexposed - any	3 (OBS)	116,415	-	OR 1.27 (0.69, 2.32)	0.20 (38%)

Abbreviations: CI, confidence interval; OBS, observational study/studies; OR, odds ratio; RE, risk estimate.

AppD4.1.4.4.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and cardiac malformations is presented in **able AppD4-68**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.4** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of cardiac malformations in a depressed/unexposed population (0.6%)⁵³⁵, it is assumed that ORs approximate the RRs, and has been interpreted as such.

able AppD4-68 Benzodiazepines and/or z-drugs – cardiac malformations outcomes from observational studies

Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Benzodiazepines ± z-drugs						
Oberlander 2008a <i>Moderate</i>	Cardiovascular congenital defects	Benzodiazepines (first trimester)	Unexposed – adjusted for depression in first trimester	1 (cohort)	108,288	RD -0.0013 (-0.0055, 0.0029)
Eros 2002 <i>Moderate</i>	Cardiovascular congenital abnormalities	Benzodiazepines ⁵³⁶ (any time)	Unexposed – adjusted for chronic maternal disorders ⁵³⁷	1 (case control)	4,467	OR 1.6 (0.9, 2.8)
Eros 2002 <i>Moderate</i>	Cardiovascular congenital abnormalities	Benzodiazepines ⁵³⁶ (Month 1)	Unexposed – adjusted for chronic maternal disorders ⁵³⁷	1 (case control)	4,467	OR 1.6 (0.7, 3.7)
Eros 2002 <i>Moderate</i>	Cardiovascular congenital abnormalities	Benzodiazepines ⁵³⁶ (Months 2-3)	Unexposed – adjusted for chronic maternal disorders ⁵³⁷	1 (case control)	4,467	OR 1.0 (0.2, 4.6)
Eros 2002 <i>Moderate</i>	Cardiovascular congenital abnormalities	Benzodiazepines ²⁴³ (Months 4-9)	Unexposed – adjusted for chronic maternal disorders ⁵³⁷	1 (case control)	4,467	OR 1.9 (0.8, 4.6)
Eros 2002 <i>Moderate</i>	Cardiovascular congenital abnormalities	Benzodiazepines ⁵³⁶ (any time)	Unexposed – adjusted for chronic maternal disorders ⁵³⁷	1 (case control)	4,467	OR 1.6 (0.7, 3.6) ⁵³⁸
Eros 2002 <i>Moderate</i>	Cardiovascular congenital abnormalities	Benzodiazepines ⁵³⁶ (Months 2-3)	Unexposed – adjusted for chronic maternal disorders ⁵³⁷	1 (case control)	4,467	OR 5.0 (0.2, 104) ⁵³⁸
Diazepam						
Ban 2014b <i>Moderate</i>	Heart anomalies	Diazepam (first trimester)	Unexposed - depression or anxiety	1 (cohort)	20,352	OR 1.29 (0.60, 2.80)
Kjær 2007 <i>Moderate</i>	Cardiovascular congenital abnormalities	Diazepam (any time)	Unexposed - matched	1 (cohort)	42,630	OR 1.0 (0.8, 1.4)

⁵³⁴ Includes Ban 2014, Leppee 2010, Oberlander 2008, Ornoy 1998 and Wikner 2007.

⁵³⁵ Pooled analysis from Petersen 2016, Ban 2014a, Huybrechts 2014a and Margulis 2013.

⁵³⁶ Includes nitrazepam, medazepam, tofisopam, alprazolam and clonazepam.

⁵³⁷ Includes psychiatric disorders.

⁵³⁸ McNemar analysis.

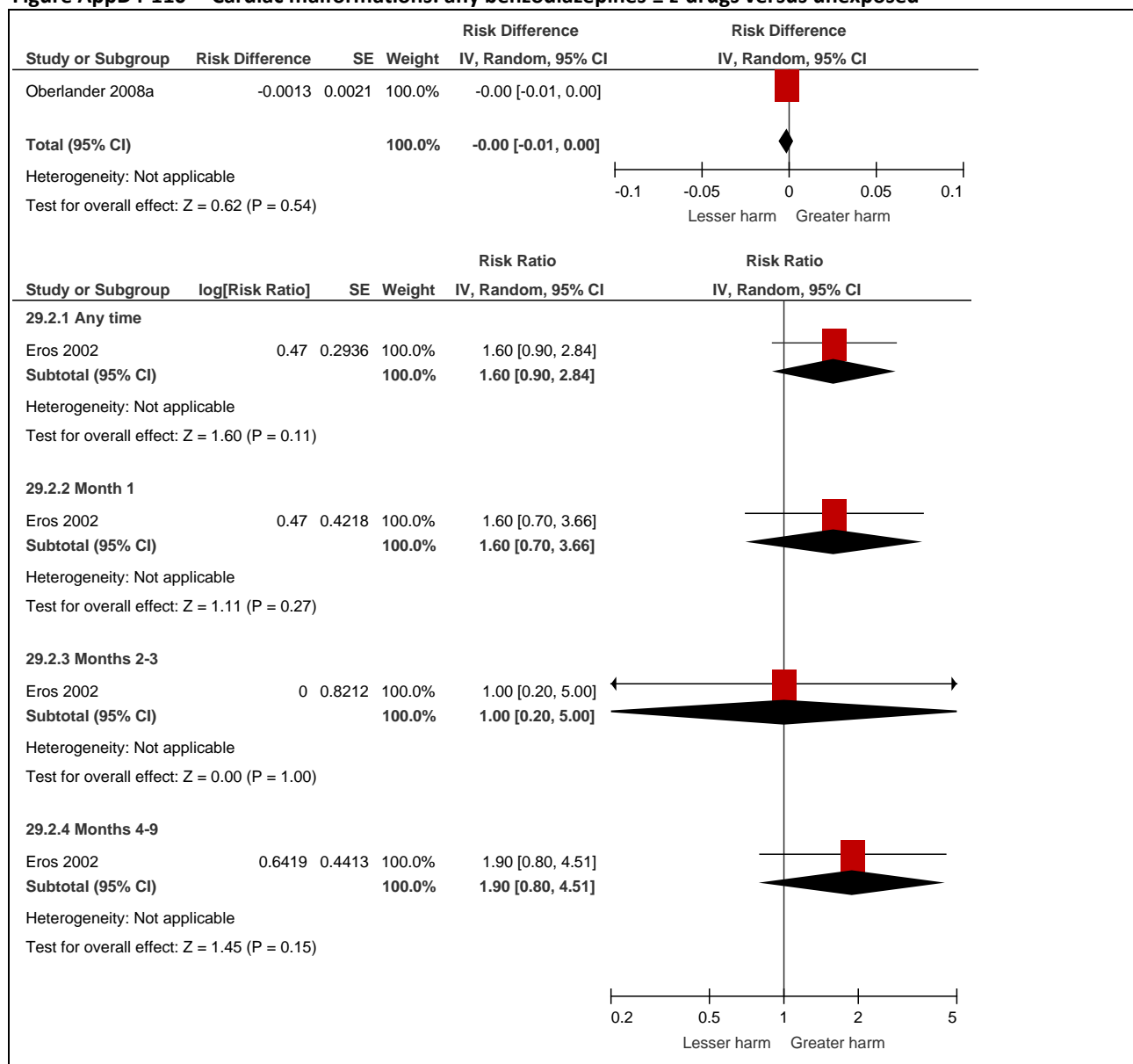
drugs

Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Temazepam						
Ban 2014b <i>Moderate</i>	Heart anomalies	Temazepam (first trimester)	Unexposed - depression or anxiety	1 (cohort)	19,572	OR 1.31 (0.35, 4.92)
Z-drugs						
Wikner 2011 <i>High</i>	Any cardiovascular defect	Z-drugs (any time)	Unexposed - any	1 (cohort)	1,127,075	RR 0.55 (0.27, 1.09)
Zopiclone						
Ban 2014b <i>Moderate</i>	Heart anomalies	Zopiclone (first trimester)	Unexposed - depression or anxiety	1 (cohort)	19,599	OR 2.03 (0.69, 6.02)

Abbreviations: CI, confidence interval; NR, not reported; OR, odds ratio; RD, risk difference; RE, risk estimate; RR, relative risk.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

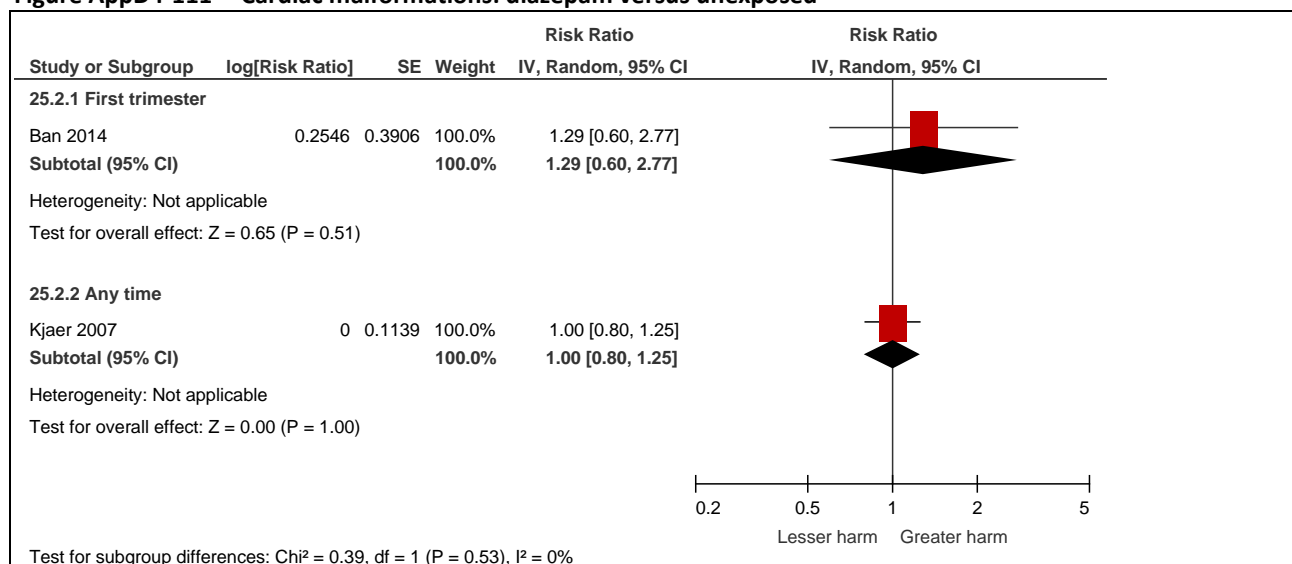
Figure AppD4-110 summarises the findings of the association between exposure to any benzodiazepines and cardiac malformations. Oberlander 2008a examined first-trimester exposure to any benzodiazepines after adjusting for depression in first trimester and found that there was no significant association (RD – 0.0013; 95% CI –0.0055, 0.0029). Eros 2002 examined exposure to any benzodiazepines at different timepoints after adjusting for chronic maternal disorders (which included psychiatric diagnoses) and found no significant association, although the risk estimates were large and the results subject to imprecision (95% CI includes a measure of appreciable benefit and/or harm).

Figure AppD4-110 Cardiac malformations: any benzodiazepines ± z-drugs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

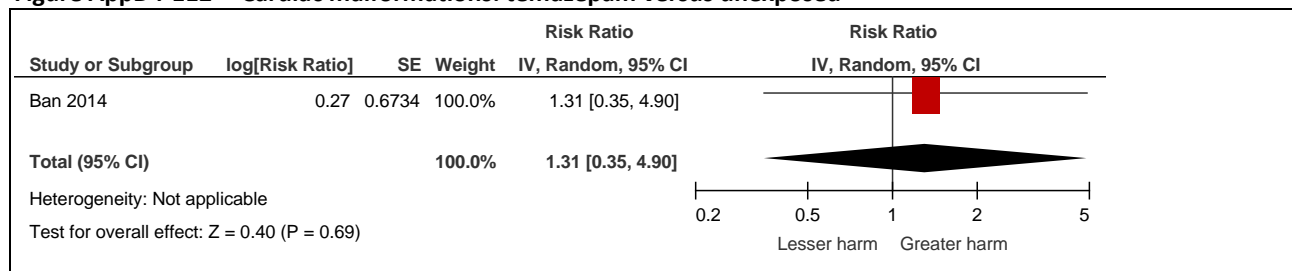
Figure AppD4-111 summarises the findings of the association between diazepam use and cardiac malformations. Ban 2014b examined first-trimester exposure with diazepam and found that there was no significant association (RR 1.29; 95% CI 0.60, 2.77). This result is imprecise because the 95% CI includes a measure of appreciable benefit and harm (RR 0.75/1.25). Kjær 2007 examined exposure to diazepam at any time during pregnancy and cardiac malformation and also found no significant association (RR 1.00; 95% CI 0.80, 1.25).

Figure AppD4-111 Cardiac malformations: diazepam versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-112 summarises the findings of the association between temazepam use and cardiac malformations. Ban 2014b examined first-trimester exposure with diazepam and found that there was no significant association (RR 1.31; 95% CI 0.35, 4.92). This result is imprecise because the 95% CI includes a measure of appreciable benefit and harm (RR 0.75/1.25).

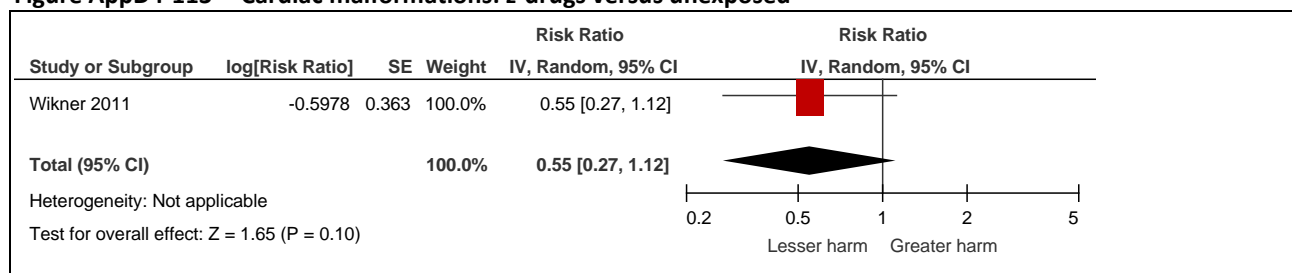
Figure AppD4-112 Cardiac malformations: temazepam versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-113 summarises the findings of the association between exposure to z-drugs as a group and cardiac malformations. Wikner 2011 examined first-trimester exposure with z-drugs⁵³⁹ and found that there was no significant association (RR 0.55; 95% CI 0.27, 1.09). This result is imprecise because the 95% CI includes a measure of appreciable benefit (RR 0.75).

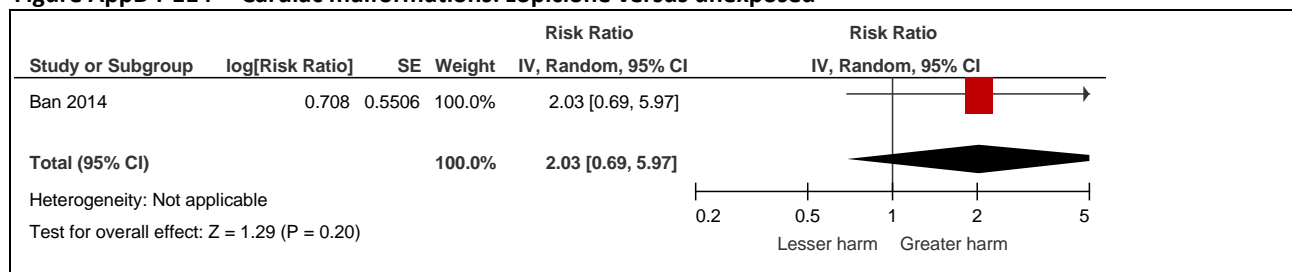
⁵³⁹ Of 1341 infants, 51.6% were exposed to zopiclone, 50.0% were exposed to zolpidem and 2.4% were exposed to zaleplon; 1.9% were exposed to two z-drugs.

Figure AppD4-113 Cardiac malformations: z-drugs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-114 summarises the findings of the association between exposure to zopiclone and cardiac malformations. Ban 2014b examined first-trimester exposure with zopiclone and found that there was no significant association (RR 2.03; 95% CI 0.69, 6.02). This result is imprecise because the 95% CI includes a measure of appreciable benefit and harm (RR 0.75/1.25).

Figure AppD4-114 Cardiac malformations: zopiclone versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.4.5 Septal malformations – benzodiazepines and z-drugs

AppD4.1.4.5.1 Results based on systematic reviews

The result of the analyses of the association between benzodiazepines and septal malformations presented in NICE 2015 is presented in **Table AppD4-69**. It should be noted that this analysis was neither adjusted for potential confounding, nor limited to or adjusted for a mental health disorder. *As no individual studies were identified for this outcome, the results of the NICE 2015 assessment have been included in the in the Evidence Profile Tables in **Section D3.1.4** of the Technical Report.*

Table AppD4-69 Benzodiazepines and/or z-drugs – septal malformation outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any benzodiazepines or z-drugs								
NICE 2015	Septal heart defects	Benzodiazepines	Unexposed - any	1 (cohort) ⁵⁴⁰	108,288	-	OR 1.48 (0.21, 10.65)	NA

Abbreviations: CI, confidence interval; OR, odds ratio; NA, not applicable; RE, risk estimate.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

⁵⁴⁰ Includes Oberlander 2008.

AppD4.1.4.5.2 Results based on individual studies

No individual studies were identified that provided analysis of this outcome, adjusted for potential confounders.

AppD4.1.4.6 Miscarriage – benzodiazepines and z-drugs

AppD4.1.4.6.1 Results based on systematic reviews

The result of the analyses of the association between benzodiazepines and miscarriage presented in NICE 2015 is presented in **Table AppD4-70**. It should be noted that this analysis was neither adjusted for potential confounding, nor limited to or adjusted for a mental health disorder. *As no individual studies were identified for this outcome for benzodiazepines as a class, the results of the NICE 2015 assessment have been included in the Evidence Profile Tables in Section D3.1.4 of the Technical Report.*

Table AppD4-70 Benzodiazepines and/or z-drugs – miscarriage outcomes from systematic reviews

Study ID <i>Additional risk of bias</i>	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any benzodiazepines or z-drugs								
NICE 2015	Miscarriage	Benzodiazepines	Unexposed - any	3 (cohort) ⁵⁴¹	1,204	-	OR 1.83 (1.19, 2.82)	0% (0.95)

Abbreviations: CI, confidence interval; OR, odds ratio; RE, risk estimate.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

AppD4.1.4.6.2 Results based on individual studies

A summary of the results regarding the association between antidepressant use and miscarriage is presented in **Table AppD4-71**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.4** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Based on the findings of the unexposed population in two studies,⁵⁴² the prevalence of miscarriage in a depressed population is estimated to be 8.1%. For this reason, ORs are not be assumed to approximate RRs and the results for studies that report ORs are presented separately.

Table AppD4-71 Benzodiazepines and/or z-drugs – miscarriage outcomes from observational studies

Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) P value
Zopiclone						
Diav-Citrin 1999 <i>Low</i>	Miscarriage	Zopiclone (any time)	Unexposed - any	1 (cohort)	80	NR 17.5% vs. 7.5%; NR

Abbreviations: CI, confidence interval; NR, not reported; OR, odds ratio; RD, risk difference; RE, risk estimate.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

Diav-Citrin 1999 examined exposure to zopiclone at any time during pregnancy and miscarriage and found that more miscarriages occurred in women exposed to zolpidem compared with no exposure; no P value was reported and the analysis was not limited or adjusted for mental health.

⁵⁴¹ Includes Laegreid 1992, Ornoy 1998 and Pastuszak 1996.

⁵⁴² Almeida 2016 and Ban 2012.

AppD4.1.4.7 Preterm birth – benzodiazepines and z-drugs

AppD4.1.4.7.1 Results based on systematic reviews

No SRs were identified that provided analysis of this outcome.

AppD4.1.4.7.2 Results based on individual studies

A summary of the results regarding the association between use of benzodiazepine and/or z-drugs and preterm birth is presented in **Table AppD4-72**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.4** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of preterm birth in the depressed or psychiatric diagnosis/unexposed population (1% for < 32 weeks and 5% for 32-36 weeks),⁵⁴³ it is assumed that the OR approximates the RR, and has been interpreted as such.

Table AppD4-72 Benzodiazepines and/or z-drugs – preterm birth outcomes from observational studies

Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Benzodiazepines ± z-drugs						
Wikner 2007 <i>Low</i>	Preterm birth (< 37 weeks)	Benzodiazepines or z-drugs ⁵⁴⁴ (early exposure)	Unexposed - any	1 (cohort)	42,875	OR 1.48 (1.26, 1.75)
Wikner 2007 <i>Low</i>	Preterm birth (< 37 weeks)	Benzodiazepines or z-drugs ⁵⁴⁵ (late exposure)	Unexposed - any	1 (cohort)	42,875	OR 2.57 (1.92, 3.43)
Wikner 2007 <i>Low</i>	Preterm birth (< 37 weeks)	Benzodiazepines or z-drugs ⁵⁴⁶ - excluding antidepressants (any time)	Unexposed - any	1 (cohort)	NR	OR 1.20 (0.97, 1.50)
Zolpidem						
Wang 2010 <i>Low</i>	Preterm birth	Zolpidem (any time)	Unexposed - any	1 (cohort)	14,982	OR 1.49 (1.28, 1.74)
Wang 2010 <i>Low</i>	Preterm birth	Zolpidem (first trimester)	Unexposed - any	1 (cohort)	13,020	OR 1.48 (1.10, 1.98)
Wang 2010 <i>Low</i>	Preterm birth	Zolpidem (second or third trimester)	Unexposed - any	1 (cohort)	14,447	OR 1.49 (1.26, 1.77)
Wang 2010	Preterm birth	Zolpidem (duration 30-90 days)	Unexposed - any	1 (cohort)	13,946	OR 1.46 (1.20, 1.76)
Wang 2010	Preterm birth	Zolpidem (duration 90-180 days)	Unexposed - any	1 (cohort)	13,016	OR 1.35 (1.00, 1.84)
Wang 2010	Preterm birth	Zolpidem (duration > 180 days)	Unexposed - any	1 (cohort)	12,990	OR 1.74 (1.31, 2.32)
Juric 2009	Preterm birth	Zolpidem and other psychotropic drugs (any time)	Unexposed – exposed to other psychotropic drugs	(cohort)	90	NR 0.18
Zopiclone						
Diav-Citrin 1999 <i>Moderate</i>	Preterm birth (< 37 weeks)	Zopiclone (any time)	Unexposed - any	1 (cohort)	69	NR 21.9% vs. 5.4%; 0.07

Abbreviations: CI, confidence interval; NR, not reported; OR, odds ratio; RE, risk estimate.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

⁵⁴³ Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

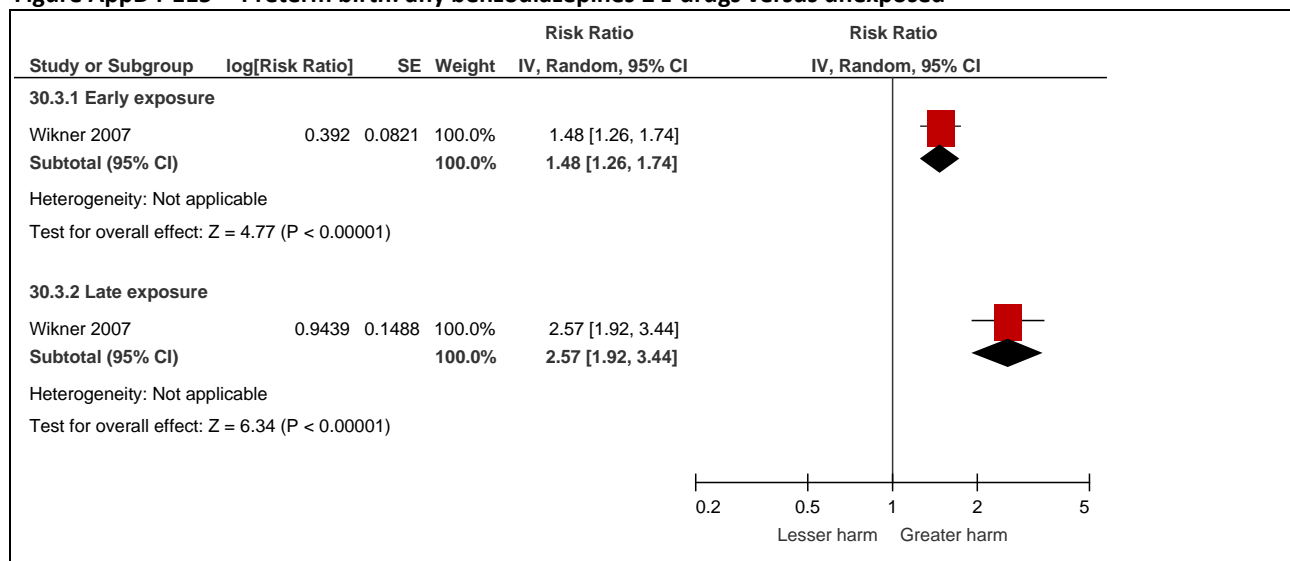
⁵⁴⁴ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs.

⁵⁴⁵ Of the 415 infant exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

⁵⁴⁶ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs. Of the 415 exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

Figure AppD4-115 summarises the findings of the association between exposure to benzodiazepines or z-drugs and preterm birth. Wikner 2007 examined the association between exposure to benzodiazepines or z-drugs during early of late pregnancy with no limiting/adjustment for mental health and found a strong association for both time periods.

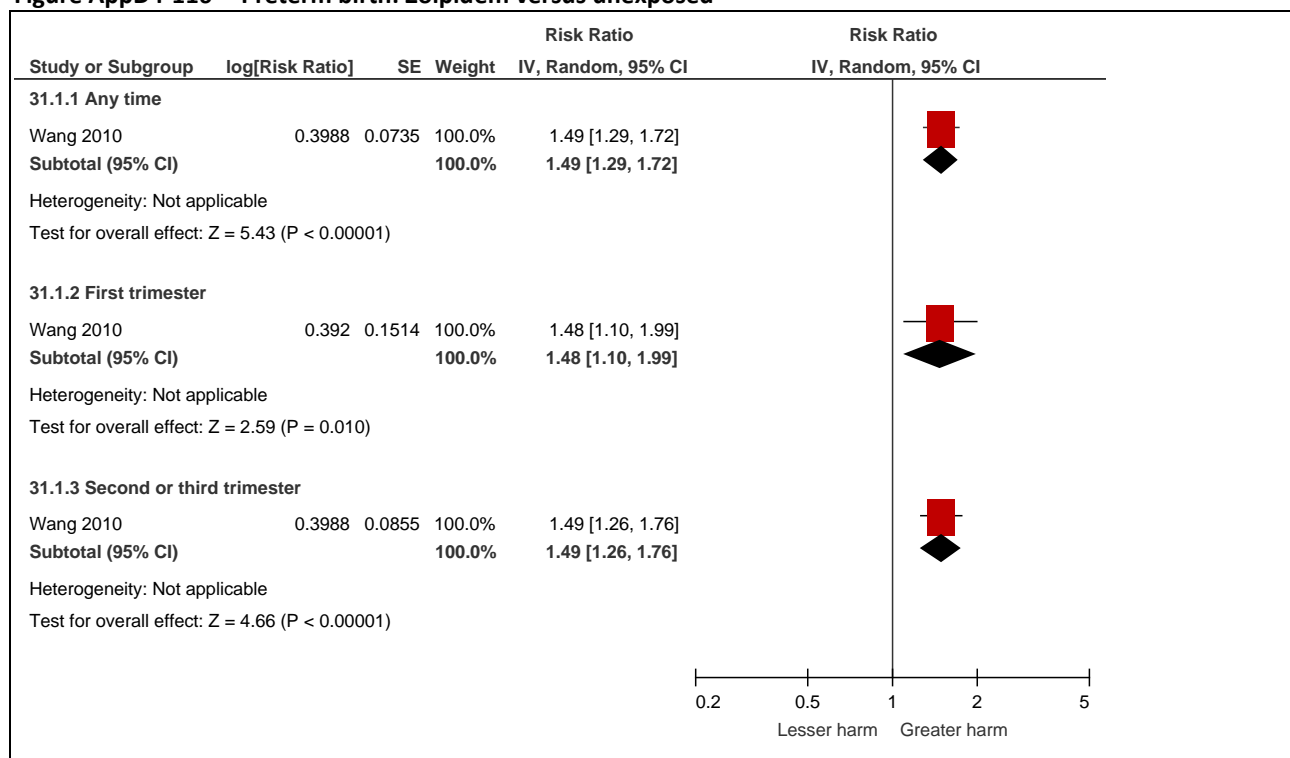
Figure AppD4-115 Preterm birth: any benzodiazepines ± z-drugs versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-116 summarises the findings of the association between exposure to zolpidem and preterm birth. Wang 2010 examined the association between exposure to zolpidem during the first trimester, second or third trimester, or at any time during pregnancy with no limiting/adjustment for mental health and found a strong association in all analyses. Similar results were seen when analysed by increasing duration of exposure.

Figure AppD4-116 Preterm birth: Zolpidem versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Juric 2009 also examined exposure to zolpidem at any time during pregnancy and in a population matched on various characteristics (including use of other psychotropic drugs) and found no association with preterm birth (P=0.18).

Diav-Citrin 1999 examined exposure to zopiclone at any time during pregnancy and preterm birth and found that preterm birth occurred in women exposed to zolpidem compared with no exposure (22% versus 5%; P=0.07). This analysis was not limited or adjusted for mental health.

AppD4.1.4.8 Small for gestational age – benzodiazepines and z-drugs

AppD4.1.4.8.1 Results based on systematic reviews

There were no included SRs that examined the association between use of benzodiazepines and/or z-drugs during pregnancy and being small for gestational age.

AppD4.1.4.8.2 Results based on individual studies

A summary of the results regarding the association between use of benzodiazepine and/or z-drugs and being small for gestational age is presented in **Table AppD4-73**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.4** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

The prevalence of being small for gestational age in the psychiatric diagnosis/unexposed population differed substantially between the two main studies included in the assessment of antidepressants (2.5% and 13.0% for Malm 2015 and Grzeskowiak 2012, respectively). As such, the assumption that the OR approximates the RR is uncertain.

Table AppD4-73 Benzodiazepines and/or z-drugs – small for gestational age from observational studies

Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Benzodiazepines ± z-drugs						
Wikner 2007 <i>Moderate</i>	Small for gestational age (< -2 SDs)	Benzodiazepines or z-drugs ⁵⁴⁷ (early exposure)	Unexposed - any	1 (cohort)	18,260	OR 1.12 (0.87, 1.44)
Wikner 2007 <i>Moderate</i>	Small for gestational age (< -2 SDs)	Benzodiazepines or z-drugs ⁵⁴⁸ (late exposure)	Unexposed - any	1 (cohort)	18,260	OR 1.39 (0.80, 2.40)
Zolpidem						
Wang 2010 <i>Low</i>	Small for gestational age (< 10 th percentile)	Zolpidem (any time)	Unexposed - any	1 (cohort)	14,982	OR 1.34 (1.20, 1.49)
Wang 2010 <i>Low</i>	Small for gestational age (< 10 th percentile)	Zolpidem (first trimester)	Unexposed - any	1 (cohort)	13,020	OR 1.36 (1.09, 1.69)
Wang 2010 <i>Low</i>	Small for gestational age (< 10 th percentile)	Zolpidem (second or third trimester)	Unexposed - any	1 (cohort)	14,447	OR 1.33 (1.18, 1.50)
Wang 2010	Small for gestational age (< 10 th percentile)	Zolpidem (duration 30-90 days)	Unexposed - any	1 (cohort)	13,946	OR 1.21 (1.05, 1.40)
Wang 2010	Small for gestational age (< 10 th percentile)	Zolpidem (duration 90-180 days)	Unexposed - any	1 (cohort)	13,016	OR 1.57 (1.27, 1.94)
Wang 2010	Small for gestational age (< 10 th percentile)	Zolpidem (duration > 180 days)	Unexposed - any	1 (cohort)	12,990	OR 1.48 (1.19, 1.85)
Zopiclone						
Diav-Citrin 1999 <i>Moderate</i>	Small for gestational age (<3 rd percentile)	Zopiclone (any time)	Unexposed - any	1 (cohort)	68	NR 6.3% vs. 5.6%; NR

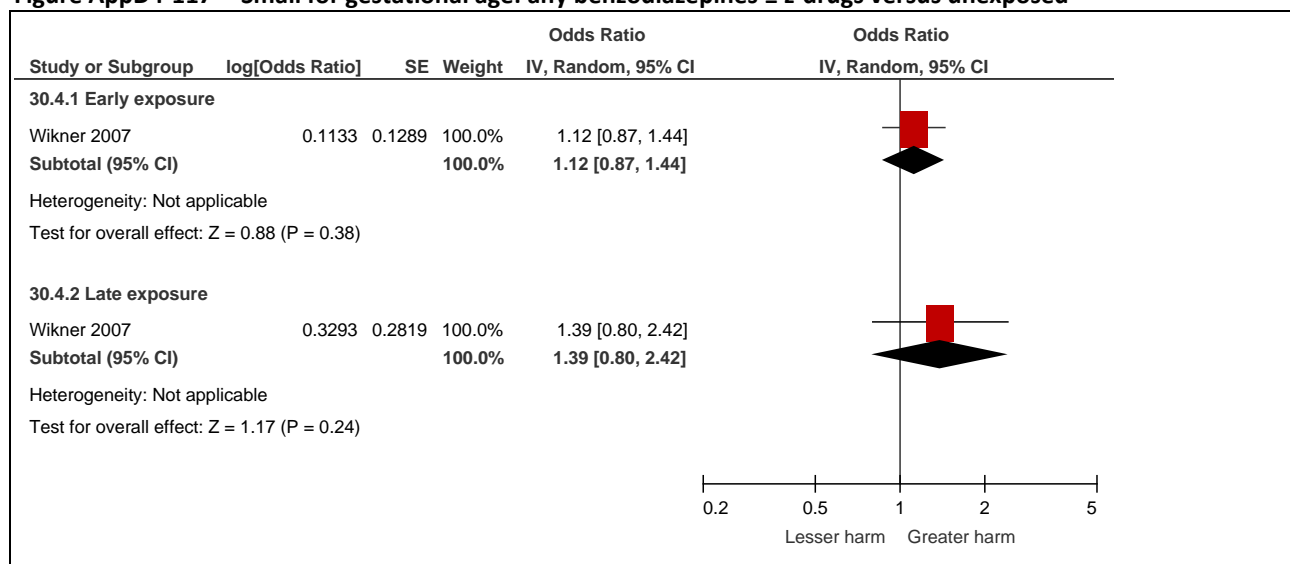
Abbreviations: CI, confidence interval; OR, odds ratio; NR, not reported; RE, risk estimate; SD, standard deviation.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

Figure AppD4-117 summarises the findings of the association between exposure to benzodiazepines or z-drugs and being small for gestational age. Wikner 2007 examined the association between exposure to benzodiazepines or z-drugs during early (OR 1.12; 95% CI 0.87, 1.44) or late pregnancy (OR 1.39; 95% CI 0.80, 2.40) with no limiting/adjustment for mental health and found no significant association for both periods; however, both findings were subject to imprecision because the 95% CI included measures of appreciable benefit and/or harm (RR 0.75/1.25).

⁵⁴⁷ Of the 2169 infants exposed in early pregnancy, 72.3% were exposed to benzodiazepines and 27.7% were exposed to z-drugs.

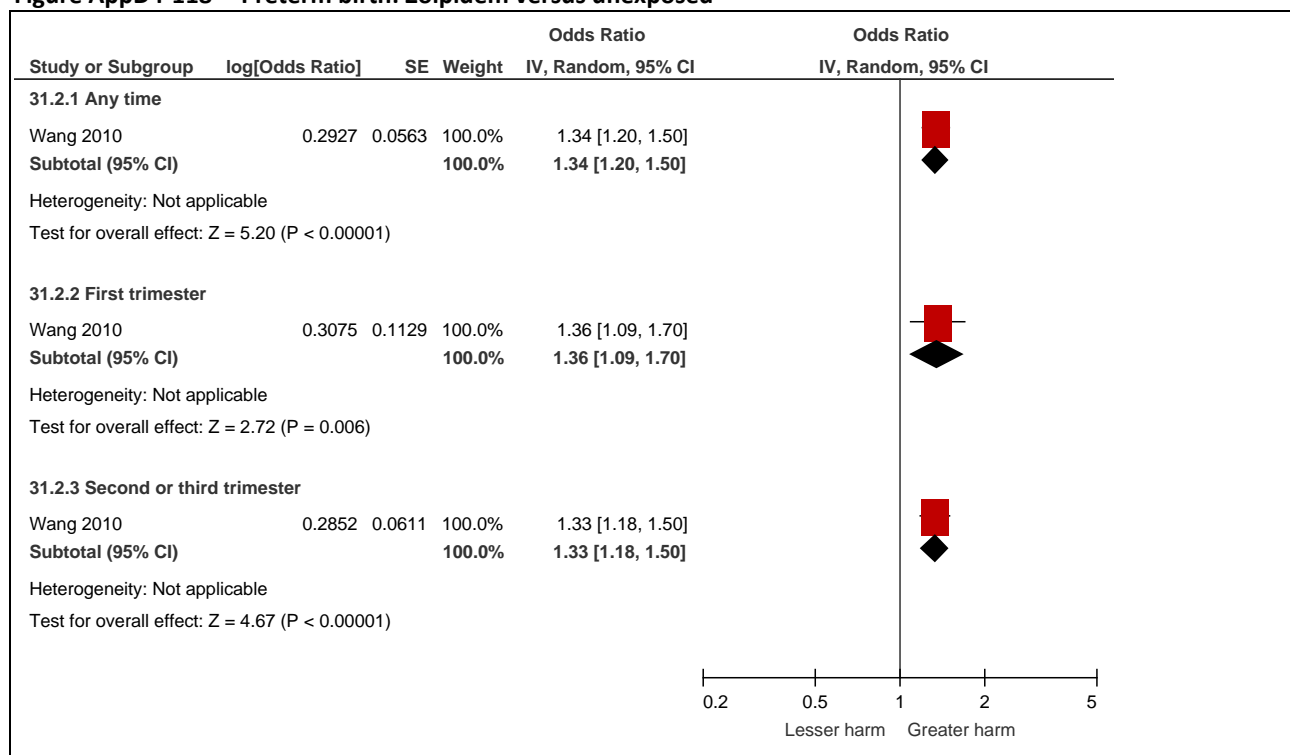
⁵⁴⁸ Of the 415 infants exposed in late pregnancy, 82.2% were exposed to benzodiazepines and 17.8% were exposed to z-drugs.

Figure AppD4-117 Small for gestational age: any benzodiazepines ± z-drugs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Figure AppD4-118 summarises the findings of the association between exposure to zolpidem and being small for gestational age. Wang 2010 examined the association between exposure to zolpidem during the first trimester, second or third trimester, or at any time during pregnancy with no limiting/adjustment for mental health and found a strong association in all analyses. Similar results were seen when analysed by increasing duration of exposure.

Figure AppD4-118 Preterm birth: Zolpidem versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Diav-Citrin 1999 examined the association between exposure to zopiclone at any time during pregnancy and being small for gestational age in a matched population. Similar proportions of neonates were

considered small for gestational age in the exposed and unexposed groups (6.3% versus 5.6%, respectively); however, no risk estimate or P value is provided.

AppD4.1.4.9 Respiratory distress – benzodiazepines and z-drugs

AppD4.1.4.9.1 Results based on systematic reviews

The results of the analysis of the association between benzodiazepines and respiratory distress presented in NICE 2015 is presented in **Table AppD4-74**. It should be noted that these analyses were neither adjusted for potential confounding, nor limited to or adjusted for a mental health disorder. *As such, these findings will not be used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-74 Benzodiazepines and/or z-drugs – respiratory distress outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
Any benzodiazepines or z-drugs								
NICE 2015	Respiratory disorder	Benzodiazepines	Unexposed - any	2 (cohort) ⁵⁴⁹	875,904	-	OR 1.26 (1.04, 1.52)	0.39 (0%)

Abbreviations: CI, confidence interval; OR, odds ratio; NA, not applicable; RE, risk estimate.

AppD4.1.4.9.2 Results based on individual studies

A summary of the results regarding the association between use of benzodiazepine and/or z-drugs and respiratory distress is presented in **Table AppD4-75**.

Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.4** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Due to the low prevalence of respiratory distress in the depressed/unexposed population (3.2% in Malm 2015), it is assumed that the OR approximates the RR, and has been interpreted as such.

Table AppD4-75 Benzodiazepines and/or z-drugs – respiratory distress outcomes from observational studies

Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Benzodiazepines ± z-drugs						
Wikner 2007 <i>Low</i>	Respiratory problems	Benzodiazepines or z-drugs ⁵⁵⁰ (early exposure)	Unexposed - any	(cohort)	38,638	OR 1.19 (0.98, 1.45)
Wikner 2007 <i>Low</i>	Respiratory problems	Benzodiazepines or z-drugs ⁵⁵¹ (late exposure)	Unexposed - any	(cohort)	38,638	OR 2.21 (1.62, 3.02)
Wikner 2007 <i>Low</i>	Respiratory difficulty	Benzodiazepines or z-drugs ⁵⁵² - excluding antidepressants (any time)	Unexposed - any	(cohort)	NR	OR 1.12 (0.88, 1.43)

⁵⁴⁹ Includes Laegreid 1992 and Wikner 2007.

⁵⁵⁰ Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs.

⁵⁵¹ Of the 415 infant exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

⁵⁵² Of the 2169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs. Of the 415 exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.

drugs

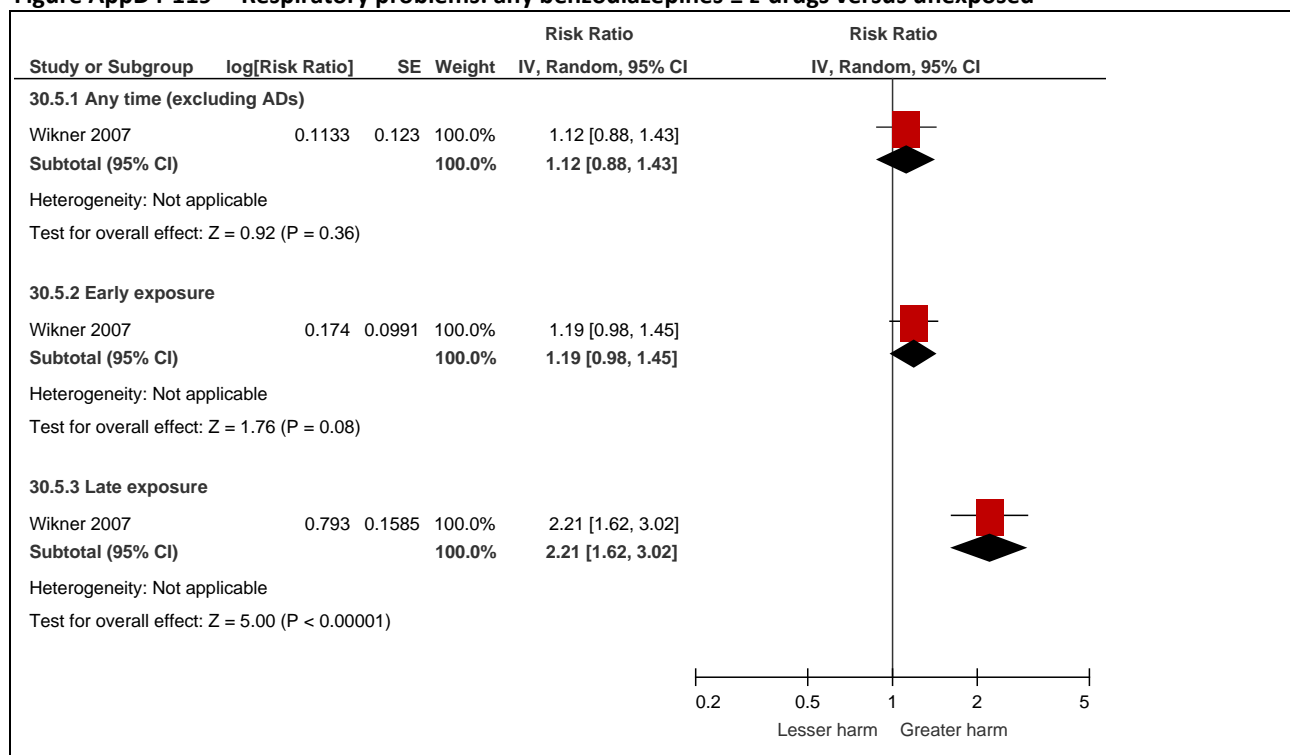
Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Zolpidem						
Juric 2009 <i>Low</i>	Respiratory difficulty	Zolpidem and other psychotropic drugs (any time)	Unexposed – exposed to other psychotropic drugs	1 (cohort)	90	NR 0.49

Abbreviations: CI, confidence interval; NR, not reported; OR, odds ratio; RE, risk estimate.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

Figure AppD4-117 summarises the findings of the association between exposure to benzodiazepines or z-drugs and respiratory problems. Wikner 2007 examined the association between exposure to benzodiazepines or z-drugs during early (OR 1.19; 95% CI 0.98, 1.45) or late pregnancy (OR 2.21; 95% CI 1.62, 3.02) with no limiting/adjustment for mental health or other treatments and found a significant association only for the late pregnancy period. The finding for early pregnancy is subject to imprecision because the 95% CI includes a measure of appreciable harm (RR 1.25). An analysis for exposure at any time during pregnancy that excludes infants exposed to antidepressants was also conducted; this showed no significant association (OR 1.12; 95% CI 0.88, 1.43), although it is also imprecise.

Figure AppD4-119 Respiratory problems: any benzodiazepines ± z-drugs versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

Juric 2009 examined the association between exposure to zolpidem at any time during pregnancy in a population matched on various characteristics (including use of other psychotropic drugs) and found no association with respiratory difficulty (P=0.18).

AppD4.1.4.10 Convulsions – benzodiazepines and z-drugs

AppD4.1.4.10.1 Results based on systematic reviews

There were no included SRs that examined the association between use of benzodiazepines and/or z-drugs during pregnancy and neonatal convulsions.

AppD4.1.4.10.2 Results based on individual studies

A summary of the results regarding the association between use of benzodiazepine and/or z-drugs and neonatal convulsions is presented in **Table AppD4-76**. Studies shown in grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.4** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

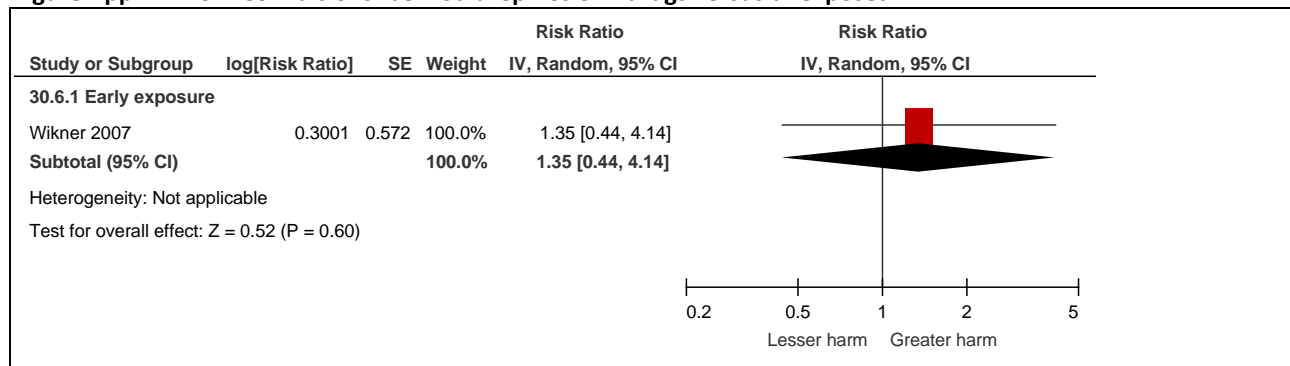
Table AppD4-76 Benzodiazepines and/or z-drugs – convulsions outcomes from observational studies

Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Benzodiazepines or z-drugs						
Wikner 2007 <i>Moderate</i>	Neonatal convulsions	Benzodiazepines or z-drugs ⁵⁵³ (early exposure)	Unexposed - any	(cohort)	1,386	RR 1.35 (0.44, 3.15) ⁵⁵⁴

Abbreviations: CI, confidence interval; RE, risk estimate; RR, relative risk.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

Figure AppD4-120 summarises the findings of the association between exposure to benzodiazepines or z-drugs and neonatal convulsions. Wikner 2007 examined the association between exposure to benzodiazepines or z-drugs during early pregnancy with no limiting/adjustment for mental health and found no association (RR 1.35; 95% CI 0.44, 3.15); however, this finding is subject to imprecision because the 95% CI includes measures of appreciable benefit and harm (RR 0.75/1.25). There was insufficient data available to examine the association between late exposure and convulsions.

Figure AppD4-120 Convulsions: benzodiazepines or z-drugs versus unexposed

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ slightly from that presented in the table due to rounding while calculating the estimate in Review Manager.

AppD4.1.4.11 Language competence – benzodiazepines and z-drugs

AppD4.1.4.11.1 Results based on systematic reviews

There were no included SRs that examined the association between use of benzodiazepines and/or z-drugs during pregnancy and language competence in the child.

AppD4.1.4.11.2 Results based on individual studies

A summary of the results regarding the association between use of benzodiazepine and/or z-drugs and language competence is presented in **Table AppD4-77**. Studies shown in grey shading represent primary

⁵⁵³ Of the 2,169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs.

⁵⁵⁴ When the expected number of a specific outcome was low (<10), a risk ratio was instead determined as the ratio between the observed and expected numbers. The 95%CI was then based on exact Poisson distributions.

evidence and are included in the individual/pooled analyses presented in the Evidence Profile Tables in **Section D3.1.4** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-77 Benzodiazepines and/or z-drugs – language competence outcomes from observational studies

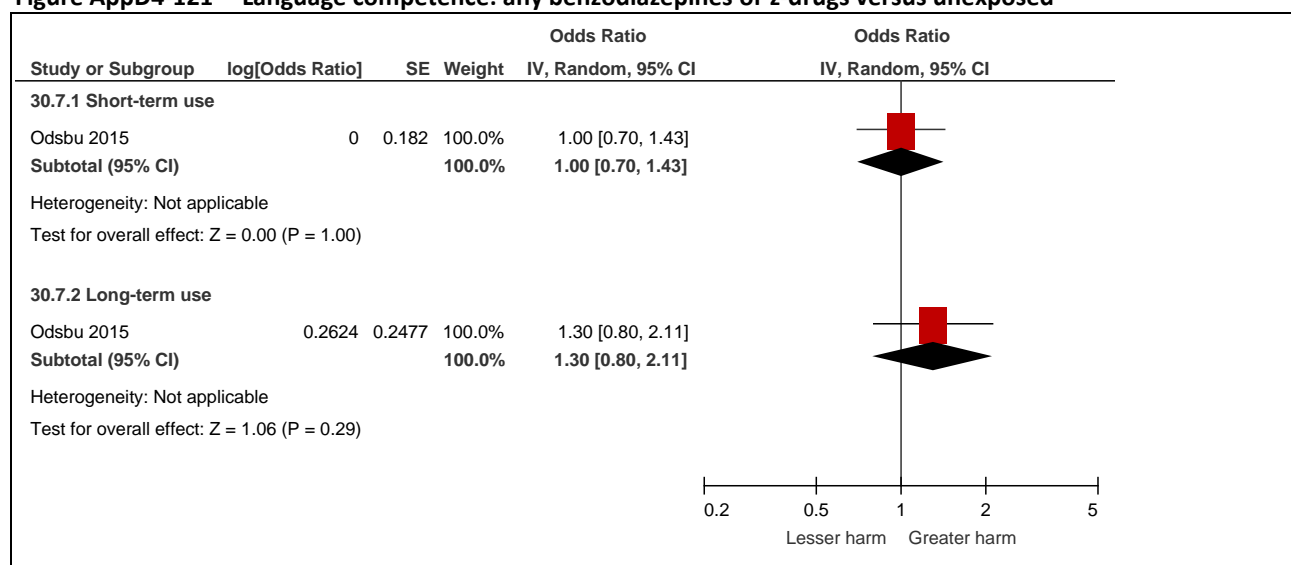
Study ID <i>Additional risk of bias</i>	Outcome	Exposure (timing)	Comparator population	# studies (type)	N	Adjusted RE (95% CI) <i>P value</i>
Benzodiazepines or z-drugs						
Odsbu 2015 <i>Moderate</i>	Lower language competence ⁵⁵⁵ (3 years)	Benzodiazepines or z-drugs (short-term use) ^{556,557}	Unexposed – adjusted for depression and anxiety	1 (cohort)	Exposed: 316 Unexposed: 51,095	OR 1.0 (0.7, 1.3)
Odsbu 2015 <i>Moderate</i>	Lower language competence ⁵⁵⁵ (3 years)	Benzodiazepines or z-drugs (long-term use) ^{556,558}	Unexposed – adjusted for depression and anxiety	1 (cohort)	Exposed: 79 Unexposed: 51,095	OR 1.3 (0.8, 2.3)

Abbreviations: CI, confidence interval; OR, odds ratio; RE, risk estimate.

Note: Data shown in dark grey shading represent primary evidence and are included in the individual/pooled analyses presented in the Evidence Profile tables in **Section AppD3.1.4** of the Technical Report.

Figure AppD4-121 summarises the findings of the association between exposure to benzodiazepines or z-drugs and language competence. Odsbu 2015 examined the association between exposure to benzodiazepines or z-drugs during pregnancy after adjusting for SSRI use, anxiety, depression during pregnancy and depression before pregnancy, and found no association with short-term use (OR 1.0; 95% CI 0.7, 1.3) or long-term use (OR 1.3; 95% CI 0.8, 2.3).

Figure AppD4-121 Language competence: any benzodiazepines or z-drugs versus unexposed



Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

Note: The upper 95% CI may differ from that presented in the table due to rounding while calculating the estimate in Review Manager.

⁵⁵⁵ Validated language grammar rating scale: (1) not yet talking, (2) talking, but unintelligible, (3) talking in one-word utterances, such as “milk” or “down”, (4) talking in 2-3 word phrases, such as “met got ball” or “give doll”, (5) talking in fairly complete sentences, such as “I got a doll” or “can I go outside?” and (6) talking in long and complicated sentences, such as “when I went to the park, I went on the swings” or “I saw a man standing on the corner”. Categories one and two were combined due to low numbers. The interpretation of the odds ratio is the change in the odds of being in a lower category of the language grammar rating scale regardless of how the outcome has been dichotomised.

⁵⁵⁶ Of the 422 exposed women, 56.6% used benzodiazepines and 43.4% used z-drugs.

⁵⁵⁷ Woman reported use on one questionnaire during pregnancy only. Women answered three questionnaires during pregnancy.

⁵⁵⁸ Woman reported use on more than one questionnaire during pregnancy. Women answered three questionnaires during pregnancy.

AppD4.1.5 Lithium

AppD4.1.5.1 Included systematic reviews – lithium

One SR was identified that provided evidence relating to the assessment of lithium harms. A summary of the characteristics of the identified SR is presented in **Table AppD4-78**.

Table AppD4-78 Characteristics of the included systematic reviews of lithium harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
NICE 2015	SR/MA 6 observational studies	Pregnant women	Lithium	Unexposed – any	Congenital malformations Heart defects Ebstein's anomaly Course of pregnancy, obstetric and neonatal complications ⁵⁵⁹ Neurodevelopmental outcomes ⁹⁹

Note: Outcomes shown in bold are those included in the Summary of Findings tables.

Abbreviations: MA, meta-analysis; SR, systematic review.

AppD4.1.5.2 Included individual studies – lithium

Eight studies were identified that provided evidence relating to the assessment of lithium harms. A summary of the characteristics of the identified studies is presented in **Table AppD4-79**.

Table AppD4-79 Characteristics of the included comparative observational studies of lithium harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes [outcomes not in PICO]
Diav-Citrin 2014	Prospective cohort Israeli Teratology Information Service (ITIS) Israel 1994–2010 Also included data from two additional services: ⁵⁶⁰ MotherSafe (Australia) 2000–2011 Motherisk Program (Canada) 2001–2005	Women contacting the ITIS in regard to gestational exposure to lithium ⁵⁶¹ (N = 183)	Lithium	Two comparator groups: Pregnant women (randomly selected from ITIS) with exposures known not to be teratogenic Pregnant women with bipolar disorder who were unexposed to lithium (untreated or treated with other medications)	Major anomalies ⁵⁶² (major anomalies without chromosomal or genetic conditions, cardiovascular anomalies ⁵⁶³ , cardiovascular anomalies excluding resolved cases, non-cardiovascular anomalies, Ebstein's anomaly) Miscarriage Stillbirth Preterm delivery (<37 weeks) [live births, elective terminations, ectopic pregnancy, gestational age at delivery, birthweight]

⁵⁵⁹ NICE 2015 noted insufficient evidence relating to lithium for neurodevelopmental outcomes, and outcomes relating to course of pregnancy, obstetric and neonatal complications.

⁵⁶⁰ According to the publication, the three participating centers are members of the Organization of Teratology Information Specialists, an organisation of counseling services pertaining to environmental exposures during pregnancy, and use similar methodologies. Data from Australia and Canada were included to increase the power of the study.

⁵⁶¹ The reported indications for treatment with lithium were as follows: bipolar disorder (65.9%), depression (16.7%), schizoaffective disorder (6.8%), schizophrenia (3.8%), mania (1.5%), and psychosis (2.2%). Concurrent psychiatric medications were taken by 66.1% of women in the cohort.

⁵⁶² Defined as structural anomalies in the offspring that have serious medical, surgical or cosmetic consequences. Significant neurodevelopmental or functional problems were also considered to be major anomalies, even in the absence of a structural anomaly, when they required special education or interventions. Mild hypospadias not requiring an intervention and functional problems without any morphological changes, or complications of preterm delivery were not considered to be major anomalies. The analysis of major congenital anomalies was performed in all live-born infants, as well as in stillbirths and in elective terminations of pregnancy as a result of prenatally diagnosed anomalies.

⁵⁶³ Such as septal defects

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes [outcomes not in PICO]
Källén 2013	Retrospective, linked, population-based cohort of live births. Medical Birth Register, Register of Birth Defects, Hospital Discharge Register, Register of Prescribed Drugs Sweden 1996–2011	Live-birth infants of mothers reporting use of antipsychotics (neuroleptics) during early pregnancy, or dispensed drug in later pregnancy (N = 1,575,847)	Antipsychotics or lithium ⁵⁶⁴	Unexposed	Relatively severe malformations (may include malformations not strictly classifiable as major ⁵⁶⁵) ⁵⁶⁶ Cardiac malformations Preterm birth <37 weeks, Small for gestational age Respiratory diagnosis [abruption of placenta, haemorrhage around delivery, large for gestational age, induction of delivery, low birth weight any neonatal diagnosis, hypoglycaemia, jaundice, CNS diagnoses, low 5 min Apgar score]
Reis 2008	Retrospective linked, population-based cohort Swedish Medical Birth Register, Register of Congenital Malformations, Hospital Discharge Register Sweden 1995–2005	Infants (or stillborns) of mothers reporting use of antipsychotics in early pregnancy. (N=958,729 women; 973,767 infants)	Antipsychotics, including lithium ⁵⁶⁷	Unexposed	Congenital malformations ⁵⁶⁸ Stillbirth Preterm birth (<37 weeks), singletons Small for gestational age or large for gestational age [low/high birth weight]
Troyer 1993 ⁵⁶⁹	Retrospective cohort Record linkage of discharge diagnosis and a medical birth registry Sweden 1973-1979	Women who were manic-depressive inpatients and delivered a child in the same year (N=350)	Lithium (first trimester)	Unexposed (to lithium) – manic depression	Preterm delivery (<38 weeks) Large for gestational age

⁵⁶⁴ For most outcomes data are aggregated for antipsychotics and lithium (17% of infants exposed to lithium).

⁵⁶⁵ Excludes the following common and clinically little important conditions: preauricular appendices, tongue tie, patent ductus at preterm birth, single umbilical artery, undescended testicle, unstable hip or hip (sub)luxation, and nevus. Unclear whether included malformations are classifiable as major.

⁵⁶⁶ Data specifically relating to lithium is only available for the relatively severe malformations outcome. For all other outcomes, no data were available for lithium.

⁵⁶⁷ Women using lithium were treated separately in the publication and presented at the end of the Results section as a Note regarding lithium exposure.

⁵⁶⁸ Congenital malformations was the only outcome reported in relation to lithium exposure.

⁵⁶⁹ Troyer 1993 and Kallen 1983 appear to include the same cohort of women, but report different outcomes.

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes [outcomes not in PICO]
Jacobson 1992	Prospective cohort Four teratogen information services: Motherisk (Toronto); the California Teratogen Information Service (CTIS) (San Diego); Philadelphia Pregnancy Helpline; Foetal Risk Assessment from Maternal Exposure (FRAME) (Ontario) United States and Canada Program initiation until Feb 1991 ⁵⁷⁰	Women who consulted one of four teratogen information centres to obtain information about the potential risks of therapeutic drugs (lithium) during pregnancy (N=148)	Lithium (first trimester) ⁵⁷¹	Unexposed (to lithium or another teratogen) ⁵⁷²	Congenital malformations (major anomaly) ⁵⁷³ Cardiac malformations Ebstein's anomaly [normal live births, ectopic pregnancy, birthweight, gestational age at birth]
Czeizel 1990	Retrospective case control Hungarian Case-Control Surveillance of Congenital Anomalies (HCCSCA) Hungary 1980-1987	<u>Cases</u> Notified cases of congenital anomalies ⁵⁷⁴ (still- and live-born) diagnosed from birth till the age of one (N=10,698) <u>Controls</u> Newborns without congenital anomalies, matched to every index patient according to sex, birth week, and district of parents' residence (N=21,546)	Lithium	Unexposed (to lithium)	Congenital anomalies (major isolated congenital anomalies and unidentified multiple congenital anomalies)
Källén 1983	Retrospective cohort Record linkage using Discharge Registry for Inpatient Psychiatric Wards (DRPW), Medical Birth Registry (MBR) and Registry of Congenital Malformations (RCM) Sweden 1973-1979	Infants born to women who had been treated as inpatients for manic- depressive disease, identified from central registries and information from hospital charts (N=121)	Lithium	Unexposed – manic depression	Congenital malformations (relatively severe) ⁵⁷⁵ Heart defects Neonatal deaths

⁵⁷⁰ Program initiation for each service: CTIS 1979, Philadelphia Pregnancy Healthline 1984, Motherisk 1985, FRAME 1989.

⁵⁷¹ An unknown proportion were also exposed to other drugs during the first trimester, such as carbamazepine, fluoxetine, trazodone, and L-thyroxine.

⁵⁷² Controls were women who were seen at the Motherisk clinic for counselling about drugs that are not known or suspected to be teratogenic. Each study patient was matched with a woman of similar age (to within 2 years).

⁵⁷³ Defined as an anomaly that has an adverse effect on either the function or social acceptability of the individual.

⁵⁷⁴ Excluded: mild congenital anomalies such as congenital dislocation of hip, congenital inguinal hernia, hemangiomas, etc.; minor variants; and congenital anomaly syndromes of known origin.

⁵⁷⁵ Subluxation of the hip, retention testis, and hydrocele testis are provided in the publication as examples of malformations that are not registered (i.e. not classified as relatively severe).

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes [outcomes not in PICO]
Schou 1976	Retrospective case control Scandinavian Register of Lithium Babies Scandinavia 1968-1976	<u>Cases</u> Babies exposed to lithium during pregnancy who had been born without malformations and had reached the age of five years or older (N=67) <u>Controls</u> Siblings not exposed to lithium during pregnancy (N=57)	Lithium	Unexposed siblings	Developmental anomalies ⁵⁷⁶

Note: Outcomes shown in bold are those included in the Summary of Findings tables.

Abbreviations: CNS, central nervous system; ITIS, Israeli Teratology Information Service; PICO, Population, Intervention, Comparator, Outcome.

AppD4.1.5.3 Major malformations – lithium

AppD4.1.5.3.1 Results based on systematic reviews

The results of the analyses of the association between lithium and major congenital malformations from the NICE 2015 SR is presented in Table AppD4-80. NICE 2015 did not differentiate between congenital malformations and major malformations.

It should be noted that one of the NICE 2015 analyses was limited to women with a psychiatric diagnosis (one study included women with bipolar disorder and the other included women with manic depression); however, none of the analyses were adjusted for other potential confounders.

As unadjusted results were used in these analyses, these findings have not been used to generate recommendations and an examination of the results of individual studies has been undertaken.

Table AppD4-80 Lithium – major congenital malformation outcomes from systematic reviews

Study ID	Outcome	Exposure	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
NICE 2015	Congenital malformations	Lithium	Unexposed – any	4 (cohort) ⁵⁷⁷	974,914	-	OR 2.10 (1.21, 3.64)	0.65 (0%)
NICE 2015	Congenital malformations	Lithium	Unexposed – psychiatric diagnosis	2 (cohort) ⁵⁷⁸	782	-	OR 2.12 (0.80, 5.61)	0.36 (0%)
NICE 2015	Congenital malformations	Lithium	Unexposed – any	1 (CC) ⁵⁷⁹	33,244	-	OR 2.21 (0.67, 7.25)	NA

Abbreviations: CC, case control; CI, confidence interval; OR, odds ratio; NA, not applicable; RE, risk estimate; SR, systematic review.

AppD4.1.5.3.2 Results based on individual studies

A summary of the results regarding the association between lithium use and major malformations is presented in Table AppD4-81. Data from the study by Reis 2008 is not included because all recorded malformations in the lithium-exposed group were not considered to be major. Only one of the included studies adjusted for potential confounders (Källén 2013) and two studies included a comparator population with a psychiatric diagnosis (Diav-Citrin 2014; Källén 1983). The studies shown in grey shading represent

⁵⁷⁶ Based on response letters and questionnaires from psychiatrists or general practitioners who had originally reported the children. No validated tools were used.

⁵⁷⁷ Bodén 2012a; Reis 2008; Kallen 1993; Jacobson 1992

⁵⁷⁸ Bodén 2012a; Kallen 1983

⁵⁷⁹ Czeizel 1990

primary evidence and are included in the individual analyses presented in the Evidence Profile table in **Section D3.1.5** of the Technical Report. Full quality assessment is limited to the primary evidence shaded below.

Table AppD4-81 Lithium – major malformation outcomes from observational studies

Study ID	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; <i>P</i> value
Unexposed comparator						
Diav-Citrin 2014	Major anomalies	Lithium ⁵⁸⁰	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 140 Unexposed: 711	5.7% vs. 3.4% <i>P</i> =NS
Diav-Citrin 2014	Major anomalies without chromosomal or genetic conditions	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 Unexposed: 711	6.5% vs. 2.7% <i>P</i> =NS
Diav-Citrin 2014 [multicentre data ⁵⁸¹]	Major anomalies without chromosomal or genetic conditions	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 152 Unexposed: 842	8.6% vs. 2.5% <i>P</i>=0.001
Diav-Citrin 2014	Non-cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 Unexposed: 711	4.1% vs. 2.1% <i>P</i> =NS
Diav-Citrin 2014 [multicentre data ⁵⁸¹]	Non-cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 152 Unexposed: 842	5.9% vs. 2.0% <i>P</i>=0.011
Källén 2013	Relatively severe malformations	Lithium (early)	Unexposed	Retrospective cohort	Infants exposed: 234 Total: 1,575,847	Adjusted ⁵⁸² RR 1.09 (0.52, 2.00)
Jacobson 1992	Major congenital malformations ⁵⁸³	Lithium (first trimester)	Unexposed (to lithium)	Prospective cohort	Exposed: NR Unexposed: NR	Unadjusted RR 1.5 (0.4, 6.7)
Czeizel 1990	Major congenital anomalies ⁵⁸⁴	Lithium	Unexposed	Retrospective case control	Exposed: 11 Unexposed: 32,244	54.5% vs. 36.3% <i>P</i> value NR
Psychiatric diagnosis comparator						
Diav-Citrin 2014	Major anomalies	Lithium ⁵⁸⁰	Unexposed – bipolar disorder	Prospective cohort	Exposed: 140 Unexposed: 61	5.7% vs. 4.9% <i>P</i> =NS
Diav-Citrin 2014	Major anomalies without chromosomal or genetic conditions	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 Unexposed: 61	6.5% vs. 3.3% <i>P</i> =NS
Diav-Citrin 2014	Non-cardiovascular anomalies	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 Unexposed: 61	4.1% vs. 1.6% <i>P</i> =NS
Källén 1983	Relatively severe congenital malformations	Lithium (first trimester) ⁵⁸⁵	Unexposed – manic depression	Retrospective cohort	Exposed: 41 Unexposed: 80	12.2% vs. 3.8% <i>P</i> value NR
Källén 1983	Relatively severe congenital malformations	Lithium ± other psychotropic drug/s (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 59 Unexposed: 80	11.9% vs. 3.8% <i>P</i> value NR

Abbreviations: CI, confidence interval; NR, not reported; NS, not significant; OR, odds ratio; RE, risk estimate; RR, relative risk.

⁵⁸⁰ The exposure was at least in the first trimester of pregnancy in 90.2% of this lithium-exposed group. The medication was taken throughout pregnancy in 58.5% of these pregnancies. Concurrent psychiatric medications were taken by 66.1% of women in this cohort.

⁵⁸¹ Multicentre data from ITIS (Israel), MotherSafe (Australia) and Motherisk Program (Canada) to increase the power of the analysis. Data are shown in Table 4 of the Diav-Citrin 2014 publication.

⁵⁸² Adjusted for year of birth, maternal age (5-year class), parity (1-4+), smoking in early pregnancy and BMI. Not adjusted for maternal indication.

⁵⁸³ One pregnancy in the lithium exposure group was terminated due to Ebstein's anomaly.

⁵⁸⁴ Includes major isolated congenital anomalies and unidentified multiple congenital anomalies.

⁵⁸⁵ Drug use was recorded at the woman's first visit to the maternity health care service, usually in the 10th to 12th week.

On the basis of data collected in the 1970's by voluntary retrospective reporting systems from Scandinavia, Canada and the United States, lithium became widely regarded as a human teratogen. However, much of the early evidence was from retrospective case series (not included in this report).

Five studies published between 1983 and 2014 provided comparative data on the association between lithium exposure during pregnancy and major malformations in the offspring. The only study that adjusted for potential confounders (year of birth, maternal age, parity, smoking in early pregnancy and BMI) was Källén 2013. The adjusted analysis found no significant difference in “relatively severe” malformations between pregnancies exposed or unexposed to lithium.

The study by Diav-Citrin 2014 defined major anomalies as structural anomalies in the offspring that have serious medical, surgical or cosmetic consequences, or significant neurodevelopmental or functional problems, even in the absence of a structural anomaly, that require special education or interventions. The overall rate of major congenital anomalies was not significantly different between the three study groups (lithium-exposed, nonteratogenic exposure comparison, and bipolar disorder comparison), even when the analysis was repeated for first-trimester exposure to lithium and after exclusion of genetic or cytogenetic anomalies. There was also no significant difference between groups in the rate of non-cardiovascular anomalies.

In an attempt to increase the power of the study by increasing the number of exposed pregnancies, Diav-Citrin 2014 included data from two additional teratology information services (one in Australia and one in Canada). In this multicenter part of the study, the overall rate of major anomalies among those exposed to lithium during the first trimester after exclusion of genetic or cytogenetic anomalies was significantly higher than that in the nonteratogenic exposure group. The rate of non-cardiovascular anomalies was also significantly higher in the lithium-exposed group.

To assess the contribution of potential confounding variables to the increase in the overall rate of major anomalies among those exposed to lithium during the first trimester after exclusion of genetic or cytogenetic anomalies, logistic regression was carried out. The regression analysis was repeated for cardiovascular anomalies, cardiovascular anomalies that did not spontaneously resolve, and non-cardiovascular anomalies. None of the predictors (i.e. additional psychiatric drugs, lithium dosage, pregnancy order, and Canada's Motherisk center) significantly contributed to the model, except for MotherSafe (Australia) as the service center, which was associated with a significantly higher risk of major anomalies (and raises the question of selection bias).

AppD4.1.5.4 Cardiac malformations – lithium

AppD4.1.5.4.1 Results based on systematic reviews

The results of the analyses of the association between lithium and cardiac malformations from the NICE 2015 SR is presented in Table AppD4-82. It should be noted that this analysis was not adjusted for potential confounding or limited to women with a psychiatric diagnosis. *As such, these findings have not been used to generate recommendations and an examination of the results of individual studies has been undertaken.*

Table AppD4-82 Lithium – cardiac malformations outcomes from systematic reviews

Study ID	Outcome	Exposure	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
NICE 2015	Heart defects	Lithium	Unexposed – any	2 (cohort) ⁵⁸⁶	973,967	-	OR 1.43 (0.59, 3.46)	0.35 (0%)

Abbreviations: CI, confidence interval; OR, odds ratio; RE, risk estimate; SR, systematic review.

⁵⁸⁶ Reis 2008; Kallen 1983

AppD4.1.5.4.2 Results based on individual studies

A summary of the results regarding the association between lithium use and cardiac malformations is presented in Table AppD4-83. Only one of the four included studies adjusted for potential confounders (Diav-Citrin 2014;) and two studies included a comparator population with a psychiatric diagnosis (Diav-Citrin 2014; Källén 1983). The Studies shown in grey shading represent primary evidence and are included in the individual analyses presented in the Evidence Profile table in **Section D3.1.5** of the Technical Report. Full quality assessment is limited to the primary evidence shaded below.

Due to the low prevalence of cardiovascular malformations in the unexposed population (<5%), it is assumed that odds ratios (ORs) approximate the relative risks (RRs), and will be interpreted as such.

Table AppD4-83 Lithium – cardiac malformation outcomes from observational studies

Study ID	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; <i>P</i> value
Unexposed comparator						
Diav-Citrin 2014	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Cases in analysis: 822	Adjusted⁵⁸⁷ OR 4.75 (1.11, 20.36)
Diav-Citrin 2014	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 Unexposed: 711	Unadjusted RR 7.23 (1.97, 26.53) 4.1% vs. 0.6% <i>P</i><0.017
Diav-Citrin 2014 [multicentre data ⁵⁸⁸]	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 152 Unexposed: 842	3.9% vs. 0.5% <i>P</i>=0.001
Diav-Citrin 2014	Cardiovascular anomalies excluding resolved cases	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 Unexposed: 711	Unadjusted RR 5.78 (0.82, 40.65) 2.4% vs. 0.3% <i>P</i> =NS
Diav-Citrin 2014 [multicentre data ⁵⁸⁸]	Cardiovascular anomalies excluding resolved cases	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 152 Unexposed: 842	2.6% vs. 0.2% <i>P</i>=0.006
Reis 2008	Relatively severe cardiac defects	Lithium (first trimester)	Unexposed (to lithium)	Retrospective cohort	Exposed: 79 Total: 973,767	5.1% ⁵⁸⁹ vs. NR <i>P</i> value NR
Jacobson 1992	Cardiac anomalies	Lithium (first trimester)	Unexposed (to lithium)	Prospective cohort	Exposed: NR Unexposed: NR	Unadjusted RR 1.1 (0.1, 16.6)
Psychiatric diagnosis comparator						
Diav-Citrin 2014	Cardiovascular anomalies	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 Unexposed: 61	4.1% vs. 3.3% <i>P</i> =NS
Diav-Citrin 2014	Cardiovascular anomalies excluding resolved cases	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 Unexposed: 72	2.4% vs. 1.6% <i>P</i> =NS
Källén 1983	Heart defects	Lithium (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 41 Unexposed: 80	7.3% vs. 2.5% <i>P</i> value NR

⁵⁸⁷ Regression analysis independent variables included pregnancy order, smoking 10 or more cigarettes a day, bipolar disorder.

⁵⁸⁸ Multicentre data from ITIS (Israel), MotherSafe (Australia) and Motherisk Program (Canada) to increase the power of the analysis. Data are shown in Table 4 of the Diav-Citrin 2014 publication.

⁵⁸⁹ Four cases of cardiac defects included one combined atrium septum defect and tricuspidal and mitral malformations, one mitral insufficiency and also hypospadias, one ventricular septum defect, and one patent ductus arteriosus in a term baby (born after 41 completed weeks). The authors stated that the defects were relatively minor.

Study ID	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; <i>P</i> value
Källén 1983	Heart defects	Lithium ± other psychotropic drug/s (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 59 Unexposed: 80	6.8% vs. 2.5% <i>P</i> value NR

Abbreviations: CI, confidence interval; NR, not reported; NS, not significant; OBS, observational study; OR, odds ratio; RE, risk estimate; RR, relative risk.

In an analysis adjusted for pregnancy order, smoking status and bipolar disorder, Diav-Citrin 2014 found that cardiovascular anomalies were significantly more common in cases of lithium exposure when compared with the nonteratogenic group. Similar results were seen in unadjusted (crude) analyses; however, there was no significant difference after excluding those anomalies that spontaneously resolved. When data from two additional teratology information services were included in the analysis to increase the power of the study, cardiovascular anomalies were significantly more common in the lithium (first trimester) group, even after excluding those cases that resolved.

The authors speculate that the higher rate of cardiovascular anomalies in the lithium bipolar group, relative to the nonteratogenic group, that fell short of statistical significance may be a result of insufficient power of the relatively small sample size of the bipolar group or may be related to exposure to potential teratogens, such as valproic acid. Alternatively, this suggests that the risk might partly be attributed to the underlying bipolar disorder (Diav-Citrin 2014). An analysis of the risk of cardiac malformations in lithium-exposed pregnancies compared with pregnancies from a bipolar disorder comparison group found no significant difference between the two groups (even after excluding anomalies that spontaneously resolved); however, no adjustment was made for other potential confounders.

The study by Källén 1983 found higher rates of heart defects in lithium-exposed pregnancies compared with a manic-depressive comparator (*P* value not reported); however, the study was small in size and the number of events was low.

AppD4.1.5.5 Septal malformations – lithium

AppD4.1.5.5.1 Results based on systematic reviews

The NICE 2015 SR did not provide an analysis of this outcome.

AppD4.1.5.5.2 Results based on individual studies

A summary of the results regarding the association between lithium use and septal malformations is presented in Table AppD4-84. Only one study (Diav-Citrin 2014) reported cases of septal defects in lithium-exposed and unexposed pregnancies. The study found no significant difference in the rate of septal defects between lithium-exposed pregnancies and a comparator group with bipolar disorder; however, the study was underpowered for this outcome and no adjustment was made for other potential confounders. This analysis is included in the Evidence Profile table in **Section D3.1.5** of the Technical Report.

Table AppD4-84 Lithium – septal malformation outcomes from observational studies

Study ID	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; <i>P</i> value
Psychiatric diagnosis comparator						
Diav-Citrin 2014	Septal defects ⁵⁹⁰	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 Unexposed: 61	2.4% vs. 1.6% <i>P</i> =NR

Abbreviations: CI, confidence interval; NR, not reported; OBS, observational study; RE, risk estimate.

⁵⁹⁰ Collated from Table 5 in Diav-Citrin 2014.

AppD4.1.5.6 Ebstein's anomaly – lithium**AppD4.1.5.6.1 Results based on systematic reviews**

As shown in Table AppD4-85, two studies reporting on Ebstein's anomaly met the inclusion criteria for the NICE 2015 review; however, NICE 2015 stated that no conclusions could be drawn because of the low number of events.⁵⁹¹

Due to the unclear findings reported in NICE 2015, an examination of the results of individual studies has been undertaken.

Table AppD4-85 Lithium – Ebstein's anomaly outcomes from systematic reviews

Study ID	Outcome	Exposure	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Unadjusted RE (95% CI)	Heterogeneity P value (I ²)
NICE 2015	Ebstein's anomaly	Lithium	Unexposed – any	2 (cohort) ⁵⁹²	3,912	-	Estimates unstable because of low number of events	

Abbreviations: CI, confidence interval; RE, risk estimate; SR, systematic review.

AppD4.1.5.6.2 Results based on individual studies

A summary of the results regarding the association between lithium use and Ebstein's anomaly is presented in Table AppD4-86. Only one study (Diav-Citrin 2014) reported cases of Ebstein's anomaly in lithium-exposed pregnancies versus unexposed pregnancies with a psychiatric diagnosis (bipolar disorder); however, no further adjustments were made for potential confounders. This analysis is included in the Evidence Profile table in **Section D3.1.5** of the Technical Report.

Table AppD4-86 Lithium – Ebstein's anomaly outcomes from observational studies

Study ID	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; P value
Unexposed comparator						
Diav-Citrin 2014	Ebstein's anomaly	Lithium (first trimester)	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 123 Unexposed: 711	0.8% vs. 0% P=NR
Jacobson 1992	Ebstein's anomaly	Lithium (first trimester)	Unexposed (to lithium)	Prospective cohort	Exposed: NR Unexposed: NR	Unadjusted RR 3.5 (0.1, 84.9) ⁵⁹³
Psychiatric diagnosis comparator						
Diav-Citrin 2014	Ebstein's anomaly	Lithium (first trimester)	Unexposed – bipolar disorder	Prospective cohort	Exposed: 123 Unexposed: 61	0.8% vs. 0% P=NR

Abbreviations: CI, confidence interval; NR, not reported; OBS, observational study; RE, risk estimate.

The absolute risk of Ebstein's anomaly among prospective cases from the Israeli Teratology Information Service was 1/123 (0.8%). The woman in this case had been treated with lithium (1,200 mg/day) and citalopram throughout pregnancy. However, taking into account retrospective cases (in which contact with the information service center was made after prenatal diagnosis by ultrasound), the risk was increased to 2.4% (Diav-Citrin 2014). There were no cases of Ebstein's anomaly in the bipolar disorder comparison group.

The study by Jacobson 1992 also reported one case of Ebstein's anomaly in the lithium-exposed group and no cases in the unexposed comparator group.

⁵⁹¹ Correa-Villasenor 1994 reported two cases of Ebstein's anomaly, both in pregnancies that were not exposed to lithium. Jacobson 1992 reported one case of Ebstein's anomaly in a lithium exposed group and no cases in an unexposed comparator group.

⁵⁹² Correa-Villasenor 1994; Jacobson 1992

⁵⁹³ One fetus in the lithium group had a severe form of Ebstein's anomaly, which was diagnosed at 16 weeks' gestation, and this pregnancy was terminated.

AppD4.1.5.7 Miscarriage – lithium**AppD4.1.5.7.1 Results based on systematic reviews**

The NICE 2015 SR did not provide an analysis of this outcome.

AppD4.1.5.7.2 Results based on individual studies

A summary of the results regarding the association between lithium use and miscarriage is presented in **Table AppD4-87**. Of the two studies reporting this outcome, only Diav-Citrin 2014 adjusted for potential confounders and included a comparator population with bipolar disorder. The outcome shown in dark shading represents primary evidence and is included in the individual analyses presented in the Evidence Profile table in **Section D3.1.5** of the Technical Report. Full quality assessment is limited to the primary evidence shaded below.

Based on the findings of an unexposed bipolar disorder population, the prevalence of miscarriage in the depressed population is estimated to be 8.3%.⁵⁹⁴ For this reason, ORs are not be assumed to approximate RRs.

Table AppD4-87 Lithium – miscarriage outcomes from observational studies

Study ID	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; <i>P</i> value
Unexposed comparator						
Diav-Citrin 2014	Miscarriage	Lithium ⁵⁹⁵	Unexposed – nonteratogenic exposure	Prospective cohort	Cases in analysis: 911	Adjusted⁵⁹⁶ OR 1.94 (1.08, 3.48)
Diav-Citrin 2014	Miscarriage	Lithium ⁵⁹⁵	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 183 Unexposed: 748	16.4% vs. 5.7% <i>P</i><0.017
Jacobson 1992	Spontaneous abortion	Lithium (first trimester)	Unexposed	Prospective cohort	Exposed: 148 Unexposed: 148	8.8% vs. 8.1% <i>P</i> =NS
Psychiatric diagnosis comparator						
Diav-Citrin 2014	Miscarriage	Lithium ⁵⁹⁵	Unexposed – bipolar disorder	Prospective cohort	Exposed: 183 Unexposed: 72	16.4% vs. 8.3% <i>P</i> =NS

Abbreviations: CI, confidence interval; NR, not reported; NS, not significant; OBS, observational study; OR, odds ratio; RE, risk estimate.

The two studies reporting the association between miscarriage and lithium exposure in pregnancy reported different results. The Jacobson 1992 study found no difference in miscarriage rates between pregnancies exposed or unexposed to lithium. The Diav-Citrin 2014 study found a significantly increased rate of miscarriages in the lithium exposure group compared with the nonteratogenic exposure comparator. To assess the association of potential confounding variables with the increase in the miscarriage rate in the lithium group, logistic regression was performed, with maternal age, previous miscarriage, smoking status, lithium, bipolar disorder, and gestational age at initial contact with the information centre, as independent variables. The significant predictors in the model were gestational age at initial contact with the information center, maternal age, previous miscarriages, and intrauterine exposure to lithium.

AppD4.1.5.8 Neonatal mortality – lithium**AppD4.1.5.8.1 Results based on systematic reviews**

The NICE 2015 SR did not provide an analysis of this outcome.

⁵⁹⁴ Based on Diav-Citrin 2014.

⁵⁹⁵ The exposure was at least in the first trimester of pregnancy in 90.2% of this lithium-exposed group. The medication was taken throughout pregnancy in 58.5% of these pregnancies.

⁵⁹⁶ Regression analysis independent variables included maternal age, previous miscarriage, smoking status, bipolar disorder, gestational age at initial contact with the information centre.

AppD4.1.5.8.2 Results based on individual studies

A summary of the results regarding the association between lithium use and neonatal mortality is presented in Table AppD4-88. No studies adjusted for potential confounders but two studies included a comparator population with a psychiatric diagnosis (Diav-Citrin 2014; Källén 1983). The studies shown in dark shading represents primary evidence and is included in the individual analyses presented in the Evidence Profile table in **Section D3.1.5** of the Technical Report. Full quality assessment is limited to the primary evidence shaded below.

Table AppD4-88 Lithium – neonatal mortality outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; <i>P value</i>
Unexposed comparator						
Diav-Citrin 2014	Stillbirth	Lithium ⁵⁹⁷	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 183 Unexposed: 748	1.6% vs. 0.7% <i>P=NS</i>
Jacobson 1992	Stillbirth	Lithium (first trimester)	Unexposed	Prospective cohort	Exposed: 138 Unexposed: 148	0.7% vs. 0% <i>P=NS</i>
Psychiatric diagnosis comparator						
Diav-Citrin 2014	Stillbirth	Lithium ⁵⁹⁷	Unexposed – bipolar disorder	Prospective cohort	Exposed: 183 Unexposed: 72	1.6% vs. 0% <i>P=NS</i>
Källén 1983	Neonatal deaths ⁵⁹⁸	Lithium (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 41 Unexposed: 80	9.8% vs. 0% <i>P value NR</i>
Källén 1983	Neonatal deaths	Lithium ± other psychotropic drug/s (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: 59 Unexposed: 80	10.2% vs. 0% <i>P value NR</i>

Abbreviations: CI, confidence interval; NR, not reported; NS, not significant; OBS, observational study; RE, risk estimate.

AppD4.1.5.9 Preterm birth – lithium

AppD4.1.5.9.1 Results based on systematic reviews

The NICE 2015 SR did not provide an analysis of this outcome.

AppD4.1.5.9.2 Results based on individual studies

A summary of the results regarding the association between lithium use and preterm birth is presented in. No studies adjusted for potential confounders but two studies included a comparator population with a psychiatric diagnosis (Diav-Citrin 2014; Troyer 1993). The Studies shown in grey shading represent primary evidence and is included in the individual analyses presented in the Evidence Profile table in **Section D3.1.5** of the Technical Report. Full quality assessment is limited to the primary evidence shaded below.

Table AppD4-89 Lithium – preterm birth outcomes from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; <i>P value</i>
Unexposed comparator						
Diav-Citrin 2014	Preterm delivery (<37 weeks)	Lithium ⁵⁹⁹	Unexposed – nonteratogenic exposure	Prospective cohort	Exposed: 131 Unexposed: 683	13.7% vs. 6.0% <i>P<0.017</i>

⁵⁹⁷ The exposure was at least in the first trimester of pregnancy in 90.2% of this lithium-exposed group. The medication was taken throughout pregnancy in 58.5% of these pregnancies.

⁵⁹⁸ Defined by the presence of a date of death in the delivery record.

⁵⁹⁹ The exposure was at least in the first trimester of pregnancy in 90.2% of this lithium-exposed group. The medication was taken throughout pregnancy in 58.5% of these pregnancies.

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; <i>P</i> value
Jacobson 1992	Premature (<36 weeks)	Lithium (first trimester)	Unexposed	Prospective cohort	Exposed: 138 Unexposed: 148	4.3% vs. 4.7% <i>P</i> =NS
Psychiatric diagnosis comparator						
Diav-Citrin 2014	Preterm delivery (<37 weeks)	Lithium ⁵⁹⁹	Unexposed – bipolar disorder	Prospective cohort	Exposed: 131 Unexposed: 59	13.7% vs. 10.2% <i>P</i> =NS
Troyer 1993	Preterm delivery (<38 weeks)	Lithium (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: ~60 Unexposed: ~290 ⁶⁰⁰	33% vs. 13% <i>P</i> value NR

Abbreviations: CI, confidence interval; NR, not reported; NS, not significant; OBS, observational study; RE, risk estimate.

The studies reporting the association between preterm delivery and lithium exposure in pregnancy were not consistent. The Jacobson 1992 study found no difference in preterm delivery rates between pregnancies exposed or unexposed to lithium. Diav-Citrin 2014 reported a significantly increased risk of preterm delivery among infants of women treated with lithium during pregnancy relative to the nonteratogenic group; however, there was no significant difference between the lithium group and the bipolar disorder group. The authors speculate that the increased risk of preterm deliveries in lithium-exposed offspring may be associated with the underlying disorder.

AppD4.1.5.10 Small or large for gestational age – lithium

AppD4.1.5.10.1 Results based on systematic reviews

The NICE 2015 SR did not provide an analysis of this outcome.

AppD4.1.5.10.2 Results based on individual studies

Several studies compared birthweights in babies exposed to lithium during pregnancy versus unexposed controls (Diav-Citrin 2014; Reis 2008; Jacobson 1992), citing previous reports of an association between lithium exposure and fetal macrosomia. However, only one study was identified that assessed the association between lithium use and being large for gestational age. The definition of large for gestational age was not provided in the publication and the study results were poorly reported (although the discussion implied that there was no difference between study arms). As such, this outcome is not presented in the Evidence Profile table in **Section D3.1.5** of the Technical Report.

Table AppD4-90 Lithium – large for gestational age from observational studies

Study ID <i>Risk of bias</i>	Outcome	Exposure (timing)	Comparator population	Study type	N	RE (95% CI) or % vs. %; <i>P</i> value
Psychiatric diagnosis comparator						
Troyer 1993	Large for gestational age	Lithium (first trimester)	Unexposed – manic depression	Retrospective cohort	Exposed: ~60 Unexposed: ~290 ²⁸⁴	5% vs NR <i>P</i> value NR (but no increase due to lithium)

Abbreviations: CI, confidence interval; NR, not reported; NS, not significant; OBS, observational study; RE, risk estimate.

⁶⁰⁰ Of 350 women in the manic-depressive cohort, 17% were exposed to lithium (12% to lithium alone and 5% to lithium plus another psychotropic drug).

AppD4.2 COMPLEMENTARY

AppD4.2.1 Omega-3 fatty acids

AppD4.2.1.1 Included systematic reviews – omega-3 fatty acids

Five systematic reviews were identified that provided quantitative evidence relating to the assessment of omega-3 fatty acids harms. No SRs were identified relating to the assessment of omega-3 fatty acids harms in a depressed postnatal population. Therefore, SRs that reported on the safety of omega-3 fatty acids in a postnatal population were included; since the objective was to identify if the intervention increased the risk of harmful outcomes for the mothers and fetus or infants, regardless of the mother mental health.

The results based on the association of omega-3 fatty acids and pregnancy and birth outcomes presented in the included SRs were based on data that used the appropriate comparator population. The data is presented in the following sections, and are grouped by outcome. Most of the included RCTs in each systematic review had adequate concealment and blinding, and were analysed by intention to treat; however, some of the studies had potential biases related to unknown allocation concealment.

Table AppD4-91 Characteristics of the included systematic reviews of omega-3 fatty acids harms

Study ID <i>Risk of bias</i>	Study characteristics	Population for outcomes assessment (N)	Exposure (subgroups)	Comparator (subgroups)	Outcomes
Kar 2016 <i>Low</i>	SR 9 RCTs	Pregnant women and neonates (N=5,980)	Omega-3 fatty acids	Placebo	Early preterm delivery, any preterm delivery, gestational age, neonatal death
Saccone 2015	SR 3 RCTs	Uncomplicated singleton pregnancy and previous pregnancy complicated by IUGR (N=575)	Omega-3 fatty acids	Placebo	IUGR
Gould 2013	SR 11 RCTs	Pregnant or lactating women (N=5,272)	Omega-3 LCPUFA	Placebo	Cognitive development Motor development Language development
Imhoff-Kunsch 2012 <i>Low</i>	SR 15 RCTs 14 Observational studies	Pregnant women and neonates (N=8,454 for RCTs)	n-3 LCPUFA	Placebo	IUGR, preterm birth, early preterm birth, SGA, stillbirth, infant death
Salvig 2011 <i>Low</i>	SR 3 RCTs	Pregnant women and neonates (N=2,108)	Marine n-3 fatty acids	Placebo or no intervention	Preterm delivery, early preterm delivery, gestational age

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; n-3 LCPUFA, n-3 long-chain polyunsaturated fatty acids; IUGR, intrauterine growth restriction; SGA, small gestational age.

AppD4.2.1.2 Preterm birth – omega-3 fatty acids

A summary of the results regarding the association between use of omega-3 fatty acids and preterm birth is presented in **Table AppD4-92**. Studies shown in grey shading represent primary evidence and are included in the pooled analyses presented in the Evidence Profile Tables in **Section D3.2.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-92 Omega-3 fatty acids – preterm birth outcomes from systematic reviews

Study ID <i>Risk of bias</i>	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity P value (I ²)
Early preterm birth (< 34 weeks)							
Kar 2016 <i>Low</i>	Early preterm delivery (<34 weeks)	Omega-3 fatty acids	Placebo	6 (RCT)	4,193	RR 0.42 (0.27, 0.66)	0.46 (0%)
Imhoff-Kunsch 2012	Early preterm birth (< 34 weeks)	n-3 LCPUFA	Placebo	5 (RCT)	4,343	RR 0.74 (0.58, 0.94)	0.42 (0%)

Study ID <i>Risk of bias</i>	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity P value (I ²)
Salvig 2011	Early preterm birth (<34 weeks)	Marine n-3 fatty acids	Placebo	3 (RCT)	921	RR 0.32 (0.09, 0.95)	NR
Kar 2016 <i>Low</i>	Early preterm delivery (<34 weeks) – <u>high risk</u>	Omega-3 fatty acids	Placebo	3 (RCT)	3,670	RR 0.36 (0.18, 0.71)	NR
Kar 2016 <i>Low</i>	Early preterm delivery (<34 weeks) – <u>any risk</u>	Omega-3 fatty acids	Placebo	3 (RCT)	523	RR 0.50 (0.24, 1.06)	NR
Preterm birth (< 37 weeks)							
Kar 2016 <i>Low</i>	Preterm delivery (<37 weeks)	Omega-3 fatty acids	Placebo	9 (RCT)	5,980	RR 0.83 (0.70, 0.98)	0.45 (0%)
Saccone 2016b	Preterm birth (< 37 weeks; women without prior preterm birth)	Omega-3 fatty acids	Placebo	7 (RCT)	3,493	RR 0.90 (0.72, 1.11)	0.67 (0%)
Imhoff-Kunsch 2012	Preterm birth (<37 weeks)	n-3 LCPUFA	Placebo	9 (RCT)	6,505	RR 0.91 (0.82, 1.01)	0.66 (0%)
Salvig 2011	Preterm birth (<37 weeks)	Marine n-3 fatty acids	Placebo	3 (RCT)	921	RR 0.61 (0.40, 0.93)	<0.05 (NR)
Kar 2016 <i>Low</i>	Preterm delivery (<37 weeks) – <u>high risk</u>	Omega-3 fatty acids	Placebo	4 (RCT)	814	RR 0.83 (0.61, 1.11)	NR
Kar 2016 <i>Low</i>	Preterm delivery (<37 weeks) – <u>any risk</u>	Omega-3 fatty acids	Placebo	5 (RCT)	5,166	RR 0.83 (0.66, 1.05)	NR
Kar 2016 <i>Low</i>	Preterm delivery (<37 weeks)	Omega-3 fatty acids - > 400 mg	Placebo	8 (RCT)	5,689	RR 0.83 (0.69, 1.00)	NR
Kar 2016 <i>Low</i>	Preterm delivery (<37 weeks)	Omega-3 fatty acids - < 400 mg	Placebo	1 (RCT)	291	RR 0.86 (0.44, 1.69)	NR
Kar 2016 <i>Low</i>	Preterm delivery (<37 weeks)	Omega-3 fatty acids - < 24 weeks	Placebo	7 (RCT)	5,156	RR 0.84 (0.69, 1.03)	NR
Kar 2016 <i>Low</i>	Preterm delivery (<37 weeks)	Omega-3 fatty acids - > 24 weeks	Placebo	2 (RCT)	824	RR 0.75 (0.45, 1.25)	NR

Abbreviations: n-3 LCPUFA, n-3 long-chain polyunsaturated fatty acids; NA, not applicable; NR, not reported.

Three SRs examined the risk of early preterm birth (< 34 weeks) following exposure to omega-3 fatty acids during pregnancy. All three SRs found a significantly reduced risk of early preterm birth, with RRs ranging from 0.32 to 0.74.

Subgroup analyses performed by Kar 2016 based on preterm birth risk level showed a highly significant reduced risk of early preterm birth in women at high risk, and a lower (although not statistically significant) risk for women at any risk (RR 0.36; 95% CI 0.18, 0.71 and RR 0.50; 95% CI 0.24, 1.06, respectively).

Four SRs examined the risk of preterm birth (< 37 weeks) following exposure to omega-3 fatty acids during pregnancy. Three of the SRs found a reduced risk of early preterm birth following exposure to omega-3 fatty acids during pregnancy; however, the finding by Imhoff-Kunsch 2012 just failed to reach statistical significance. The meta-analysis by Saccone 2016b showed no significant difference. While it included fewer studies than the Kar 2016, the included studies were limited to those conducted in women without prior preterm delivery.

Subgroup analyses performed by Kar 2016 based on preterm birth risk level, dose of omega-3 fatty acids and duration of treatment also found similar reduced risks of preterm birth; however, all failed to reach statistical significant, most likely due to imprecision.

AppD4.2.1.3 *Small for gestational age – omega-3 fatty acids*

A summary of the results regarding the association between use of omega-3 fatty acids and the infant being small for gestation age is presented in **Table AppD4-92**. Studies shown in grey shading represent primary evidence and are included in the pooled analyses presented in the Evidence Profile Tables in **Section D3.2.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-93 Omega-3 fatty acids – small for gestational age from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity P value (I ²)
Small for gestational age or Intrauterine growth restriction							
Kar 2016	SFGA	Omega-3 fatty acids	Placebo	8 (RCT)	5,469	RR 0.82 (0.66, 1.03)	0.09 (41%)
Saccone 2016b	SFGA (women with previous SGA infants)	Omega-3 fatty acids	Placebo	3 (RCT)	558	RR 1.13 (0.83, 1.54)	0.38 (0%)
Imhoff-Kunsch 2012	SFGA or IUGR	n-3 LCPUFA	Placebo	5 (RCT)	3,461	RR 1.06 (0.92, 1.21)	0.69 (0%)

Abbreviations: n-3 LCPUFA, n-3 long-chain polyunsaturated fatty acids; NA, not applicable; NR, not reported; IUGR, intrauterine growth restriction; SFGA, small for gestational age.

Two SRs examined the risk of the infant being small for gestational age following exposure to omega-3 fatty acids during pregnancy. The SR by Kar 2016 limited the outcome to ‘small for gestational age’ in any women and found a non-significant decreased risk (RR 0.85; 95% CI 0.66, 1.03; p=0.09). Saccone 2016b limited the population to women with a previous small for gestational age infant and found no significant difference for women randomised to omega-3 fatty acids or placebo (RR 1.13; 95% CI 0.83, 1.54). This finding was subject to imprecision because the upper 95% CI includes a measure of appreciable harm (RR 1.25).

An additional SR by Imhoff-Kunsch 2012 defined the outcome as ‘small for gestational age’ or ‘intrauterine growth restriction’ (IUGR) and found no difference between omega-3 fatty acids and placebo.

AppD4.2.1.4 Neonatal mortality – omega-3 fatty acids

A summary of the results regarding the association between use of omega-3 fatty acids and neonatal mortality is presented in **Table AppD4-94**. Studies shown in grey shading represent primary evidence and are included in the pooled analyses presented in the Evidence Profile Tables in **Section D3.2.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-94 Omega-3 fatty acids – neonatal mortality outcomes from systematic reviews

Study ID	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity P value (I ²)
Kar 2016	Neonatal death	Omega-3 fatty acids	Placebo	7 (RCTs)	6,751	RR 0.51 (0.26, 1.01)	NR
Saccone 2016b	Perinatal death	Omega-3 fatty acids (from ≤ 20 weeks gestation)	Placebo	2 (RCT)	2,462	RR 0.27 (0.09, 0.79)	0.85 (0%)
Imhoff-Kunsch 2012	Infant deaths	n-3 LCPUFA	Placebo	6 (RCTs)	6,235	RR 0.69 (0.38, 1.23)	0.89 (0%)
Imhoff-Kunsch 2012	Stillbirth	n-3 LCPUFA	Placebo	8 (RCTs)	7,038	RR 0.80 (0.50, 1.26)	0.51 (0%)

Abbreviations: CI, confidence interval; n-3 LCPUFA, n-3 long-chain polyunsaturated fatty acids; NA, not applicable; NR, not reported; RE, risk estimate; RR, relative risk.

Three SRs examined the risk of neonatal mortality following exposure to omega-3 fatty acids during pregnancy. The SR by Kar 2016 which examined ‘neonatal death’ found a non-significant decreased risk (RR 0.51; 95% CI 0.26, 1.01; p=0.05). Saccone 2016b limited the examination to studies where women were exposed from ≤ 20 weeks gestation and found a significantly decreased risk of perinatal mortality (RR 0.27; 95% CI 0.09, 0.79). Imhoff-Kunsch 2012 examined both infant deaths and stillbirth separately and found no difference between omega-3 fatty acids and placebo, although the risk for infant deaths was small (RR 0.69; 95% CI 0.38, 1.23).

AppD4.2.1.5 Cognitive development – omega-3 fatty acids

A summary of the results regarding the association between use of omega-3 fatty acids and cognitive development is presented in **Table AppD4-95**. Studies shown in grey shading represent primary evidence and are included in the pooled analyses presented in the Evidence Profile Tables in **Section D3.2.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-95 Omega-3 fatty acids – cognitive development outcomes from systematic reviews

Study ID <i>Risk of bias</i>	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity P value (I ²)
Gould 2013	Cognitive development – < 12 months (BSID-II)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	1 (RCT)	249	MD 1.00 (-0.96, 2.96)	NA
Gould 2013	Cognitive development – 12-24 months (BSID-II, BSID-III)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	2 (RCT)	801	MD -0.08 (-1.72, 1.57)	0.60 (0%)
Gould 2013	Cognitive development – 2-5 years (GMDS, K-ABC)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	2 (RCT)	156	MD 3.92 (0.77, 7.08)	0.90 (0%)
Gould 2013	Cognitive development – 5-12 years (GMDS, K-ABC)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	2 (RCT)	225	MD 0.36 (-2.61, 3.32)	0.88 (0%)
Gould 2013	Cognitive development – 12-24 months (BSID- III)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	726	MD 0.06 (-1.66, 1.78)	NA
Gould 2013	Cognitive development – 2-5 years (GMDS)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	72	MD 3.70 (-1.02, 8.42)	NA
Gould 2013	Cognitive development – 5-12 years (NR)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	82	MD 0.00 (-5.52, 5.52)	NA

Abbreviations: BSID, Bayley Scales of Infant Development; CI, confidence interval; GMDS, Griffiths Mental Development Scales; K-ABC, Kaufman Assessment Battery for Children; LCPUFA, long-chain polyunsaturated fatty acids; MD, mean difference; NA, not applicable; RCT, randomised controlled trial; RE, risk estimate.

One SR examined the association between exposure to omega-3 fatty acids during pregnancy and lactation and cognitive development in the child at various ages (Gould 2013). No difference in cognitive development scores were seen for children exposed to omega-3 fatty acids versus placebo at < 12 months, 12-24 months and 5-12 years. However, at 2-5 years, significantly higher cognitive development scores were seen for children who were exposed to omega-3 fatty acids compared with placebo (MD 3.92; 95% CI 0.77, 7.08).

Gould 2013 also examined the association between exposure to omega-3 fatty acids during pregnancy only and cognitive development in the child at various ages. No difference in cognitive development scores were seen for children exposed to omega-3 fatty acids versus placebo at 12-24 months, 2-5 years and 5-12 years. The finding at 2-5 years was imprecise because the upper 95% CI included a measure of appreciable benefit (SMD 0.5).

AppD4.2.1.6 Motor development – omega-3 fatty acids

A summary of the results regarding the association between use of omega-3 fatty acids and motor development is presented in **Table AppD4-96**. Studies shown in grey shading represent primary evidence and are included in the pooled analyses presented in the Evidence Profile Tables in **Section D3.2.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-96 Omega-3 fatty acids – motor development outcomes from systematic reviews

Study ID <i>Risk of bias</i>	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity P value (I ²)
Gould 2013	Motor development - < 12 months (BSID-II)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	1 (RCT)	249	MD 1.20 (-1.41, 3.81)	NA
Gould 2013	Motor development – 12-24 months (BSID-II)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	2 (RCT)	801	MD 1.52 (-2.29, 5.32)	0.09 (64%)
Gould 2013	Motor development – 2-5 years (GMDS)	Omega-3 LCPUFA (pregnancy and lactation)	Placebo	1 (RCT)	72	MD 4.60 (-1.14, 10.34)	NA
Gould 2013	Motor development – 12-24 months (BSID-III)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	726	MD 0.06 (-1.52, 1.64)	NA

Abbreviations: BSID, Bayley Scales of Infant Development; CI, confidence interval; GMDS, Griffiths Mental Development Scales; LCPUFA, long-chain polyunsaturated fatty acids; MD, mean difference; NA, not applicable; RCT, randomised controlled trial; RE, risk estimate.

One SR examined the association between exposure to omega-3 fatty acids during pregnancy and lactation and motor development in the child at various ages (Gould 2013). No difference in motor development scores were seen for children exposed to omega-3 fatty acids versus placebo at < 12 months, 12-24 months and 2-5 years. The findings at 12-24 months and 2-5 years were imprecise because the upper 95% CI included a measure of appreciable benefit (SMD 0.5).

Gould 2013 also examined the association between exposure to omega-3 fatty acids during pregnancy only and motor development in the child at 12-24 months only, and found no difference in motor development scores.

AppD4.2.1.7 Language development – omega-3 fatty acids

A summary of the results regarding the association between use of omega-3 fatty acids and language development is presented in **Table AppD4-97**. Studies shown in grey shading represent primary evidence and are included in the pooled analyses presented in the Evidence Profile Tables in **Section D3.2.1** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-97 Omega-3 fatty acids – language development outcomes from systematic reviews

Study ID <i>Risk of bias</i>	Outcome	Exposure (subgroup)	Comparator population	# studies (type)	N	Adjusted RE (95% CI)	Heterogeneity P value (I ²)
Gould 2013	Language development – 12-24 months (BSID-III)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	726	MD -1.47 (-3.58, 0.64)	NA
Gould 2013	Language development – 2-5 years (PPVT)	Omega-3 LCPUFA (pregnancy only)	Placebo	1 (RCT)	70	MD 3.90 (-0.73, 8.53)	NA

Abbreviations: BSID, Bayley Scales of Infant Development; CI, confidence interval; LCPUFA, long-chain polyunsaturated fatty acids; MD, mean difference; NA, not applicable; PPVT, Peabody Picture Vocabulary Test; RCT, randomised controlled trial; RE, risk estimate.

One SR examined the association between exposure to omega-3 fatty acids during pregnancy only and language development in the child at various ages (Gould 2013). No difference in language development scores were seen for children exposed to omega-3 fatty acids versus placebo at 12-24 months and 2-5 years. The findings at 2-5 years were imprecise because the upper 95% CI included a measure of appreciable benefit (SMD 0.5).

AppD4.2.2 St John's wort

AppD4.2.2.1 Included systematic reviews – St John's wort

No SRs provide 'higher quality' evidence; i.e. based on analyses adjusted for potential confounders and compared to an untreated population with depression or a psychiatric condition. All three SRs provide results of individual studies only; there were no synthesised/pooled analyses reported by the SRs; hence, no data has been extracted from the SRs. Different SRs included a mix of different interventions and different outcomes relevant to infant harm. The characteristics of the included SRs are presented in **Table AppD4-98** below.

Table AppD4-98 Characteristics of the included systematic reviews of St John's wort harms

Study ID	Study characteristics	Population	Exposure/s	Comparator/s	Outcomes
Dante 2014	SR Included studies relevant to St John's wort: 2 cohorts, 2 case reports	Pregnant women	St John's wort Other CAMs included: ginger, cranberry, garlic, blue cohosh, primrose oil, Echinacea, castor oil, raspberry leaf, valerian, green tea, peppermint, aloe, chamomile, almond oil	-	Fetal outcomes (congenital abnormalities, central nervous system damage, Apgar scores, birth weight, heart failure)
Budzynska 2012	SR Included studies relevant to St John's wort: 1 cohort and 2 case reports	Breast-feeding women	St John's wort Other CAMs included: garlic extract, cassia senna L, traditional herbal teas, various preparations of herbs; warm or cold food; wine; baths (mother wort); dietary supplements, herbal liqueur	-	Infant harms (colic, drowsiness, rashes, unusual behavior [lethargy, rashes, photosensitivity, sleep patterns])
Freeman 2009	SR Included studies relevant to St John's wort: 1 cohort and 2 case reports	Women with perinatal depression	St John's wort Omega-3 Folate SAmE Bright light therapy Exercise Acupuncture	-	Infant harms (neonatal syndrome, colic, drowsiness, or lethargy)

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: CAM, Complementary and Alternative Medicine; RCTs, randomized controlled studies; SAmE, S-adenosyl-methionine; SJW, St John's wort.

AppD4.2.2.2 Included individual studies – St John's wort

Due to the lack of 'higher quality' SR evidence, an assessment of individual studies was undertaken. **Table AppD4-99** provides the characteristics of the three prospective cohort studies identified via the included SRs and updated search for individual observational studies, while **Table AppD4-100** provides a summary of results of these studies. Each will be discussed in turn.

A prospective cohort study by Kolding et al (2015), analysed participants from the Danish National Birth Cohort study, which was an ongoing, follow-up study of pregnant women and their offspring from 1993 to 2003. The authors identified malformations in the offspring of 8.1% of St John's wort-exposed women (N=38) compared with 3.3% women in the unexposed comparator group (N=90,128). There was no significant difference between the St John's wort-exposed group and the comparator group ($p=0.13$). In addition, no significant difference was found either on preterm birth (2.7% versus 4.5%; $p=1.00$), or miscarriage (2.6% versus 1.05; p value not reported). There were only 38 women in the cohort exposed to St John's wort and no adjustment was made for exposure to other treatments, in particular antidepressants, which were used by women in both groups. In addition, the exposed and non-exposed groups were not limited to those with depression (5.3% in the exposed group and 0.9% in the unexposed group), so potential confounding by indication cannot be ruled out. Finally, due to the small exposed sample available, no adjustment for other potentially confounding variables was conducted. For these reasons the evidence provided by this study is of very low quality and will not be formally considered for use in formulating a recommendation. The authors conclude that "while the lack of observed associations between HP [St John's wort] exposure and adverse pregnancy outcomes provides some reassurance, the small sample size of pregnancies exposed to date requires further studies to corroborate existing findings and rule out potentially differences in risk. Since use of this drug is not in the prescription database, data have to come from ad hoc studies, preferably with prospective data."

Another prospective cohort study by Moretti et al (2009), using data from a teratogen information service, reported on pregnant women using St John's wort mainly for depression (72%) compared with depressed women using antidepressants and healthy women not exposed to teratogens. Unexposed groups included (i) unexposed women with depression who were on standard antidepressant treatments and (ii) unexposed women on not exposed to teratogens. Exposed and unexposed groups were matched on three potential confounders: gestational age at intake, maternal age and gravidity. The authors found that pregnancy outcomes were similar in the three groups, with the analysis of all the cohorts without multiple gestations showing there was no significant difference between St John's wort and the comparator groups. The authors concluded that "Though further large scale studies are still needed, this first study on the effects of St John's wort in human pregnancy does provide some evidence of fetal safety."

Table AppD4-99 Characteristics of the included observational studies of St John's wort harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Kolding 2015	Prospective cohort study Denmark (Danish National Birth Cohort) 1996 – 2003	Pregnant women who had singleton live births (N=90,166)	St John's wort	No exposure	Malformation Gestational age Preterm birth Birth weight Apgar scores
Moretti 2009	Cohort Canada (Mother-risk program) 1993 – 2007	Pregnant women (N=162)	St John's wort	Depressed women exposed to pharmacological therapies or healthy women not exposed to any teratogens	Malformation Live birth Miscarriage Elective abortion Gestational age Preterm delivery Birthweight

Note: Exposure/s, comparator/s and outcome/s shown in bold are those relevant to this Review.

AppD4.2.2.3 Malformations – St John's wort

A summary of the results from observational studies regarding the association between use of St John's wort and malformations is presented in **Table AppD4-100**. Studies shown in grey shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.2.2** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

Table AppD4-100 St John's wort – malformation outcomes from observational studies

Study ID	Outcome	Exposure	Population	Comparator population	N	RE (95% CI) or % vs %; p value
Kolding 2015	Malformation	St John's wort	Pregnant women with singleton livebirths	Unexposed/any	86,782	8.1% ⁶⁰¹ vs. 3.3%; 0.13
Moretti 2009	Major malformations	St John's wort	Pregnant women	Matched ⁶⁰² Unexposed/depression and unexposed/any (no teratogens)	166	5.3% ⁶⁰³ vs 4.2% ⁶⁰⁴ vs 0; 0.26

Abbreviations: CI, confidence interval; RE, risk estimate.

AppD4.2.2.4 Miscarriage – St John's wort

A summary of the results from observational studies regarding the association between use of St John's wort and miscarriage is presented in **Table AppD4-101**. As the Kolding 2015 study did not adjust for potential confounders, this finding will not be included in the Evidence Profile table.

Table AppD4-101 St John's wort – miscarriage outcomes from observational studies

Study ID	Outcome	Exposure	Population	Comparator population	N	RE (95% CI) or % vs %; p value
Kolding 2015	Miscarriage	St John's wort	Pregnant women	Unexposed/any	90,166	2.6% vs. 1.0%; NR

Abbreviations: CI, confidence interval; NR, not reported; RE, risk estimate.

AppD4.2.2.5 Preterm birth – St John's wort

A summary of the results from observational studies regarding the association between use of St John's wort and preterm birth is presented in **Table AppD4-102**. Studies shown in grey shading represent primary evidence and are presented in the Evidence Profile Tables in **Section D3.2.2** of the Technical Report. Full quality assessment is limited to the studies that are assessed in detail below.

⁶⁰¹ Includes three malformations – bilateral hip dislocation, heart septum defect and hypospadias.

⁶⁰² Comparator populations matched on gestational age at intake, maternal age and gravidity.

⁶⁰³ Offspring malformations are reported in the St. John's wort group as a proportion of first trimester exposures that were liveborn (1 obstructed ureter and 1 hypospadias).

⁶⁰⁴ Offspring malformations in the disease matched cohort included 1 plagiocephaly and 1 esophageal atresia with tracheoesophageal fistula.

Table AppD4-102 St John's wort – preterm birth outcomes from observational studies

Study ID	Outcome	Exposure	Population	Comparator population	N	RE (95% CI) or % vs %; p value
Kolding 2015	Preterm (<37 weeks) ⁶⁰⁵	St John's wort	Pregnant women with singleton livebirths	Unexposed/any	86,782	2.7% vs. 4.5%; 1.00
Moretti 2009	Preterm delivery	St John's wort	Pregnant women	Matched ⁶⁰⁶ Unexposed/depression and unexposed/any (no teratogens)	166	4.7% vs 20.5% vs 13.3%; 0.10

Abbreviations: CI, confidence interval; RE, risk estimate.

⁶⁰⁵ Includes liveborn singleton births only.

⁶⁰⁶ Comparator populations matched on gestational age at intake, maternal age and gravidity.

AppD4.3 **PHYSICAL****AppD4.3.1** **Electroconvulsive therapy****AppD4.3.1.1** *Included systematic reviews – ECT*

No SRs provide ‘higher quality’ evidence; i.e. based on analyses adjusted for potential confounders or compared to an untreated population with depression or a psychiatric condition or adjusted for indication-related potential confounders. Of the four SRs identified, one presented a pooled analysis of the reported data identified in the individual case reports (**Table AppD4-103**). Different SRs included a mix of different infant-related outcomes; those relevant to this Review were cardiac malformations, miscarriage, perinatal death mental retardation and respiratory distress. The relevant results of the included SRs describing the infant harms related to antenatal exposure to ECT are described in **Section AppD4.3.1.2** below.

Table AppD4-103 Characteristics of the included systematic reviews of electroconvulsive therapy harms

Study ID	Study characteristics	Population	Exposure (subgroups)	Comparator/s	Outcomes	Analysis
Quantitative assessment						
Leikness 2015	SR 67 case reports/series	Pregnant women with depression/bipolar disorder (including psychotic depression)	ECT	-	Various fetal and maternal adverse events	Pooled data
Qualitative assessment						
Calaway 2016	SR 13 studies; 9 case series/ 4 case reports	Pregnant women	ECT in first trimester	-	Various fetal adverse events	-
Pompili 2014	SR 31 case reports, 1 retrospective study, 1 observational study, 2 SRs, 2 narrative reviews	Pregnant women with major depressive disorder	ECT	-	Various fetal and maternal adverse events	-
Anderson 2009	SR 57 case reports/series	Pregnant women with MDD, bipolar disorder, schizophrenia or psychotic depression	ECT	-	Various fetal and maternal adverse events	⁶⁰⁷

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: ECT, electro convulsive therapy; PPD, postpartum depression; PP, postpartum psychosis; SR, systematic review.

⁶⁰⁷ Pooled data for efficacy assessment only.

AppD4.3.1.2 Included individual studies – ECT

Due to the lack of ‘higher quality’ SR evidence, an assessment of individual studies was undertaken. **Table AppD4-104** provides a summary of the single individual prospective cohort study identified via the included SRs and updated search for individual observational studies, that met the ‘higher quality’ criteria for individual studies; i.e. adjusted for potential confounders and limited to/adjusted for maternal mental health.

Table AppD4-104 Characteristics of the included observational studies of electroconvulsive therapy harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Babu 2013	Prospective cohort study India March 2006- September 2007	Women with postpartum psychosis Mean age=23 years (N=78)	ECT	No ECT	Adverse effects (anterograde amnesia, prolonged seizures, infant harms)

Abbreviations: ECT, electro convulsive therapy

AppD4.3.1.3 Antenatal exposure – ECT**AppD4.3.1.3.1 Results based on systematic reviews**

One SR provided pooled results from identified case reports. Leikness et al (2015) investigated the risk of ECT during pregnancy; most women received the treatment in the 2nd trimester and received a mean number of 9.4 treatments. The main reason for treatment was psychotic depression/bipolar disorder. Lethal outcomes for the fetus or baby were stated to have diverse causes, such as long lasting severe grand mal seizure induced by ECT. Overall, the child mortality rate was 7.1 % (12/169); from 1970 to 2013 mortality rate was 9.4 % (5/54), while from 1942 to 1970, 6.1 % (7/115). The authors conclude that “ECT during pregnancy should be a last resort treatment. For example, in cases of severe depression, catatonia, medication resistant illness, extremely high suicide risk, psychotic agitation, severe physical decline due to malnutrition or dehydration or other life threatening conditions (for example malignant neuroleptic syndrome), where other treatment options are not possible or very inadequate.”

The remaining three SRs provided a narrative review of infant harms. Calaway et al (2016), assessed the safety of ECT in the first trimester of pregnancy. There were several adverse outcomes reported in six patients, although they were not all attributable to ECT. In total, 12.5% of first-trimester pregnancies incurred an adverse event, and miscarriage occurred 3.13% of the time when excluding the two adverse outcomes (street accident and congenital pulmonary cysts), which the original authors did not attribute to ECT. The authors conclude that “Although the data are limited, they suggest that ECT is relatively safe when administered during the first trimester of pregnancy. The possible adverse consequences of ECT during the first trimester of pregnancy should be carefully weighed against the potential benefits of ECT on untreated mental illness.”

Pompili et al (2014) identified a mix of studies (mostly case reports) that reported on the adverse outcomes of ECT in the treatment of depression on pregnant women. One study reported fetal complications with ECT in 28 of 300 women, most common being fetal cardiac arrhythmia (1.6%). Three more studies found fetal or neonatal complications: one study found that 11 out of 25 of those complications were likely to be related to ECT, another study found that overall child mortality was 7.1% for the studies looked at from 1942 to 2013, and the final study found maternal complications in 20 out of 339 cases, being mainly status epilepticus, hematuria, miscarriages, uterine contractions, vaginal bleeding and premature labour (29% of cases). Overall, there were 22 complications found, most of them were mild and limited. There were four

major complications including two death of the fetus, and two major congenital abnormalities. The authors concluded that “ECT is probably currently under-used in many psychiatric settings because of its stigmatized perception by patients and by mental health professionals. ECT seems to be effective for treating major psychiatric disorders during pregnancy, and the risks of adverse events are low.”

Anderson et al (2009), reported 25 fetal or neonatal complications of the 339 cases reviewed, and found that 11 of these were likely related to ECT (eight transient fetal arrhythmias, one fetal death secondary to status epilepticus, one miscarriage in the first trimester 24-hours post ECT, and one case of multiple fetal cortical and fetal deep white matter infarctions after multiple ECT courses in the pregnant mother). The authors concluded that “Although there are limited available data in the literature, it seems that ECT is an effective treatment for severe mental illness during pregnancy and that the risks to fetus and mother are low.”

AppD4.3.1.4 Postnatal exposure – ECT

AppD4.3.1.4.1 Results based on individual studies

Babu et al (2013), reported on the adverse effects of the use of ECT in women with postpartum psychosis. While the study was comparative, and included an untreated population with postpartum psychosis as the comparator, the analysis was not adjusted for other potential confounders and so does not meet the criteria for ‘higher quality’ evidence defined for this Review. While the findings of this study will be presented in the Technical Reports, a full GRADE assessment will not be carried out.

Thirty-four (43.6%) out of the included 78 patients were treated with ECT. Of the women who received ECT, 15 continued to breastfeed their infants; there were no infants with clinically observable adverse effect of ECT on the exposed/breast-fed group.

AppD4.3.2 Transcranial magnetic stimulation

AppD4.3.2.1 Included systematic reviews – TMS

No SRs were found that investigated the effect on infant harms of treatment of depression during the antenatal or postnatal period using TMS. Therefore, assessment of data from individual studies was undertaken.

AppD4.3.2.2 Included individual studies – TMS

One study was identified that reported on infant harms due to TMS; a summary of the main characteristics of the included study can be found in **Table AppD4-105** and the main results of this study is summarised in **Table AppD4-106**.

Table AppD4-105 Characteristics of the included observational studies of TMS harms

Study ID	Study characteristics Country Timeframe	Population (N)	Exposure/s	Comparator/s	Outcomes
Eryilmaz 2015	Prospective cohort study (non-concurrent control) Turkey 2008–2013	Pregnant patients with a diagnosis of major depressive disorder Mean age=33 (N=44)	rTMS	Untreated/depression	Low birth weight, fetal anomalies , feeding problems, respiratory complications , metabolic disorders, cardiac problems , hematologic problems, and central nervous system (CNS) problems

Note: Exposure/s, comparator/s and outcome/s shown in bold are those included in the Summary of Findings tables.

Abbreviations: MDD, major depressive disorder; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation, TMS, transcranial magnetic stimulation.

Eryilmaz et al (2015), investigated the infant harms associated with the use of rTMS for depression during pregnancy in a prospective cohort study with an untreated, depressed control group. It should be noted that there was no adjustment for potential confounding in this study, and the control group was not concurrent; the authors note the possibility of recall bias for assessment of outcomes in the control group. There were few neonatal adverse events seen in the study: two infants in the rTMS group had neonatal hyperbilirubinemia and another had febrile convulsions at 13 months, while in the untreated, depressed group, four infants had neonatal hyperbilirubinemia. There were no differences in weight, height or head circumference at birth or time of testing (mean age 32 months). Assessment of developmental delay using the Ankara Developmental Screening Inventory (ADSI) showed no difference between the rTMS-exposed and untreated depression groups. The authors conclude that “rTMS exposure during pregnancy is not associated with poorer cognitive or motor development outcomes in children aged 18–62 months. Although language development as reported by the mothers was found to be poorer than expected in the rTMS-treated group, the delay was found to be similar to the language delay observed in offspring of untreated mothers, as reported in previous studies of prenatal depression treated with selective serotonin reuptake inhibitors.”

Table AppD4-106 Characteristics of the included observational studies of TMS harms

Study ID	Outcome	Exposure	Comparator population	Study type	N	RE (95% CI)
Eryilmaz 2015	Delays in language (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	OR 0.38 (0.09, 1.66)
Eryilmaz 2015	Delays in social and self-help skills (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	OR 0.75 (0.06, 8.98)

Study ID	Outcome	Exposure	Comparator population	Study type	N	RE (95% CI)
Eryilmaz 2015	Delays in fine motor (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	OR 1.53 (0.27, 8.63)
Eryilmaz 2015	Delays in gross motor (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	No events
Eryilmaz 2015	Delays in total development (ADSI subscale)	rTMS (25 Hz stimulation for 2 sec/20-30 sec interval)	Untreated/depression	1 (cohort)	44	No events

Abbreviations: ADSI, Ankara Developmental Screening Inventory Subscale Scores; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; SD, standard deviation.

Appendix D5 RISK-OF-BIAS ASSESSMENT

The following section presents the risk-of-bias assessments for each of the included studies that provides data to the Evidence Profile and Summary of Findings tables. The ratings for each study have been used to help determine the overall quality of the evidence presented in the Evidence Profile and Summary of Findings tables. All included studies were observational in nature (cohort studies and case-control studies) and the questions from the Newcastle-Ottawa scale were used to assess the risk of bias. Important characteristics of the studies that impact on the risk of bias have been taken directly from the studies and presented in the tables.

AppD5.1 PHARMACOLOGICAL

AppD5.1.1 Antidepressants

Almeida 2016

Study type: retrospective registry-based cohort study		Almeida 2016
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from the Quebec Pregnancy/Children Cohort in Quebec, Canada. Registries linked included: the Régie de l'assurance maladie du Québec (RAMQ) (diagnoses, medical procedures, prescribers, and socioeconomic status of women and children); the Public Prescription Drug Insurance database of Québec (drug name, start date, dose, and duration); the hospitalization archive database (Med-Echo: diagnoses and procedures); and the Québec Statistics database (patient sociodemographic data and birth weight). The cohort comprises predominantly women and children of lower socioeconomic status insured by the RAMQ for their medications; while this may affect generalisability, it is unlikely to affect internal validity.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Women were considered exposed if they had received at least one prescription for the medication in the first trimester (the first 84 days) of pregnancy. Purchases only recorded (not actual adherence to medication) but authors note that it has been found to have good agreement with medical charts.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Analyses included in the review limited to comparative population of women with a depression diagnosis who were unexposed to antidepressants. In addition, analysis adjusted for number of mental health visits in 3 months before pregnancy. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Adjusted for use of other teratogenic medication in the first trimester.	

Study type: retrospective registry-based cohort study		Almeida 2016
c) study controlled for most other important potential confounders	Adjusted for age, being a welfare recipient, number of prescription medication in 3 months before pregnancy, number of physician visits in 3 months before pregnancy, any hospitalizations in 3 months before pregnancy, and year of delivery. None of the included women were taking antihypertensives, or had a diagnosis of hypertension, both of which may be associated with miscarriage. Analyses were corrected for induced abortions.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	The outcome of interest was the occurrence of a clinically recognised miscarriage in the index pregnancy, defined as fetal loss before 20 weeks of gestation. These were identified by the presence of either an ICD-9 code of 634 or 761.8; or physician billing codes pertaining to a miscarriage. Induced abortions were identified by the presence of ICD-9 codes 635, 636, or 637; or corresponding physician billing codes; and the absence of codes for a spontaneous abortion on the same date.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Drs. Robyn Tamblyn and Michal Abrahamowicz are James McGill Professors. Dr. Almeida is the recipient of a Canadian Institutes of Health Research doctoral award. The authors report no conflict of interest.		
Final score: Low risk of bias.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Ban 2012

Study type: retrospective linked primary care record-based cohort study		Ban 2012
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Included all singleton pregnancies in women aged 15–45 years between 1990 and 2009 from The Health Improvement Network (THIN) that ended in live birth, still birth, miscarriage, or termination. The medical records of the mothers and the children were linked to provide prospectively recorded information throughout pregnancy and in the year before pregnancy. THIN is a nationally representative database of computerised primary care records from across the UK that has been validated for pharmacoepidemiology studies, and contains diagnoses, events, symptoms, and drug prescriptions.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Exposure to medication was defined according to the presence or absence of a relevant recording in each woman's primary care electronic health records within the first 90 days following the estimated date of conception (the first trimester of pregnancy). Records of prescriptions of all antidepressants, hypnotics, and anxiolytics that are primarily indicated for the treatment of depression or anxiety according to British national guidelines were extracted. Purchases only recorded (not actual dispensing or adherence to medication).	★
b) structured interview		★
c) written self-report		

Study type: retrospective linked primary care record-based cohort study		Ban 2012
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Analysis included in review limited to a population of women with unmedicated antenatal depression or anxiety in first trimester. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms and no consideration of depression/anxiety (or severity) in later pregnancy or around birth. Likely to impact on the perinatal death outcome.	★
b) study controls for other treatment	Women with different psychotropic medications included in mutually exclusive groups.	
c) study controlled for most other important potential confounders	Analysis included in review adjusted for maternal age at the end of pregnancy, household socioeconomic status, maternal smoking status before delivery and body mass index before pregnancy.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Examined live birth, stillbirth and miscarriage. The authors identified all pregnancies that ended in termination and included them in the overall study population. For pregnancies ending in a live birth, records of both mothers and offspring were searched (linked by delivery details and encrypted residential address) for recordings of infant death within 28 days postpartum, and combined these with stillbirths as a measure of perinatal death. Since the legislation on termination of pregnancy in Northern Ireland is more restrictive than that in other parts of the UK, we excluded women registered at general practices in this province.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Children followed up for up to 20 years	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
JW is supported by a University of Nottingham/National Institute for Health Research (NIHR) Senior Clinical Research Fellowship. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have declared that no competing interests exist.		
Final score: Low risk of bias.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Ban 2014a

Study type: retrospective linked primary care record-based cohort study		Ban 2014
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Included all singleton live births for women aged 15–45 years between 1990 and 2009 from The Health Improvement Network (THIN), in which the medical records of the mothers and the children were linked to provide prospectively recorded information throughout pregnancy and in the year before pregnancy. THIN is a nationally representative database of computerised primary care records from across the UK that has been validated for pharmacoepidemiology studies, and contains diagnoses, events, symptoms, and drug prescriptions.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		

Study type: retrospective linked primary care record-based cohort study		Ban 2014
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Antenatal exposure to SSRIs and TCAs during the first trimester of pregnancy was defined according to the presence or absence of relevant drug prescriptions in women's records from 4 weeks before to 12 weeks after the first day of the estimated last menstrual period. Using 4 weeks before the last menstrual period enabled the inclusion of drug prescriptions received immediately before pregnancy and potentially used during early pregnancy. Purchases only recorded (not actual dispensing or adherence to medication).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limited comparator population to children exposed to depression but not medicated. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Excluded women with prescriptions for antimanic and antipsychotic drugs before birth. Included adjustment for epilepsy.	
c) study controlled for most other important potential confounders	Adjusted for maternal age at the end of pregnancy, year of childbirth, Townsend deprivation index, maternal smoking history, maternal body mass index before pregnancy, and maternal diabetes, hypertension, asthma, and epilepsy in the year before conception or during pregnancy.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	All diagnoses of major congenital anomalies (MCAs) were identified in the children's medical records using Read codes that we classified into 14 system-specific groups according to the European Surveillance of Congenital Anomalies (EUROCAT) subgroups, ³⁹ which are based on the codes listed in the tenth edition of the International Classification of Diseases (ICD-10, mainly in chapter Q). A comparison of prevalence estimates across all system-specific groups (and specific MCA diagnoses for the most prevalent system-specific subgroups, accounting for 77% of all MCAs) between THIN and the UK registers of the EUROCAT network has shown that THIN is a valid and complete source of data to investigate MCAs in live-born children. Likely underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Children followed up for up to 20 years	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
L.S. received grants from the Wellcome Trust and personal fees from GlaxoSmithKline. All other authors report no competing interests.		
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Bérard 2015

Study type: retrospective registry-based cohort study (same study cohort as Boukhris 2016)		Bérard 2015
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from the Quebec Pregnancy/Children Cohort in Quebec, Canada. Registries linked included: the Régie de l'assurance maladie du Québec (RAMQ) (diagnoses, medical procedures, prescribers, and socioeconomic status of women and children); the Public Prescription Drug Insurance database of Québec (drug name, start date, dose, and duration); the hospitalization archive database (Med-Echo: diagnoses and procedures); and the Québec Statistics database (patient sociodemographic data and birth weight). The cohort comprises predominantly women and children of lower socioeconomic status insured by the RAMQ for their medications but the author notes while this may affect generalisability, it is unlikely to affect internal validity.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Prescription fillings were identified for sertraline, non-sertraline SSRIs and non-SSRIs dispensed to women in the cohort from the Quebec public prescription drug insurance database, with the timing of exposure determined by the dispensed date and duration of prescription. The relevant exposure time window was the first trimester confirmed by ultrasound. The authors note that exposure data has been validated against maternal report in this study, and that another study has reported that 94% of all drugs dispensed to pregnant women are actually taken.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limits inclusion in the study to women with a diagnosis of depression or anxiety, or exposure to antidepressants in the 12 months prior to the date of the last menstrual period. There, was no adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms. However, the authors did use visit to a psychiatrist as a proxy for severity.	★
b) study controls for other treatment	Adjusted for other medication use.	
c) study controlled for most other important potential confounders	Adjusted for maternal age, welfare status, diabetes, hypertension and asthma.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Major congenital malformations diagnosed in the first year of life were identified in the RAMQ and Med-Echo databases and defined according to ICD-10. Minor malformations were excluded because they are likely diagnosed selectively (leading to outcome misclassification); chromosomal abnormalities were also excluded given that they are likely not related to the drug of interest. Revision codes of major congenital malformations in the Quebec Pregnancy Cohort have been validated against patient charts. Likely underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Follow-up of children continued from birth until one year.	★
b) no		

Study type: retrospective registry-based cohort study (same study cohort as Boukhris 2016)		Bérard 2015
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The study was supported by the Fonds de la recherche en santé du Québec and the Réseau Québécois de recherche sur le médicament. A.B. is a consultant for plaintiffs in litigation involving antidepressants. The remaining authors report no conflict of interest.		
Final score: moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Bérard 2016

Study type: retrospective registry-based cohort study (same study cohort as Boukhris 2016)		Bérard 2016
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from the Quebec Pregnancy/Children Cohort in Quebec, Canada. Registries linked included: the Régie de l'assurance maladie du Québec (RAMQ) (diagnoses, medical procedures, prescribers, and socioeconomic status of women and children); the Public Prescription Drug Insurance database of Québec (drug name, start date, dose, and duration); the hospitalization archive database (Med-Echo: diagnoses and procedures); and the Québec Statistics database (patient sociodemographic data and birth weight). The cohort comprises predominantly women and children of lower socioeconomic status insured by the RAMQ for their medications but the author notes while this may affect generalisability, it is unlikely to affect internal validity.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Recorded prospectively in the Public Prescription Drug Insurance Database. Data on prescription filling for ADs were validated against medical records and maternal reports, with the timing of exposure defined by the date the prescription was filled and duration of therapy. Exposure to ADs was defined according to trimester of use (≥14weeks' gestation, first trimester; 15-26weeks' gestation, second trimester; and ≥ 27 weeks' gestation, third trimester). The exposure time window of interest for ASD was the second and/or third trimester. Purchases only recorded (not actual adherence to medication) but authors note a study that shows that 94% of drugs dispensed to pregnant women are actually taken.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Includes adjustment for history of maternal psychiatric conditions including affective disorders, such as depression, anxiety, or bipolar disorder (yes or no), and other psychiatric disorders (yes or no). No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Adjusted for other psychiatric disorders.	

Study type: retrospective registry-based cohort study (same study cohort as Boukhris 2016)		Bérard 2016
c) study controlled for most other important potential confounders	Use of ADs 1 year before the first day of gestation, use of ADs in the first trimester, infant characteristics (sex, year of birth), and maternal variables (maternal age at first day of gestation, high school completed [≥ 12 y], recipient of social assistance, living alone, chronic or gestational hypertension, chronic or gestational diabetes, and other psychiatric disorders).	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Autism spectrum disorder was defined as a medical service claim or hospitalisation with a diagnosis of ASD (childhood autism [International Classification of Diseases, Ninth Revision (ICD-9) code 299.0 or ICD-10 code F84.0], atypical autism [ICD-9 code 299.0 or ICD-10 code F84.1], Asperger syndrome [ICD-9 code 299.8 or ICD-10 code F84.5], other pervasive developmental disorders [ICD-9 code 299.8 or ICD-10 code F84.8], and pervasive developmental disorders not otherwise specified [ICD-9 code 299.9 or ICD-10 code F84.9]).	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Follow-up of children continued from birth until the date of the event (index date: ASD), death (censoring), or the end of the study period (December 31, 2009; censoring), whichever occurred first. Mean time of follow-up was 6.2 years. Analysis included year of birth.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
This study was supported by the Canadian Institutes of Health Research (grant number 132750). The funding body had no involvement in the data collection or analysis, the preparation of the manuscript, or the decision to submit the paper for publication. Dr Bérard is a consultant for plaintiffs in litigations involving antidepressants. The remaining authors report no conflict of interest.		
Final score: Moderate risk of bias due to lack of adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Boukhris 2016

Study type: retrospective registry-based cohort study		Boukhris 2016
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from the Quebec Pregnancy/Children Cohort in Quebec, Canada. Registries linked included: the Régie de l'assurance maladie du Québec (RAMQ) (diagnoses, medical procedures, prescribers, and socioeconomic status of women and children); the Public Prescription Drug Insurance database of Québec (drug name, start date, dose, and duration); the hospitalization archive database (Med-Echo: diagnoses and procedures); and the Québec Statistics database (patient sociodemographic data and birth weight). The cohort comprises predominantly women and children of lower socioeconomic status insured by the RAMQ for their medications but the author notes while this may affect generalisability, it is unlikely to affect internal validity.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		

Study type: retrospective registry-based cohort study		Boukhris 2016
3. Ascertainment of exposure		
a) secure record	Recorded prospectively in the Public Prescription Drug Insurance Database. Data on prescription filling for ADs were validated against medical records and maternal reports, with the timing of exposure defined by the date the prescription was filled and duration of therapy. Exposure to ADs was defined according to trimester of use (≥ 14 weeks' gestation, first trimester; 15-26 weeks' gestation, second trimester; and ≥ 27 weeks' gestation, third trimester). The exposure time window of interest for ASD was the second and/or third trimester. Purchases only recorded (not actual adherence to medication) but authors note a study that shows that 94% of drugs dispensed to pregnant women are actually taken.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Includes adjustment for history of maternal psychiatric conditions including affective disorders, such as depression, anxiety, or bipolar disorder (yes or no), and other psychiatric disorders (yes or no). No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Adjusted for other psychiatric disorders.	
c) study controlled for most other important potential confounders	Use of ADs 1 year before the first day of gestation, use of ADs in the first trimester, infant characteristics (sex, year of birth), and maternal variables (maternal age at first day of gestation, high school completed [≥ 12 y], recipient of social assistance, living alone, chronic or gestational hypertension, chronic or gestational diabetes, and other psychiatric disorders).	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Autism spectrum disorder was defined as a medical service claim or hospitalisation with a diagnosis of ASD (childhood autism [International Classification of Diseases, Ninth Revision (ICD-9) code 299.0 or ICD-10 code F84.0], atypical autism [ICD-9 code 299.0 or ICD-10 code F84.1], Asperger syndrome [ICD-9 code 299.8 or ICD-10 code F84.5], other pervasive developmental disorders [ICD-9 code 299.8 or ICD-10 code F84.8], and pervasive developmental disorders not otherwise specified [ICD-9 code 299.9 or ICD-10 code F84.9]).	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Follow-up of children continued from birth until the date of the event (index date: ASD), death (censoring), or the end of the study period (December 31, 2009; censoring), whichever occurred first. Mean time of follow-up was 6.2 years. Analysis included year of birth.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The study was supported by the Canadian Institutes of Health Research and the Québec Training Network in Perinatal Research. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr Bérard reported serving as a consultant for plaintiffs in the litigations involving antidepressants and birth defects. No other disclosures were reported.		
Final score: Moderate risk of bias due to lack of adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Brown 2016

Study type: retrospective registry-based cohort study/Finland		Brown 2016
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from the following national registers in Finland: Medical Birth Register, Drug Reimbursement Register, Hospital Discharge Register, National Population Register.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same national registers; however, the non-exposed cohort was based on identification of psychiatric diagnoses from hospital-based data only, whereas the exposed group may have included women with general practice-diagnosed psychiatric illness. Potential for selection bias.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	The group exposed to SSRIs and the comparison groups were obtained from the drug reimbursement register, which has been maintained since 1995. This register contains data on all reimbursed prescription drug purchases throughout Finland and covers virtually all prescription drug purchases (99% in 2007). Purchases only recorded (not actual adherence to medication) but in another publication using this population cohort authors note previous research has shown a good correlation between prescription register data and self-reported antidepressant use.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication	Includes analysis of SSRI-exposed versus unmedicated depression/psychiatric disorder. Also, adjusted analysis for exposure to anxiolytics/sedatives, maternal history of psychiatric diagnoses, and paternal history of psychiatric diagnoses. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms. Attempted to take severity into account in subgroup analysis by limiting to (i) women on monotherapy and (ii) women who exhibited suicidal behaviour.	★
b) study controls for other treatment	Adjusted for exposure to antiepileptic drugs.	
c) study controls for most other important potential confounders	Analyses adjusted for: sex, previous births, marital status, socioeconomic status, gestational age, mother's country of birth, parental death, smoking, maternal substance abuse, paternal age, maternal age, place of residence and entitlement to chronic diseases.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	The outcomes were coded using ICD-10 and categorized as specific developmental disorders of speech and language (F80), specific developmental disorders of scholastic skills (F81), and specific developmental disorder of motor function (F82). To separately examine each of the categories, participants diagnosed as having combinations of disorders were excluded from the analyses.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	87% of children included were 9 years or younger. Mean age at diagnoses for each outcome was 4.4 years for speech/language disorder, 7.7 years for scholastic disorder and 3.6 years for motor disorder.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★

Study type: retrospective registry-based cohort study/Finland		Brown 2016
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The study was funded by grant P50MH090966 by the National Institutes of Health, the Sackler Foundation of Columbia University, and Turku University. Dr Brown received funding from grant SR01 ES019004 from the National Institute of Environmental Health Sciences. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr Gyllenberg has received research grants from the Sigrid Juselius Foundation, the Foundation for Pediatric Research in Finland, and the Finnish Medical Foundation. Dr McKeague was partially funded by grant 2R01 GM095722-05 from the National Institutes of Health. No other disclosures were reported.		
Final score: High risk of bias due potential for selection bias between exposed and psychiatric disorder/unexposed populations and lack of adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Cole 2007a

Study type: retrospective claims-based cohort study/UnitedHealthcare		Cole 2007a
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The population from this study was drawn from the Ingenix Research Data Mart (RDM) The RDM contains medical and pharmacy claims data from UnitedHealthcare affiliated health plans. Represented approximately 2% of the US population. Has a greater proportion of membership in the South/Southeast and Midwest, and a lower proportion of membership in the Northeast and West. Included women aged between 12 and 49 with live-born delivery between Jan 1995 and Sep 2004.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	Active comparator group (any antidepressants) from the same cohort. Random sample of those originally identified: 7:1 ratio to bupropion for birth years 1995 to 2002 and 2:1 sample for birth years 2003-2004.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Identifies women dispensed bupropion during the first trimester, or prior to first trimester but with days of supply extending into first trimester. From pharmacy records. Dispensed only.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limited to comparison with women receiving other antidepressants. Also adjusted for diagnoses of bipolar disorder. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other medications	Cohort is limited to women who received bupropion or other antidepressants during pregnancy. Data was collected on other potential teratogens. Using stepwise logistic regression, dispensing of lithium, phenytoin and fluconazole were identified as covariates and included in adjusted analyses. Analysis presented in review restricted to subset of bupropion cohort without dispensing of suspected teratogens, and other antidepressants.	★
c) study controls for most other important potential confounders	Analyses adjusted for: maternal age category, geographic region of the health plan, infant sex, diagnoses of bipolar disorder, eclampsia within one year of delivery, dispensing of fluconazole within 1 year of delivery through end of the first trimester, and number of physician visits within 10-12 months before delivery. No adjustment for smoking or alcohol.	★

Study type: retrospective claims-based cohort study/UnitedHealthcare		Cole 2007a
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment	Outcome identified via ICD-9 diagnosis codes. The criteria for inclusion into the final case group were: (1) a structural abnormality with surgical, medical, or cosmetic significance; (2) available medical records within 1 year following birth; and (3) documentation of the defect in question through the abstracted medical record. Exclusion criteria included minor anomalies, birthmarks, physiologic conditions (such as a patent ductus arteriosus or undescended testicles in a premature baby, a patent foramen ovale, congenital hip dislocation after a breech delivery), known chromosomal or genetic conditions, and insufficient evidence available to confirm the diagnosis. A clinical geneticist on the study, team (JMS) reviewed each abstracted record, blinded to the exposure status of the mother, and determined whether the malformation fulfilled the criteria. Likely to be selection bias due to inclusion if live births only.	★
b) record linkage		★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Identified in first 9 months of life	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
As noted in the publication “This paper has potential financial conflicts of interest.” Likely funded by GlaxoSmithKline.		
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Cole 2007b

Study type: retrospective claims-based cohort study/UnitedHealthcare		Cole 2007b
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The population from this study was drawn from the Ingenix Research Data Mart (RDM) The RDM contains medical and pharmacy claims data from UnitedHealthcare affiliated health plans. Represented approximately 2% of the US population. Has a greater proportion of membership in the South/Southeast and Midwest, and a lower proportion of membership in the Northeast and West. Included women aged between 12 and 49 with live-born delivery between Jan 1995 and Sep 2004.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	Active comparator group (any antidepressants) from the same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Identifies women dispensed paroxetine monotherapy or polytherapy during the first trimester, or prior to first trimester but with days of supply extending into first trimester. From pharmacy records. Dispensed only.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		

Study type: retrospective claims-based cohort study/UnitedHealthcare		Cole 2007b
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limited to comparison with women receiving other antidepressants. Also adjusted for diagnoses of bipolar disorder. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other medications	Cohort is limited to women who received bupropion or other antidepressants during pregnancy. Data was collected on other potential teratogens. Using stepwise logistic regression, dispensing carbamazepine, phenytoin, hydrocodone/acetaminophen, norgestimate-ethinyl estradiol, levothyroxine, and sertraline.	★
c) study controls for most other important potential confounders	Analyses adjusted for: maternal age category, geographic region of the health plan, infant sex, diagnosis (within 1 year before delivery) of gestational diabetes, cancer, hemorrhage in early pregnancy, fetal abnormalities affecting the mother, general symptoms, respiratory system or other chest symptoms, and special examinations; and a categorical variable for the number of physician visits within 10–12 months before delivery (0 visits, 1 or 2 visits, or 3 or more visits). No adjustment for smoking or alcohol.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment	Outcome identified via ICD-9 diagnosis codes. The criteria for inclusion into the final case group were: (1) a structural abnormality with surgical, medical, or cosmetic significance; (2) available medical records within 1 year following birth; and (3) documentation of the defect in question through the abstracted medical record. Excluded were minor anomalies, birthmarks, physiologic conditions (such as a patent ductus arteriosus or undescended testicles in a premature baby, a patent foramen ovale, congenital hip dislocation after a breech delivery), known chromosomal or genetic conditions, and cases where evidence was insufficient to confirm the diagnosis. A clinical geneticist reviewed each abstracted record, blinded to the exposure status of the mother, and determined whether the malformation fulfilled the criteria.	★
b) record linkage		★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Identified in first 9 months of life	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Funded by Genzyme Corporation, Cambridge, MA, USA. The sponsor of this project, who had provided funding as it was one of their products being studied, had the right of commenting but the author had the right to accept or reject their comments.		
Final score: Low risk of bias.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Djulus 2006

Study type: prospective cohort study		Djulus 2006
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The cohort was made up primarily of women who contacted five teratology services in Canada (Motherisk Program), Israel (Israel Teratogen Information Service), Australia (Mothersafe Program), US (Pregnancy Riskline) and Italy (Telefono Ross). Also recruited through the Safety research Unit in Southampton, UK.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★

Study type: prospective cohort study		Djulus 2006
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	Captured during interviews at initial contact and 2 to 6 months' post birth. Corroborated with physician report.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Analysis included in review based on women taking antidepressants only.	★
b) study controls for other treatment	8% of women also had a benzodiazepine and 4% also had an anticonvulsant. There were no major malformations in the offspring of these women.	
c) study controlled for most other important potential confounders	Matched for maternal age at conception, gestational age at first contact, tobacco use, alcohol consumption and chronic conditions.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage		★
c) self-report	Birth outcomes captured at post-birth interview. Documented on a structured form and corroborated with physician.	
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	2-6 months	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Supported in part by Wyeth-Ayerst Canada and Shopper Drug Mart, Canada. The sponsors had no role in the design and conduct of the study; the collection, management, analysis and interpretation of the data; the preparation, review and approval of the manuscript; or decision to submit for publication. No potential conflicts of interest were reported by the contributing authors.		
Final score: Moderate risk of bias due to no information on follow-up.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

El Marroun 2014

Study type: prospective cohort study		El Marroun 2014
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The study was embedded in an ongoing prospective population-based cohort, the Generation R Study, in Rotterdam, The Netherlands. All pregnant women resident in Rotterdam were invited to participate. In total, 8880 mothers were enrolled during pregnancy: Of 8800 potentially eligible mothers 4264 -5976 took part, depending on the outcome. Non-participants were younger, more likely to be of non-Dutch origin, less educated and smoked more. Thus, there are some differences between the study and community populations; however, these were adjusted for in the analysis.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		

Study type: prospective cohort study		El Marroun 2014
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	Ascertainment of maternal SSRI use in pregnancy came from two sources: (a) self-report assessed with questionnaires and (b) prescription records from pharmacies. Prescription records were available for 60% of the same and agreement using Yule's Y was 0.93.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limited comparison to children exposed to depression who were not exposed to SSRIs. Adjusted for maternal depressive symptoms at 3 years. No adjustment for maternal illness severity during pregnancy was conducted and adjustment for postnatal depression was only conducted at one timepoint (3 years).	★
b) study controls for other treatment	See below.	
c) study controlled for most other important potential confounders	Adjusted for maternal age at intake, gender of the child, maternal education, ethnicity, maternal smoking habits, gestational age at birth and maternal depressive symptoms at 3 years. Age of the biological father, maternal drinking habits and use of benzodiazepine were not used as covariates as they did not affect the association.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage		★
c) self-report	Presented analyses based on maternal assessment of symptoms related to autism at 1.5, 3 and 6 years. Scales used were the Child Behavior Checklist 1.5-5 and the Social Responsiveness Scale.	
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Up to 6 years	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost	Analyses included only 8098 children who participated in pre- and postnatal follow-up.	
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The Sophia Children's Hospital Fund (SSWO-616) supported this work financially. The first phase of the Generation R Study was made possible by financial support from the Erasmus Medical Centre and The Netherlands Organization for Health Research and Development (Zon MW Geestkracht Program 10.000.1003 & ZonMw TOP 40-00812-98-11021, NWO Brain & Cognition Program Grant 433-09-311 and VIDI Grant 017.106.370). F.C.V. is head of the Department of Child and Adolescent Psychiatry at Erasmus Medical Centre, which publishes the Achenbach System of Empirically Based Assessment (ASEBA) and from which the department receives remuneration.		
Final score: High risk of bias due to self-rated nature of outcome and inadequate adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Figueroa 2010

Study type: retrospective linked primary care record-based cohort study		Figueroa 2010
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★

Study type: retrospective linked primary care record-based cohort study		Figueroa 2010
b) somewhat representative of the average cohort in the community	The MarketScan data used in this study were obtained from large self-insured employers from all states, except Alaska and Hawaii. This study analyses claims data on 38,074 children and their families, who were born during 1997–2002, and where there was information on service utilisation by the mother during pregnancy and by the children until they were at least 4 years old (including years 1997–2006). The MarketScan data contain information from outpatient, inpatient, and prescription claims, including diagnoses, services provided, and the date of the service. The data also contain eligibility and demographic information including gender, age, and metropolitan statistical area. Includes only families with employer health insurance so may not be totally representative of the community. Included live deliveries only.	
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	National drug coding numbers were used to identify specific medications. Dummy variables were created to identify the presence or absence of claims for the different medications in the period before pregnancy, during each trimester of pregnancy, and after pregnancy. Trimesters of pregnancy were estimated by subtracting 93 days at a time from the delivery date. Dummy variables for exposure to other psychotropic classes during pregnancy, including stimulants, anticonvulsants, benzodiazepines, and antipsychotics, were also created and controlled for. Purchases only recorded (not actual dispensing or adherence to medication). No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Adjusted for maternal and paternal mental health diagnoses, the presence or absence of maternal mental health-related visits by period of time, the use of other psychotropics during pregnancy. Multiple dummy variables were created based on the presence or absence of any mental health-related visit by the mother during the following periods of time: the year before pregnancy, during pregnancy, the 6 months postpartum, from 6 months postpartum until the child was 2 years old, from age 2 to 3 years, from age 3 to 4 years, from age 4 to 5 years, and from age 5 to 6 years.	★
b) study controls for other treatment	Dummy variables for exposure to other psychotropic classes during pregnancy, including stimulants, anticonvulsants, benzodiazepines, and antipsychotics, were also created and controlled for.	
c) study controlled for most other important potential confounders	Adjusted for maternal age group, gender of the child, urban or rural metropolitan statistical area, year of birth, and age at last claim and at end of eligibility.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	The main outcome variable for this study was a dummy variable determining whether there was any indication of ADHD at the age of 5 years or earlier. Outpatient and inpatient claims with a primary or secondary diagnosis of ADHD and prescription claims for stimulants, determined by national drug coding, were identified. The age of 5 years was arbitrarily chosen as the optimal tradeoff between the benefit of including children old enough that they are already attending preschool and are more likely to be diagnosed and the limitation of a diminishing number of children with claims data several years after their birth.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Children followed up for up to 4-5 years	★

Study type: retrospective linked primary care record-based cohort study		Figueroa 2010
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Not stated		
Final score: High risk of bias due to inadequate adjustment for confounding and lack of adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Furu 2015

Study type: retrospective register-based cohort study		Furu 2015
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Women from Denmark, Finland, Iceland, Norway, and Sweden who gave birth to a live singleton infant between 1996 and 2010. From nationwide health registers in each Nordic country data were obtained on births, dispensed drugs, birth defects, and potential confounders. These registers include prospectively collected health information on all inhabitants. A civil personal registration number is assigned to each resident at birth or immigration, enabling data linkage between the registers. Reporting to the registers is mandatory and regulated by national laws. The data included in this Review were based on a sibling-controlled analysis which restricted the study population to women with at least two children in the dataset, and only where the siblings were discordant for both exposure and outcome. While this may limit the generalisability of the findings to the wider population, the comparison should remain internally valid.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	The Nordic prescription registers include data on dispensed drugs, substance, brand name, and formulation, together with date of dispensing. Infants were considered to have been exposed in utero if they were born to women who filled a prescription for an SSRI from 30 days before the first day of the last menstrual period until the end of the first trimester (defined as 97 days after the last menstrual period). Purchases only recorded (not actual dispensing or adherence to medication)	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limited analysis to discordant siblings. The within-family analysis helps to minimise the impact of confounding by indication. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	See below.	
c) study controlled for most other important potential confounders	Adjusted for maternal age, year of birth, birth order, smoking, maternal diabetes, country, and use of other prescribed drugs (antiepileptics, anxiolytics and hypnotics, and angiotensin converting enzyme inhibitors).	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★

Study type: retrospective register-based cohort study		Furu 2015
b) record linkage	From the medical birth, patient, and malformation registers data was retrieved on maternal characteristics, the pregnancy and delivery, and major birth defects diagnosed within 365 days after birth. The patient registers record information on diagnoses and hospital visits. During the study period, birth defects were recorded according to ICD-10 in Denmark, Norway, Sweden, and Iceland, whereas ICD-9-CM codes (Atlanta modification for birth defects) were used in Finland . underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Not stated but likely to be.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
This study was funded by the authors' affiliations and the Swedish pharmacy company Apoteksbolaget. Apoteksbolaget had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.		
Final score: Moderate risk of bias for malformations for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Gidaya 2014

Study type: retrospective registry-based case-control study		Gidaya 2014
SELECTION		
1. Is the case definition adequate?		
a) yes, with independent validation	Identified via the Danish National Hospital Register and Danish Psychiatric Central register using ICD-10 codes: F840, F841, F845, F848, and F849 (childhood autism, atypical autism, Asperger's syndrome and pervasive developmental disorder-unspecified, respectively). Subjects were considered a case if any of these codes were present. However, a previous validation study has shown that 94% of diagnoses of childhood autism were confirmed.	★
b) yes, e.g. record linkage or based on self-reports		
c) no description		
2. Representativeness of the cases		
a) Consecutive or obviously representative series of cases	Taken from population-based registers	★
b) Potential for selection biases or not stated		
3. Selection of controls		
a) community controls	Via population-based registers	★
b) hospital controls		
c) no description		
4. Definition of controls		
a) no history of disease (endpoint)	Controls were defined from the Danish Civil Registration System as individuals without ASD admission diagnoses. Ten controls per case were individually matched on birth month and year. Matching on birth month and year assured the same follow-up period for cases and controls, and thus the same opportunity to be identified in the register with an ASD diagnosis.	★
b) no description of source		

Study type: retrospective registry-based case-control study		Gidaya 2014
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Maternal psychiatric history prior to delivery was obtained by searching ICD codes in DCPR records starting in 1969. Psychiatric conditions that are indicators for SSRI use were given special consideration. One variable was created for history of maternal depression, the principal indication for SSRI use, and another for the presence of any other indication, including anxiety, obsessive-compulsive disorder, phobia, adjustment disorder and schizophrenia in the register. The authors note that the majority of women are treated for depression via general practice, and not a psychiatrist, so this wouldn't be picked up by the Danish Psychiatric Central Register and appropriately adjusted for in the analysis. Thus, adjustment for the underlying indication is likely to be deficient in this study. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Not stated.	
c) study controlled for most other important potential confounders	Adjusted for parental age, sex of the child, history of maternal depression, other SSRI indications (and conditions on matching variables of child birth month and year)	★
EXPOSURE		
1. Ascertainment of exposure		
a) secure record	Drawn from the Danish Drug Prescription Register, which records all dispensed prescribed medication from any pharmacy, except hospital dispensaries, in Denmark. Purchases only recorded (not actual adherence to medication).	★
b) structured interview where blind to case/control status		★
c) interview not blinded to case/control status		
d) written self-report of medical record only		
e) no description		
2. Same method of ascertainment for cases and controls		
a) yes		★
b) no		
3. Non-response rate		
a) same rate for both groups	Not applicable; population-based registry study	★
b) non-respondents described		
c) rate different and no designation		
FUNDING/CONFLICT OF INTEREST		
All authors and declare: no support from any organization for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.		
Final score: High risk of bias due to inadequate adjustment for confounding by indication and lack of adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for case-control studies.

Grzeskowiak 2012

Study type: retrospective health network-based cohort study		Grzeskowiak 2012
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★
b) somewhat representative of the average cohort in the community	Included all singleton live births between September 2000 and December 2008 from the Women's and Children's Health Network in South Australia. Linkable health administrative data is used from the following sources: the Women's and Children's Hospital (WCH) Perinatal Statistics Collection and the WCH Pharmacy Dispensing Records. The WCH is a specialist tertiary level teaching hospital and may include women with higher-risk pregnancies. However, this would not affect the internal validity of the study.	
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		

Study type: retrospective health network-based cohort study		Grzeskowiak 2012
3. Ascertainment of exposure		
a) secure record	Women were classified as exposed if they received a dispensing for an SSRI during pregnancy. The authors note that the hospital pharmacy dispensing records have been validated previously as an indicator of late gestation exposure to antidepressants during pregnancy.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Comparator population limited to those with a psychiatric illness and no exposure to SSRIs. Psychiatric illness identified via the Perinatal Statistics Collection from each woman's medical records after delivery by a specially trained research midwife. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Adjusted for other conditions (including epilepsy) and anxiolytic use.	
c) study controlled for most other important potential confounders	Adjusted for: adjusted for maternal age, socioeconomic status, smoking status, race, asthma, preexisting diabetes, alcohol abuse, substance abuse, hypertension, parity, epilepsy, thyroid disorder and anxiolytic use. Preterm delivery additionally adjusted for history of premature delivery.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	The estimated length of gestation at delivery is recorded in the perinatal statistics collection and is based on the last menstrual period and ultrasound examination. Preterm delivery was defined as gestation < 37 weeks. A percentage of optimal birth weight (POBW) score less than the 10 th percentile was used to defines small for gestational age infants. The POBW is the ratio of the observed to the "optimal" birth weight, with the latter calculated from a regression equation, which takes into account major nonpathological determinants of intrauterine growth including gestational age, infant sex, maternal height and parity.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Outcomes captured at birth	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Dr Morrison was supported by a Heart Foundation South Australian Cardiovascular Research Network Fellowship (CR10A4988). Mr Grzeskowiak and Dr Gilbert have no conflicts of interest to declare.		
Final score: Low risk of bias		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Harrington 2014

Study type: prospective population-based case-control study		Harrington 2014
SELECTION		
1. Is the case definition adequate?		
a) yes, with independent validation	To confirm ASD diagnoses, children were assessed with the Autism Diagnostic Interview–Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). A final autism diagnosis required meeting criteria on the communication, social interaction, and repetitive behavior domains of the ADI-R and scoring at or above the social plus communication cutoff for autism on the ADOS. Children with DD diagnosed by regional centers and general population controls were screened for autism by using the Social Communication Questionnaire (SCQ). The ADI-R and ADOS were administered for children who screened positive (SCQ ≥15), and if they met criteria, were reclassified as ASD. The Vineland Adaptive Behavior Scales and Mullen Scales of Early Learning were used to define DD (composite score #70 on either scale).	★
b) yes, e.g. record linkage or based on self-reports		
c) no description		
2. Representativeness of the cases		
a) Consecutive or obviously representative series of cases	Participants were families enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study. CHARGE eligibility criteria included being 2 to 5 years old, born in California, having a parent who speaks English or Spanish, and living with at least one biological parent and in the study catchment area of specified California Regional Centers, which coordinate services for persons with developmental disabilities.	★
b) Potential for selection biases or not stated		
3. Selection of controls		
a) community controls		★
b) hospital controls		
c) no description		
4. Definition of controls		
a) no history of disease (endpoint)	The typical development (TD) group comprised children recruited from the general population scoring >69 on the Mullen Scales of Early Learning and Vineland Adaptive Behavior Scales and <15 on the SCQ. Siblings of probands were excluded, regardless of case status.	★
b) no description of source		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	The analyses included in this Review were limited to a subset of participants with a history of anxiety/mood disorder No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Other medications considered for inclusion in model but not found to be confounders.	
c) study controlled for most other important potential confounders	Adjusted for regional center, child's year of birth, and birthplace of mother.	★
EXPOSURE		
1. Ascertainment of exposure		
a) secure record		★
b) structured interview where blind to case/control status	Unclear if blinded but prenatal records were used where available for cross-source comparison of self-reported SSRI use. Overall percentage agreement between self-reported and prenatal medical record report of SSRI use during pregnancy was 96.7%, with $k = 0.66$. These statistics were highest for the DD group (98.2% agreement, $k = 0.85$) compared with ASD and TD groups (95.8% and 97.4% agreement, respectively; both $k = 0.61$)	★
c) interview not blinded to case/control status		
d) written self-report of medical record only		
e) no description		
2. Same method of ascertainment for cases and controls		
a) yes		★
b) no		
3. Non-response rate		
a) same rate for both groups		★
b) non-respondents described		
c) rate different and no designation	Not reported	

Study type: prospective population-based case-control study	Harrington 2014
FUNDING/CONFLICT OF INTEREST	
This research was supported by US National Institute on Environmental Health Sciences grants P01-ES11269 and R01-ES015359, the MIND Institute, and Autism Speaks. Funded by the National Institutes of Health (NIH). The authors have indicated they have no financial relationships relevant to this article to disclose. The authors have indicated they have no potential conflicts of interest to disclose.	
Final score: Moderate risk of bias due to lack of adjustment for disease severity.	

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for case-control studies.

Hayes 2012

Study type: retrospective Medicaid-based cohort study	Hayes 2012
SELECTION	
1. Representativeness of the exposed cohort	
a) truly representative of the average cohort in the community	Included of 228,876 singleton pregnancies among women aged 15-44 years who were enrolled in the Tennessee Medicaid program from 1995 to 2007, with 180 days of continuous enrollment before their last menstrual period (LMP) through 90 days after delivery. ★
b) somewhat representative of the average cohort in the community	
c) selected group of users (e.g. nurses, volunteers)	
d) no description of the derivation of the cohort	
2. Selection of the non-exposed cohort	
a) Drawn from the same community as the exposed cohort	From same cohort. Unexposed in trimester of interest. ★
b) drawn from a different source	
c) no description of the derivation of the non-exposed cohort	
3. Ascertainment of exposure	
a) secure record	Filled prescriptions of antidepressant medications were counted for the 180 days before LMP, during each trimester of pregnancy, and for the 90 days after delivery. Prescriptions are typically for a 30-day supply of medication. Purchases only recorded (not actual dispensing or adherence to medication). ★
b) structured interview	
c) written self-report	
d) no description	
4. Demonstration that outcome of interest was not present at start of study	
a) yes	★
b) no	
COMPARABILITY	
1. Comparability of cohorts on the basis of the design or analysis	
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Adjusted for the following indication-related variable: depression diagnosis before LMP, anxiety disorder, substance abuse diagnosis, filling antidepressant prescriptions before LMP, Psychiatric medication polytherapy and coexisting psychiatric diagnosis (bipolar disorder, obsessive compulsive disorder or schizophrenia). No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms. ★
b) study controls for other treatment	Captured under comorbidities and other psychiatric diagnoses.
c) study controlled for most other important potential confounders	Other variables adjusted for included: gestational age (unless gestational age, preterm labor, or early preterm labor were the outcome), maternal age, smoking during pregnancy, maternal race, education, comorbidity, adequacy of prenatal care, maternal parity (unless limited to primiparous women), infant sex and year of delivery. ★
OUTCOME	
1. Assessment of outcome	
a) independent blind assessment	★
b) record linkage	Determined with the use of ICD-9 diagnostic codes. ★
c) self-report	
d) no description	
2. Was follow-up long enough for outcomes to occur	
a) yes	★
b) no	
3. Adequacy of follow-up of cohorts	
a) complete follow-up – all subjects accounted for	★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	★
c) follow-up rate high and no description of those lost	
d) no statement	

Study type: retrospective Medicaid-based cohort study	Hayes 2012
FUNDING/CONFLICT OF INTEREST	
Supported by research grants R03 MH 088902 (R.M.H.), K12 scholar HD 043483 and 1RC4MH092755-01 (P.W.), and K24 AI 77930 (T.V.H.) and by Vanderbilt CTSA grant UL1 RR024975-01 from the National Institutes of Health. R.C.S. received research funding from Bristol-Myers Squibb, Eli Lilly and Company, Euthymics Bioscience, Forest Pharmaceuticals, Janssen Pharmaceutica, Novartis Pharmaceuticals, Otsuka Pharmaceuticals, Pamlab, Pfizer, Repligen, and St. Jude Medical. R.C.S. has consulted for Eli Lilly and Company, Cyberonics, Evotec AG, Forest Pharmaceuticals, Gideon Richter PLC, Janssen Pharmaceutica, Medtronic, Otsuka Pharmaceuticals, Pamlab, Inc, Pfizer, Repligen, and Sierra Neuropharmaceuticals. The remaining authors report no conflict of interest.	
Final score: Low risk of bias.	

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Huybrechts 2014a

Study type: retrospective Medicaid-based cohort study	Huybrechts 2014
SELECTION	
1. Representativeness of the exposed cohort	
a) truly representative of the average cohort in the community	<p>The study cohort was drawn from the Medicaid Analytic eXtract for 46 U.S. states and Washington, D.C., for the period of 2000 through 2007. Montana and Connecticut were excluded because of difficulty in linking data for mothers and infants, Michigan was excluded because of incomplete data, and data from Arizona were not available. The Medicaid Analytic eXtract data set contains individual-level demographic and Medicaid enrollment information, as well as data on all physician services and hospitalizations and the accompanying diagnoses and procedures and all filled outpatient medication prescriptions. The study identified all completed pregnancies in women and linked these pregnancies to live-born infants. The population included in this Review was further limited to those with a depression diagnosis.</p> <p>★</p>
b) somewhat representative of the average cohort in the community	
c) selected group of users (e.g. nurses, volunteers)	
d) no description of the derivation of the cohort	
2. Selection of the non-exposed cohort	
a) Drawn from the same community as the exposed cohort	From same cohort. ★
b) drawn from a different source	
c) no description of the derivation of the non-exposed cohort	
3. Ascertainment of exposure	
a) secure record	<p>The etiologically relevant window for exposure extended from the date of the last menstrual period through day 90 of pregnancy (first trimester). The maternal use of antidepressants was determined by a review of pharmacy dispensing records, using the dispensing date and the number of days of supply. Women were considered to have had exposure if the days of supply overlapped with the first trimester. The reference group consisted of women without exposure to antidepressants during the first trimester. Purchases only recorded (not actual dispensing or adherence to medication).</p> <p>★</p>
b) structured interview	★
c) written self-report	
d) no description	
4. Demonstration that outcome of interest was not present at start of study	
a) yes	★
b) no	
COMPARABILITY	
1. Comparability of cohorts on the basis of the design or analysis	
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	<p>Limited the included population to women with depression. In addition, propensity-matched on other indications for antidepressant use: other mental health disorders, PMS smoking and CFS. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms; however, the following variables were used as a proxy for severity: number of depression diagnoses as an outpatient or inpatient.</p> <p>★</p>
b) study controls for other treatment	See below.

Study type: retrospective Medicaid-based cohort study		Huybrechts 2014
c) study controlled for most other important potential confounders	Other variables included in the propensity-matching included: sociodemographic information (year of delivery, state of residence, age, race, and parity), we considered known or suspected risk factors for congenital cardiac malformations and proxies for such risk factors: multiple gestation, chronic maternal illness (hypertension, diabetes, epilepsy, and renal disease), use of suspected teratogenic medications, use of other psychotropic medications (anticonvulsant, antipsychotic, anxiolytic, and hypnotic agents; other benzodiazepines; and barbiturates), use of antidiabetic and antihypertensive medications, and the number of distinct prescription drugs used, excluding antidepressants, as a general marker of coexisting conditions.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Congenital cardiac malformations were identified on the basis of the presence of inpatient or outpatient diagnostic codes from the ICD-9 in the maternal or infant records during the first 90 days after delivery. Both maternal and infant codes were used because an infant's claims may be recorded under the mother's identification number for the first several months after birth. The authors note that a "non-trivial proportion of cases were not confirmed on record review." Likely underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Outcomes followed up for 3 months after birth.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Supported by an award from the Agency for Healthcare Research and Quality (R01 HS018533), a career development grant from the National Institute of Mental Health of the National Institutes of Health (NIH) (K01MH099141, to Dr. Huybrechts), and a training grant in reproductive, perinatal, and pediatric epidemiology from the National Institute of Child Health and Human Development of the NIH (T32HD060454, to Dr. Palmsten).		
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Huybrechts 2015

Study type: retrospective Medicaid-based cohort study		Huybrechts 2015
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The study cohort was drawn from the Medicaid Analytic eExtract for 46 U.S. states and Washington, D.C., for the period of 2000 through 2010. Montana and Connecticut were excluded because of difficulty in linking data for mothers and infants, Michigan was excluded because of incomplete data, and data from Arizona were not available. The Medicaid Analytic eExtract data set contains individual-level demographic and Medicaid enrollment information, as well as data on all physician services and hospitalizations and the accompanying diagnoses and procedures and all filled outpatient medication prescriptions. The study identified all completed pregnancies in women and linked these pregnancies to live-born infants. The population included in this Review was further limited to those with a depression diagnosis.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		

Study type: retrospective Medicaid-based cohort study		Huybrechts 2015
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	The etiologically relevant window for exposure extended from the date of the last menstrual period through day 90 of pregnancy (first trimester). The maternal use of antidepressants was determined by a review of pharmacy dispensing records, using the dispensing date and the number of days of supply. Women were considered to have had exposure if the days of supply overlapped with the first trimester. The reference group consisted of women without exposure to antidepressants during the first trimester. Purchases only recorded (not actual dispensing or adherence to medication).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	The analysis included in the review limited the included population to women with depression. In addition, relevant covariates considered for confounding adjustment included the following antidepressant indications depression, other mental health disorders, pain-related diagnoses, migraine, sleep disorders, premenstrual tension syndrome, smoking, chronic fatigue syndrome. In addition, propensity score-stratification was used to further control for proxies of depression severity and other potential confounders, and high-dimensional propensity score stratification was used to further reduce residual confounding by controlling for proxies of unmeasured confounders. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms; however, the following variables were used as a proxy for severity: number of outpatient and inpatient depression diagnoses.	★
b) study controls for other treatment	See below.	
c) study controlled for most other important potential confounders	Covariates considered for confounding adjustment included: year of delivery, age, race, multiple gestation, other chronic maternal illness (hypertension, preexisting diabetes, gestational diabetes, epilepsy, renal disease, asthma, obesity), other psychotropic medication use (anticonvulsants, antipsychotics, anxiolytics, benzodiazepines, other hypnotics, barbiturates, lithium), antidiabetic, antihypertensive and asthma medications, and nonsteroidal anti-inflammatory drugs. The number of distinct prescription drugs excluding antidepressants dispensed, number of physician outpatient visits, and number of hospital days (measured between 60 and 140 days after LMP to avoid measuring health care use intensity during the exposure window) were used as a general marker of comorbidity. Caesarean delivery was not adjusted for because it has been shown that conditioning on such an intermediate perinatal factor is susceptible to overadjustment bias.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Persistent pulmonary hypertension of the newborn was defined based on the presence of inpatient ICD-9 diagnostic codes for persistent fetal circulation (747.83) or primary pulmonary hypertension (416.0x) in the maternal or infant records during the first 30 days after delivery. Both maternal and infant codes were used because an infant's claims may be recorded under the mother's identification number for the first several months after birth. Although PPHN is typically diagnosed at birth, the window was extended to 30 days after delivery to allow for late submission of health care claims. The positive predictive value for this outcome definition was 89.6% in a validation study based on primary medical record review in cases treated at the delivery hospital.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Outcomes followed up for up to 30 days after birth.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★

Study type: retrospective Medicaid-based cohort study		Huybrechts 2015
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
This study was supported by grant R01 HSO18533 from the Agency for Healthcare Research and Quality. Dr Huybrechts was supported by career development grant K01MH099141 from the National Institute of Mental Health. Dr Bateman was supported by career development grant K08HD075831 from the National Institute of Child Health and Human Development. Dr Palmsten was supported by training grant T32HD060454 in Reproductive, Perinatal and Pediatric Epidemiology from the National Institute of Child Health and Human Development. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.		
Final score: low risk of bias.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Hviid 2013

Study type: retrospective registry-based cohort study. Substantially overlaps with Sørensen 2013 cohort		Hviid 2013
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from national registers in Denmark including: Medical Birth Registry, National Patient Register, National Prescription Registry, Danish Psychiatric Central Register and Danish Civil Registration System.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same national registers.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Recorded prospectively in the National Prescription Registry. Purchases only recorded (not actual adherence to medication).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Includes adjustment for a number of potentially indication-related variables including: psychiatric diagnoses before delivery (excludes diagnoses made in primary care) and other drug use during pregnancy; however, Gidaya 2014 note that the majority of women are treated for depression via general practice, and not a psychiatrist, so this wouldn't be picked up by the Danish Psychiatric Central Register and appropriately adjusted for in the analysis. Thus, adjustment for the underlying indication is likely to be deficient in this study. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	See below.	
c) study controlled for most other important potential confounders (+ illness severity for neurodevelopmental outcomes)	In addition to adjustment for age and calendar period, the rate ratios were adjusted for the mother's age at birth, country of origin, place of residence, parity, psychiatric diagnoses before delivery, other drug use during pregnancy, smoking status during pregnancy, employment status, and level of education. Unless otherwise stated, variables were measured at the beginning of the pregnancy.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★

Study type: retrospective registry-based cohort study. Substantially overlaps with Sørensen 2013 cohort		Hviid 2013
b) record linkage	The coding classification used during the study period was the International Classification of Diseases, 10th Revision (ICD-10). Autism spectrum disorders were classified in two groups: autistic disorder (ICD-10 code F84.0) and other autism spectrum disorders (including atypical autism, Asperger's syndrome, and other or unspecified pervasive developmental disorder; ICD-10 codes F84.1, F84.5, F84.8, and F84.9).	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Followed up from birth until January 1, 2010 or until the child reached 10 years of age, died or was lost to follow-up, or received a diagnosis of autism spectrum disorder, whichever came first. Analysis included adjustment for calendar period. Mean age of follow-up was 5.6 years.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Supported by the Danish Health and Medicines Authority.		
Final score: High risk of bias due inadequate adjustment for confounding by indication and lack of adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Jiang 2016

Study type: systematic review and meta-analysis		Jiang 2016
INTERNAL VALIDITY		
The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper	Yes	
A comprehensive literature search is carried out	Yes	
At least two people should have selected studies	Yes	
At least two people should have extracted data	Yes	
The status of publication was not used as an inclusion criterion	Yes	
The excluded studies are listed	No	
The relevant characteristics of the included studies are provided	Yes	
The scientific quality of the included studies was assessed and reported	Yes	
Was the scientific quality of the included studies used appropriately?	Yes	
Appropriate methods are used to combine the individual study findings	Yes; but unclear what studies have been included in subgroup analyses.	
The likelihood of publication bias was assessed appropriately	Yes	
Conflicts of interest are declared	Yes	
FUNDING/CONFLICT OF INTEREST		
Supported by the Fundamentals Research Funds for Central Universities, China. The authors declare that they have no competing interest.		
OVERALL ASSESSMENT OF SR		
What is your overall assessment of the methodological quality of this review?	High	

Note: Quality assessment completed using the Scottish Intercollegiate Guideline Network (SIGN) checklist for systematic reviews.

Johnson 2016

Study type: prospective cohort study		Johnson 2016
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★
b) somewhat representative of the average cohort in the community	Mother-child dyads were recruited from a larger sample of women enrolled in a prospective longitudinal study at the Emory Women's Mental Health Program, Atlanta, Georgia, US. The sample of women who participated in the preschool follow-up study showed no differences from those who took part, based on age at pregnancy, highest level of education, gestational age of child or method of delivery. No comparison of severity of symptoms made. To be included in the analysis reported here, the children had to be in the age range 2.5 to 5.5 years. Thus, the cohort represents a particular subgroup in the community.	
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		

Study type: prospective cohort study		Johnson 2016
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	Use of psychotropic medications and alcohol, tobacco and caffeine assessed using a weekly tracking sheet completed by a study physician.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Population in study limited to those who were attending a program that specialises in treatment of perinatal mental illness. The Structured Interview for DSM-IV Axis I Disorders-Patient Edition was used to assess history and administered by a trained researcher at enrolment. The mood modules were administered at each prenatal visit. The proportion of visits that met the criteria for a mood disorder was used as a covariate in the analysis. The Beck Depression Inventory was also administered and the preschool BDI was adjusted for in the analysis.	★
b) study controls for other treatment	Covariates tested included other psychotropic medication classes, bupropion, mood stabilisers (including antiepileptics and atypical antipsychotics), anxiolytics and hypnotics.	
c) study controlled for most other important potential confounders	A large number of covariates were tested in the analyses. For the analysis of continuous mother-rated pervasive developmental disorder scores, the only significant variables were preschool BDI, postpartum antidepressant, and prenatal tobacco.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage		★
c) self-report	Pervasive developmental disorder was measured using the subscale of the Child Behaviour Checklist by (i) the mother and (ii) an alternative caregiver.	
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Between 2.5 and 5.5 years	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost	Analyses included only 8098 children who participated in pre- and postnatal follow-up.	
d) no statement		
FUNDING/CONFLICT OF INTEREST		
National Institute of Mental Health (NIMH) grant 1RC1MH008609-01 supported data collection and data entry for the preschool visit; NIMH Translational Research Center in Behavioural Sciences grant TRCBS P50 MH-77928 supported data collection, entry and analysis for data collected during pregnancy; and NIH Specialized Center of Research on Sex and Gender Effects grant SCOR P50 MH 68036 supported additional data collection and entry for prenatal arm of study. Drs Johnson and Smith are supported by NARSAD Young Investigator awards. Br Brennan as supported by a NARSAD Independent Investigator award. The funding agencies had no role in the design and conduct of the study; collection, management analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.		
Final score: High risk of bias due to self-rated nature of outcome and lack of adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Kieler 2012

Study type: retrospective registry-based cohort study. Substantially overlaps with Hviid 2013 cohort		Kieler 2012
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from national registers in Denmark, Finland, Iceland, Norway and Sweden including: medical birth registers, the prescription registers, cause of death registers, patients registers (hospital admissions; and the Danish Psychiatric Central Register). Analyses used in review are limited to those in women with hospital-diagnosed depression.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same national registers.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Recorded prospectively in the national prescription registries. Purchases only recorded (not actual adherence to medication). The authors note good agreement has been reported between use of antidepressants during pregnancy and dispensed drugs.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Analysis included in this Review limited to women with a previous admission to hospital for a psychiatric disorder. No additional adjustment for other depression-related variables. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	See below.	
c) study controlled for most other important potential confounders (+ illness severity for neurodevelopmental outcomes)	Main analysis adjusted for maternal age, dispensed NSAIDs and antidiabetes drugs, pre-eclampsia, chronic diseases during pregnancy, country of birth, birth year, level of delivery hospital and birth order.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Based on ICD-10 code P29.3 or I27.0 in the newborn (diagnosed within 7 days of birth).	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Mean age at the end of follow-up was 8.8 years (0–14 years). Analysis not adjusted for year of birth. Also looked at subcodes P29.3A in Denmark, P29.3 in Finland and P29.3B in Sweden.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The study was funded by the Swedish Pharmacy Company and by the authors' affiliations. The Swedish Pharmacy Company was not involved in the design and conduct of the study; collection, management, analysis, or interpretation of the data; and preparation, review, or approval of the manuscript. All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.		
Final score: Low risk of bias.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Kieviet 2015

Study type: described as a cohort study but appears to have been analysed as a prospective case-control study		Kieviet 2015
SELECTION		
1. Is the case definition adequate?		
a) yes, with independent validation	Poor neonatal adaptation was defined as at least Finnegan score of four or more during hospital admission, because a cutoff of four is generally accepted for PNA. However, the authors note that the use of the Finnegan scoring list has not been validated for the detection of PNA after antidepressant exposure, although they also state that it is the best available and most frequently used scoring list.	★
b) yes, e.g. record linkage or based on self-reports		
c) no description		
2. Representativeness of the cases		
a) Consecutive or obviously representative series of cases	Cohort of women treated with SSRI, SNRI or NaSSA during at least the third trimester of pregnancy from Sint Lucas Andreas Hospital in Amsterdam, The Netherlands. The authors note that the women who deliver in that hospital are a representative sample of pregnant women in Amsterdam, because women give birth in the hospital closest to their home. However, there were a lot of exclusions including women who used any illicit drugs, had regular use of more than two alcohol units a week, or were exposed to more than one of each antidepressant type, or used a combination of types. Therefore, the results might not be generalisable to the broader population of women with depression who are treated during pregnancy.	★
b) Potential for selection biases or not stated		
3. Selection of controls		
a) community controls	From the same original treated cohort.	★
b) hospital controls		
c) no description		
4. Definition of controls		
a) no history of disease (endpoint)	No PNA based on Finnegan assessment	★
b) no description of source		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Overall population limited to those receiving an SSRI, SNRI or NaSSA during pregnancy, so all would have depression or another psychiatric diagnosis. Depression measured during pregnancy and just after and considered as a covariate in the analysis (although was not included because it wasn't shown to be significantly associated with PNA). No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Not reported.	
c) study controlled for most other important potential confounders	Results included in this Review adjusted for prematurity and type of feeding because these were the only variables (apart from treatment type) that were significantly associated with PNA. The other non-depression-related variable considered but not included was smoking.	★
EXPOSURE		
1. Ascertainment of exposure		
a) secure record		★
b) structured interview where blind to case/control status	Via midwife data collection which occurs prior to infant birth	★
c) interview not blinded to case/control status		
d) written self-report of medical record only		
e) no description		
2. Same method of ascertainment for cases and controls		
a) yes		★
b) no		
3. Non-response rate		
a) same rate for both groups		★
b) non-respondents described		
c) rate different and no designation		
FUNDING/CONFLICT OF INTEREST		
No external funding was secured for this study. The authors have no conflict of interests to disclose. All authors declare that they have no financial agreement, professional affiliation or involvement with any company to declare.		
Final score: Moderate risk of bias due to lack of validation of outcome assessment instrument.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for case-control studies.

Laugesen 2013

Study type: retrospective registry-based cohort study		Laugesen 2013
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from national registers in Denmark including: Medical Birth Registry, National Patient Register, National Prescription Registry, Danish Psychiatric Central Register and Danish Civil Registration System.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same national registers.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Recorded prospectively in the National Prescription Registry. Purchases only recorded (not actual adherence to medication).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Includes adjustment for maternal and paternal psychiatric diagnoses; excludes diagnoses made in primary care; in the ASD study using this cohort, Gidaya 2014 note that the majority of women are treated for depression via general practice, and not a psychiatrist, so this wouldn't be picked up by the Danish Psychiatric Central Register and appropriately adjusted for in the analysis. Thus, adjustment for the underlying indication is likely to be deficient in this study. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	See below.	
c) study controlled for most other important potential confounders (+ illness severity for neurodevelopmental outcomes)	Adjusted for gender of the child, calendar time at birth, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal diseases during pregnancy (infections, epilepsy) and maternal medication (anxiolytics/hypnotics/ sedatives) use during pregnancy.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	ADHD was detected either as a diagnosis of ADHD or redemption of a prescription for ADHD medication: (i) using the Danish Psychiatric Registry and the Danish National Registry of Patients, children were identified in the study population with inpatient and outpatient hospital diagnoses of ADHD; or (ii) redemption of a prescription for ADHD medication on the Danish National Prescription Register.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Mean age of follow-up 8 years.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		

Study type: retrospective registry-based cohort study	Laugesen 2013
FUNDING/CONFLICT OF INTEREST	
This study was supported by grants from 'Max og Anna Friedmanns Legat til Sygdomsbekæmpelse', 'Familien Hede Nielsens Fond' and from the Department of Clinical Epidemiology's Research Foundation. Research was conducted independently of the funders. Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the current study. No competing interests reported.	
Final score: High risk of bias due to inadequate adjustment for confounding by indication and lack of adjustment for maternal disease severity.	
Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.	

Malm 2015

Study type: retrospective registry-based cohort study/Finland	Malm 2015
SELECTION	
1. Representativeness of the exposed cohort	
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from the following national registers in Finland: Medical Birth Register, Drug Reimbursement Register, Hospital Discharge Register, National Population Register. Exposed population identified via the Drug Reimbursement Register which includes 98% of all prescription dispensing in Finland. ★
b) somewhat representative of the average cohort in the community	
c) selected group of users (e.g. nurses, volunteers)	
d) no description of the derivation of the cohort	
2. Selection of the non-exposed cohort	
a) Drawn from the same community as the exposed cohort	From same national registers; however, the non-exposed cohort was based on identification of psychiatric diagnoses from hospital-based data only, whereas the exposed group may have included women with general practice-diagnosed psychiatric illness. Potential for selection bias. ★
b) drawn from a different source	
c) no description of the derivation of the non-exposed cohort	
3. Ascertainment of exposure	
a) secure record	Recorded prospectively in Drug Reimbursement Register. Purchases only recorded (not actual adherence to medication) but authors have previously noted that research has shown a good correlation between prescription register data and self-reported antidepressant use. ★
b) structured interview	★
c) written self-report	
d) no description	
4. Demonstration that outcome of interest was not present at start of study	
a) yes	★
b) no	
COMPARABILITY	
1. Comparability of cohorts on the basis of the design or analysis	
a) study controls for underlying indication	Includes analysis of SSRI-exposed versus psychiatric disorder unexposed. Included all mothers who had a diagnosis of a psychiatric disorder related to SSRI use from 1 year before the beginning of gestation until discharge (#3 weeks) from hospital after delivery but who had no purchases of antidepressants or antipsychotics from 3 months before the beginning of gestation until delivery. The diagnoses included nonaffective and undefined psychoses, bipolar, depression or undefined affective disorders and anxiety and other emotional. This group was derived exclusively from specialised services. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms. ★
b) study controls for other treatment	See below.
c) study controls for most other important potential confounders	Adjusted for sex, birth period, maternal age at delivery, place of residence, marital status, parity, smoking, socioeconomic status, purchase of anxiolytics, sedative-hypnotics, or antiepileptic drugs, pre-pregnancy diabetes, and other chronic diseases including thyroid insufficiency, post-transplantation conditions, disseminated connective tissue diseases (including rheumatoid arthritis), chronic asthma, chronic obstructive pulmonary disease, chronic hypertension and inflammatory bowel diseases. ★
OUTCOME	
1. Assessment of outcome	
a) independent blind assessment	★

Study type: retrospective registry-based cohort study/Finland		Malm 2015
b) record linkage	Categorically defined late preterm (32–36 gestational weeks) and very preterm birth (<32 weeks), small for gestational age (birth weight more than two standard deviations below national standards for sex and length of gestation) and neonatal problems, including neonatal breathing problems. Persistent pulmonary hypertension of the newborn and major congenital anomalies were also identified in an analysis of first-trimester exposure.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Supported by NIH grant P50MH090966. Dr. Gyllenberg has received research grants from the Sigrid Juselius Foundation, the Foundation for Pediatric Research (Finland), and the Finnish Medical Foundation. The other authors report no financial relationships with commercial interests.		
Final score: Moderate risk of bias due to potential for selection bias between exposed and psychiatric disorder/unexposed populations.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Malm 2016

Study type: retrospective registry-based cohort study/Finland		Malm 2016
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from the following national registers in Finland: Medical Birth Register, Drug Reimbursement Register, Hospital Discharge Register, National Population Register. Exposed population identified via the Drug Reimbursement Register which includes 98% of all prescription dispensing in Finland.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same national registers and drawn from the unexposed population; however, the psychiatric disorder/no exposure cohort was based on identification of psychiatric diagnoses from hospital-based data only, whereas the exposed group may have included women with general practice-diagnosed psychiatric illness. Comparison in this Review will be limited to the cohort with prior use of SSRIs, as this cohort is likely to be the most comparable to the exposed cohort, as it will include women with general practice-diagnosed psychiatric disorders.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Recorded prospectively in Drug Reimbursement Register. Purchases only recorded (not actual adherence to medication) but authors note previous research has shown a good correlation between prescription register data and self-reported antidepressant use.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication	Includes analysis of SSRI-exposed versus psychiatric disorder unexposed, and SSRI-exposed versus SSRI discontinued. The SSRI discontinued population is the comparator of preference for this Review. Also, adjusted for maternal and paternal history of psychiatric diagnosis. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★

Study type: retrospective registry-based cohort study/Finland		Malm 2016
b) study controls for other treatment	See below.	
c) study controls for most other important potential confounders	Analyses adjusted for: <i>depression (F32-39)</i> : sex; socioeconomic status (SES); smoking during pregnancy; maternal history of other psychiatric diagnosis; maternal history of substance abuse; paternal history of psychiatric diagnosis. <i>Anxiety (F40-41)</i> : sex; marital status; SES; smoking during pregnancy; exposure to antiepileptic drugs; preterm birth; birth weight (<2,500g; ≥2,500g); maternal history of other psychiatric diagnosis; parental death. <i>ASD (F84)</i> : sex; maternal age; SES; maternal history of other psychiatric diagnosis; entitlement to special reimbursement for chronic disease (ever); preterm birth; neonatal care unit. <i>ADHD (F90)</i> : sex; SES; smoking during pregnancy; neonatal care unit; maternal history of other psychiatric diagnosis; maternal history of substance abuse; paternal history of psychiatric diagnosis; parental death.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	The outcome variables included the following: depression, including depressive disorders and unspecified affective disorders (ICD-10 F32–F39); anxiety, including anxiety disorder (F40–F41); autism spectrum disorder (ASD; F84, but excluding Rett syndrome, F84.2); and attention-deficit/hyperactivity disorder (ADHD; F90). Only ICD codes used after the diagnosis was established (ICD-10 F-codes for psychiatric disorders) were included; codes used in the evaluation process (ICD-10 Z-codes) were excluded. Individuals with a depression diagnosis only during the first 2 years of life were excluded if the diagnosis was not recorded at later stages.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no	May be underestimated for depression and anxiety, because only 20-30% of the cohorts were greater than 8 years, which is when most of the diagnoses are seen. Also, some difference between age distribution in groups; children in psychiatric diagnosis/unexposed group and SSRI discontinued groups slightly older. Not adjusted for in analysis although survival analysis used. Mean age across groups ranged from 4.5 years to 5.6 years. Risk of selection bias for these outcomes.	
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
This research was supported by National Institutes of Health grant P50MH090966 (all authors), the Sackler Institute for Developmental Psychobiology of Columbia University (M.W., J.G.), grants from the Sigrid Juselius Foundation, the Foundation for Pediatric Research in Finland, and the Finnish Medical Foundation (D.G.). Dr. Weissman has received funding from the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Sackler Foundation, and the Templeton Foundation; and has received royalties from Oxford University Press, Perseus Press, the American Psychiatric Association Press, and MultiHealth Systems, in the past 3 years. None of these disclosures pose conflicts of interest. Drs. Malm, Brown, Gissler, Gyllenberg, McKeague, Wickramaratne, Artama, Gingrich, Sourander, and Ms. Hinkka-Yli-Salomäki report no biomedical financial interests or potential conflicts of interest.		
Final score: Moderate risk of bias due to lack of adjustment for maternal disease severity for ASD and ADHD. High risk of bias due to selection bias and lack of adjustment for maternal disease severity for depression and anxiety.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Margulis 2013

Study type: retrospective linked primary care record-based cohort study		Margulis 2013
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The Clinical Practice Research Datalink (CPRD), is an automated health care database that contains the electronic medical records, prescriptions, enrollment and demographic information from over 11 million individuals in the UK. Within CPRD, the UK Medicines and Healthcare products Regulatory Agency links mothers and children to create the Mother–Baby Link. The Mother–Baby Link only includes pregnancies that ended in a live birth.	★
b) somewhat representative of the average cohort in the community		

Study type: retrospective linked primary care record-based cohort study		Margulis 2013
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	From each single-ingredient antidepressant prescription, a therapy episode was derived that started on the prescription issue date and had a duration equal to the days supply. Women who had one or more therapy episodes for SSRIs overlapping with the first trimester of pregnancy and did not have therapy episodes for other antidepressants in the same period were categorised as SSRI users. Women with no antidepressant therapy episodes in the 3 months before pregnancy or in the first or second trimester of pregnancy were categorised as non-users. Purchases only recorded (not actual dispensing or adherence to medication).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Propensity score-matched on a number of variables including diagnosis of depression or other mental conditions in baseline year and contact with or referral to a psychiatrist. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	See below.	
c) study controlled for most other important potential confounders	Propensity score-matched on other variables including: year of delivery, maternal age at delivery, pre-pregnancy marital status, index of multiple deprivation at the practice level, family history of congenital malformations, pre-pregnancy body mass, pre-pregnancy diabetes, cigarette smoking, alcohol intake, number of health care encounters in baseline year (visits to and consultations in multiple types of facilities [e.g. home, clinic] for first-time and repeat issues, emergency and non-emergency care, and telephone contacts during and outside of office hours) and number of non-antidepressant drugs prescribed in baseline year.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	To ascertain cardiac malformations in the first year of life, we identified cardiac and surgical codes for cardiac congenital malformations from pregnancy day 180 until the earliest of: first birthday, CPRD-contributing practice transferred-out date, death date or the end of the data collection period (November 30, 2010). Cardiac malformations were grouped in subtypes following a development-based classification system based on the timing of embryologic development and physiological considerations. Likely underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Children followed up for up 1 year and 6 years.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		

Study type: retrospective linked primary care record-based cohort study	Margulis 2013
FUNDING/CONFLICT OF INTEREST	
Funding for this study came from the US Food and Drug Administration (FDA). AVM received a stipend from the US Department of Energy's Oak Ridge Institute for Science and Education (ORISE).	
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.	

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Nakhai-Pour 2010

Study type: retrospective population-based nested case-control study		Nakhai-Pour 2010
SELECTION		
1. Is the case definition adequate?		
a) yes, with independent validation	Cases were defined as women with a diagnosis or a procedure for spontaneous abortion between the first day and the 20th week of gestation. The index date was defined as the calendar date of the spontaneous abortion.	★
b) yes, e.g. record linkage or based on self-reports		
c) no description		
2. Representativeness of the cases		
a) Consecutive or obviously representative series of cases	The study used data from the Quebec Pregnancy Registry, which is built with the linkage of three administrative databases: the Régie de l'assurance maladie du Québec (RAMQ), the Med-Echo database and the Institut de la statistique du Québec database. The RAMQ database provides prospectively collected data on filled prescriptions, physician-based diagnoses according to ICD-9, visits to physicians and emergency departments, medical services dispensed, admissions to hospital, and characteristics of health care providers and patients in the province of Quebec. Med-Echo is a provincial database that records data on acute care hospital admissions for all 7.8 million Quebec residents, including gestational age (defined from the first day of their last menstrual period to the end of pregnancy, confirmed by ultrasound) for planned and spontaneous abortions and deliveries. The Institut de la statistique du Québec data- base provides data on all births and deaths in Quebec, including birth weight and gestational age of deliveries. Women are followed in the Quebec Pregnancy Registry from the date of entry (the first day of gestation) until the end of pregnancy (planned or spontaneous abortion, or delivery). Data in the RAMQ, Med-Echo and Institut de la statistique du Québec databases, including data on gestational age, have been validated previously.	★
b) Potential for selection biases or not stated		
3. Selection of controls		
a) community controls	Controls were selected from among women registered in the Quebec Pregnancy Registry.	★
b) hospital controls		
c) no description		
4. Definition of controls		
a) no history of disease (endpoint)	Controls were women who did not have a spontaneous abortion at or before the same gestational age as their matched case did.	★
b) no description of source		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Analysis adjusted for depression, anxiety and bipolar disorder, visits to psychiatrists, and exposure to antidepressants in the year before pregnancy. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	See below.	
c) study controlled for most other important potential confounders	Adjusted for maternal sociodemographic characteristics (age, social assistance status and place of residence), gestational age at index date, comorbidities (diabetes mellitus, cardiovascular disease, asthma, and untreated thyroid disease), history of spontaneous abortion and therapeutic abortion, number of prescribers, number of visits to physicians, duration of exposure to medications other than antidepressants in the year before pregnancy, and number of prenatal visits, visits to obstetricians and other medication use during pregnancy. Categories are mutually exclusive, and two different models were performed to obtain findings for the classes and types of antidepressants.	★

Study type: retrospective population-based nested case-control study		Nakhai-Pour 2010
EXPOSURE		
1. Ascertainment of exposure		
a) secure record	From the RAMQ database. The authors note that the evaluation of exposure based on filled prescriptions might not have reflected actual intake. However, they hypothesized that women who filled a prescription for an antidepressant took at least one dose, since within the Quebec drug plan, they need to cover part of the cost of their medications. Therefore, given the design of the study, they suggest this would not invalidate our findings.	★
b) structured interview where blind to case/control status		★
c) interview not blinded to case/control status		
d) written self-report of medical record only		
e) no description		
2. Same method of ascertainment for cases and controls		
a) yes		★
b) no		
3. Non-response rate		
a) same rate for both groups	Not applicable; claims-based registry study	★
b) non-respondents described		
c) rate different and no designation		
FUNDING/CONFLICT OF INTEREST		
The study was supported by the FRSQ and the Réseau Québécois de recherche sur l'utilisation du médicament (RQRUM). The sponsors had no role in the design of the study, the analysis or interpretation of the data, or the writing of the manuscript. Anick Bérard is the recipient of a career award from the Fonds de la recherche en santé du Québec (FRSQ) and is on the endowment research chair on Medications, Pregnancy and Lactation at the Faculty of Pharmacy of the University of Montréal. Anick Bérard was a consultant for a plaintiff in the litigation involving Paxil. No competing interests declared by Hamid Reza Nakhai-Pour or Perrine Broy.		
Final score: Low risk of bias.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for case-control studies.

Nulman 2015

Study type: prospective cohort study		Nulman 2015
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Mothers were selected and recruited from the prospectively collected database of Motherisk (an information and consultation service for women and their health providers on the reproductive risk/safety of environmental and genetic factors) at The Hospital for Sick Children in Toronto, Canada. Women diagnosed with depression using DSM-IV criteria and their two children, exposed and unexposed to SRIs (SSRIs or SNRIs) were included.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	Initial information about medication use was obtained at the time of the first call to Motherisk, as per a standard database intake form. To reduce recall bias, a routine telephone follow-up of children 6 to 9 months after delivery was performed and details on medication use were also elicited here.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limited population to women with depression and compared exposed and unexposed siblings within this group. Adjustment for severity of maternal symptoms during and after pregnancy.	★

Study type: prospective cohort study		Nulman 2015
b) study controls for other treatment	Excluded mothers on psychotropic drug polytherapy for comorbid psychiatric conditions, known teratogens (e.g. antiepileptic drugs, isotretinoin) or substances of abuse (e.g. alcohol).	
c) study controlled for most other important potential confounders	Additionally adjusted for child's age and birth order (the only covariates shown to be associated with the outcomes)	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment	Psychological assessments were performed using the WPPSI-II (IQ), and CBCL and CPRS-R (behavioural problems). A psychometrist masked to group affiliation tested all children individually using age-appropriate tests.	★
b) record linkage		★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	3-6 years	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	The authors note that 17 women refused participation and 45 sibling pairs were lost to follow-up. Their demographic characteristics were compared and there were no differences for any parameters tested.	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Supported in part by Wyeth-Ayerst Canada and Shopper Drug Mart, Canada. The sponsors had no role in the design and conduct of the study; the collection, management, analysis and interpretation of the data; the preparation, review and approval of the manuscript; or decision to submit for publication. No potential conflicts of interest were reported by the contributing authors.		
Final score: Low risk of bias.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Oberlander 2006

Study type: retrospective linked primary care record-based cohort study		Oberlander 2006
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Data was from five administrative sources housed in the British Columbia Linked Health Database: BC registry of births, hospital separation records, Pharmacare registry of subsidised prescriptions, the Medical Services Plan physician billing records and the registry of Medical Services Plan subscribers. Following matching of datasets and accounting for data errors records for multiple births, the final cohort included 119,547 of 203,250 potentially eligible live births.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Prescriptions for SSRIs, antipsychotics and benzodiazepines were identified in the PharmaNet dataset. Included women who had filled a prescription for an SSRI 49 days or more after conception but who had not received any other antidepressants, antipsychotics or benzodiazepines during pregnancy. 90% of mothers in this group had received a diagnosis of depression either during pregnancy or in the previous year.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		

Study type: retrospective linked primary care record-based cohort study		Oberlander 2006
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Using propensity scores, population was matched on the following variables: related to the underlying indication: pre-pregnancy – number of visits to a psychiatrist, number of times diagnosed as depressed, number of times receiving an ICD-9 code that might include depression, number of times diagnosed as having a mental health disorder, excluding those diagnosed as having depression; prenatal – diagnosed as depressed, diagnosed with a 3-digit code that might include depression, number of times diagnosed as depressed, number of treatments by a psychiatrist, filled a prescription for an antipsychotic, filled a prescription for a tricyclic antidepressant.	★
b) study controls for other treatment	Excluded women exposed to benzodiazepines and antipsychotics from the control groups.	
c) study controlled for most other important potential confounders	Also propensity score-matched on: Pre-pregnancy – number of times provided counselling by a general practitioner, number of visits to a physician, income decile, drugs subsidised; and prenatal: age, number of prenatal visits. No adjustment for smoking, alcohol, illicit drug use, socioeconomic conditions beyond income decile.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Based on databases available.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The study was supported in part by the British Columbia Ministry of Children and Family Development through the Human Early Learning Partnership (HELP) and by the Michael Smith Foundation for Health Research, through the Child and Youth Developmental Trajectory Research Unit. Dr Oberlander is supported by a HELP Senior Career Award and has the R. Howard Webster Professorship in Child Development (University of British Columbia, Faculty of Graduate Studies). Dr Misri has participated in speakers' bureaus for GlaxoSmithKline Inc, Lundbeck, Wyeth, AstraZeneca, and Eli Lilly and Company; has served as a consultant for GlaxoSmithKline Inc, AstraZeneca, and Wyeth; and has conducted research for AstraZeneca, GlaxoSmithKline Inc, Lundbeck, March of Dimes, The British Columbia Medical Research Foundation, the Vancouver Foundation, and the Canadian Institutes of Health Research.		
Final score: Low risk of bias.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Oberlander 2008a

Study type: retrospective linked primary care record-based cohort study		Oberlander 2008a
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Data was from five administrative sources housed in the British Columbia Linked Health Database: BC registry of births, hospital separation records, Pharmacare registry of subsidised prescriptions, the Medical Services Plan physician billing records and the registry of Medical Services Plan subscribers. Following matching of datasets and accounting for data errors records for multiple births, the final cohort included 119,547 of 203,250 potentially eligible live births.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		

Study type: retrospective linked primary care record-based cohort study		Oberlander 2008a
3. Ascertainment of exposure		
a) secure record	Prescriptions for SRIs (SSRIs + venlafaxine) and benzodiazepines were identified in the PharmaNet dataset. Exposure in the first trimester was determined if the dispensing period (i.e. days of dosing covered by the prescription) overlapped with the period from the LMP to LMP plus 90 days. Prescriptions only recorded (not actual dispensing or adherence to medication).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Adjusted for depression in the first trimester, times visiting a psychiatrist in the previous year, number of time receiving a diagnosis of depression in the previous year. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Diagnosis of epilepsy or seizures was identified from maternal records regardless of timing of exposure.	
c) study controlled for most other important potential confounders	Adjusted for maternal age, prenatal care visits, number of visits to a physician in previous year, maternal illness characteristics, diseases, and complications of pregnancy diagnosed more than 60 days before birth, and a dummy variable indication the mother filed a prescription after she knew she was pregnant. Methadone use was used as a proxy marker for other maternal characteristics such as poor nutrition or other drug use.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Neonatal outcomes were identified using ICD-9 codes for major congenital abnormalities (740.0 to 759.9) and the subset of cardiovascular defects (745.0-747.9). Congenital anomalies considered minor were excluded. Specific codes for ventricular septal defects (745.4) and atrial septal defects (745.5) were also used. Likely underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Probably. Study notes 39-month period of data collection but not clear what the average period of time after birth data was checked at.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
BC Ministry of Children and Family Development; The Michael Smith Foundation for Health Research. T.F.O. is supported by a HELP Senior Career Award and is the R.Howard Webster professor in Child Development (UBC, Faculty of Graduate Studies). None of the authors has a conflict of interest with these data or our findings.		
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Petersen 2016

Study type: retrospective linked primary care record-based cohort study		Petersen 2016
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Included all singleton live births between 1990 and 2011 from The Health Improvement Network (THIN), in which the medical records of the mothers and the children were linked to provide prospectively recorded information throughout pregnancy and in the year before pregnancy. THIN is a nationally representative database of computerised primary care records from across the UK that has been validated for pharmacoepidemiology studies, and contains diagnoses, events, symptoms, and drug prescriptions.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Women were considered to be on antidepressants during pregnancy only if two or more prescriptions were recorded and the gaps between prescriptions were less than 4 months.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limited comparator population for analysis included in this Review to women exposed to antidepressants. Analysis additionally adjusted for antipsychotic and anxiolytic use. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Data on exposure to antipsychotics, anxiolytics, hypnotics and antiepileptic drugs collected but unclear if considered in analysis.	
c) study controlled for most other important potential confounders	Adjusted analysis included in this Review also adjusted for age, alcohol, diabetes, illicit drugs, obesity, smoking and Townsend deprivation score (SES).	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Diagnoses of congenital heart anomalies were identified in the children's medical records using Read codes. Likely underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Children followed up for up to 5 years	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The idea for the study was conceived at the time Dr Petersen received fellowship funding from the United Kingdom Medical Research Council to study prescribed medicine in pregnancy (grant code G0601726). The funders had no influence on the design, analysis or interpretation of the study. No authors had conflicts to disclose.		
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Rai 2013

Study type: registry-based nested case-control study		Rai 2013
SELECTION		
1. Is the case definition adequate?		
a) yes, with independent validation	Children with autism spectrum disorders were identified in the Stockholm youth cohort using a multisource case ascertainment method, with registers covering all pathways of autism diagnosis and care within Stockholm County. Diagnoses recorded in these registers (codes from the ICD-9 [299] and ICD-10 [F84], respectively, or DSM-IV [299]) were supplemented by a record of care in specialist centres for autism with and without intellectual disability, where an autism diagnosis and cognitive testing is a prerequisite. Comorbid intellectual disability status using ICD-9 (317-319), ICD-10 (F70-79), and DSM-IV (317-319) were also identified in the child or adult mental health registers or the national patient register. Two validation procedures—a case note validation study by a consultant child psychiatrist and a neuropaediatrician and a cross validation study with a national twin study—both found a high validity of the diagnoses for autism spectrum disorder recorded in the registers used for case ascertainment.	★
b) yes, e.g. record linkage or based on self-reports		
c) no description		
2. Representativeness of the cases		
a) Consecutive or obviously representative series of cases	Taken from population-based registers	★
b) Potential for selection biases or not stated		
3. Selection of controls		
a) community controls	From the same Stockholm youth cohort.	★
b) hospital controls		
c) no description		
4. Definition of controls		
a) no history of disease (endpoint)	From the same Stockholm youth cohort, the authors matched each case of autism spectrum disorder to 10 living controls without autism by date (month and year) of birth and sex.	★
b) no description of source		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	The authors identified the psychiatric history of parents using two sources: the Stockholm County adult psychiatric outpatient register, which records the dates and diagnoses for any contact with specialist outpatient psychiatric services in Stockholm County, and the Swedish national patient register, which contains the dates and discharge diagnoses of all) and specialist outpatients in Sweden. Using these sources, the authors identified mothers and fathers with depression if they had a registered diagnosis of a depressive episode, recurrent depressive disorder, persistent mood disorder, and other or unspecified mood disorder. The authors note that most people with depression don't seek help or are managed in primary care. Thus, adjustment for the underlying indication is likely to be deficient in this study. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Adjusted for other psychiatric disorder.	
c) study controlled for most other important potential confounders	Adjusted for any maternal psychiatric disorder, maternal age, paternal age, parental income, education, occupation, maternal country of birth, and birth parity.	★
EXPOSURE		
1. Ascertainment of exposure		
a) secure record		★
b) structured interview where blind to case/control status	The Swedish medical birth register contains data on current drug use reported by mothers at their first antenatal interview (median 10 weeks' gestation), coded using the WHO ATC codes. The medical birth register has been shown to identify 78% of all antidepressants prescribed during the first trimester, and the drug name registered in prescription records and that recorded in the register has been reported to show high concordance (97%).	★
c) interview not blinded to case/control status		
d) written self-report of medical record only		
e) no description		
2. Same method of ascertainment for cases and controls		
a) yes		★
b) no		

Study type: registry-based nested case-control study		Rai 2013
3. Non-response rate		
a) same rate for both groups	Not applicable; population-based registry study	★
b) non-respondents described		
c) rate different and no designation		
FUNDING/CONFLICT OF INTEREST		
The study was funded by the Swedish Research Council (grant No 2012-3017). The data linkages and staff costs have also been supported by grants from the Stockholm County Council (2007008), Swedish Council for Working Life and Social Research (2007-2064), Swedish Research Council (523-2010-1052), and Swedish Regional agreement on medical training and clinical research (ALF). No funder had any role in the study design; data collection, analysis, or interpretation; in the writing of the report; or in the decision to submit the article for publication. All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.		
Final score: High risk of bias due to inadequate adjustment for confounding by indication and lack of adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for case-control studies.

Ramos 2008

Study type: retrospective claims database-based case-control study		Ramos 2008
SELECTION		
1. Is the case definition adequate?		
a) yes, with independent validation	Women were assigned to the 'case' group if their infants were diagnosed with at least one major congenital malformation identified at delivery or during the 12 months after delivery belonging to the following categories of congenital anomaly: ICD-9 codes 740-759. The year following delivery in was included in order to identify as many birth defects as possible, given the fact that congenital malformation diagnoses could have been delayed. Only major congenital malformations were considered, and thus minor malformations were excluded (ICD-9 codes 743.6, 744.1, 744.2-744.4, 744.8, 744.9, 747.0, 747.5, 750.0, 752.4, 752.5, 754.6, 755.0, 755.1, 757.2-757.6, 757.8, 757.9, 758.4). Women whose infants were stillborn were also assigned to the case group, in order not to underestimate the association between duration of antidepressant use and major congenital malformations. Likely underestimates malformations because miscarriages are excluded from the analysis. Potential for selection bias.	★
b) yes, e.g. record linkage or based on self-reports		
c) no description		
2. Representativeness of the cases		
a) Consecutive or obviously representative series of cases	Identified via the RAMQ database which includes information on all medical services (diagnoses and procedures) received by all Quebec residents. Although RAMQ covers all Quebec residents for the cost of physician visits, hospitalisations and procedures, it covers only a proportion of residents for the cost of medications. The RAMQ drug plan covers individuals aged 65 years and older, recipients of social assistance (welfare recipients), and workers and their families (adherents) who do not have access to a private drug insurance programme, accounting for approximately 43% of the overall Quebec population. It is estimated that 30% of women aged 15-45 years in Quebec are covered by the RAMQ drug plan for their medications (RAMQ data). While this may impact on the generalisability of the findings, it does not affect the internal validity. Population limited to women who had received at least one diagnosis of a psychiatric disorder defined according to the ICD-9 classification (codes 290-319) before pregnancy; have used antidepressants for at least 30 days in the year prior to pregnancy; and have had a pregnancy ending with a delivery (live birth or stillbirth).	★
b) Potential for selection biases or not stated		
3. Selection of controls		
a) community controls	Via same claims-based registers	★
b) hospital controls		
c) no description		
4. Definition of controls		
a) no history of disease (endpoint)	The control group comprised women whose infants were not diagnosed with any congenital malformation.	★
b) no description of source		

Study type: retrospective claims database-based case-control study		Ramos 2008
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Study limited to women with a psychiatric diagnosis or antidepressant use. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms, but variables used as a proxy of severity included number of days on antidepressants in the year before pregnancy, number of psychiatric disorder diagnoses received before and during pregnancy, number of visits to the psychiatrist the year before and during pregnancy, use of anxiolytic/sedative drugs such as benzodiazepines and of anticonvulsants such as barbiturates during pregnancy, and antidepressant use during the second and third trimesters of pregnancy.	★
b) study controls for other treatment	Considered number of additional medications and comorbid conditions (including diabetes, hypertension, asthma) and use of use of anxiolytic/sedative drugs such as benzodiazepines and of anticonvulsants such as barbiturates during pregnancy.	
c) study controlled for most other important potential confounders	A survey was sent out to eligible women to capture additional information from women on potential confounders. 35% of women responded. Adjustment for these additional confounders did not alter the findings of the study. Adjusted for maternal age, being on welfare, urban dweller, living alone, measures related to psychiatric disorders and measures of comorbidities not related to psychiatric disorders before and during pregnancy, hypertension and diabetes diagnoses before and during pregnancy, gender of baby, prenatal visits and year of pregnancy.	★
EXPOSURE		
1. Ascertainment of exposure		
a) secure record	From the RAMQ database	★
b) structured interview where blind to case/control status		★
c) interview not blinded to case/control status		
d) written self-report of medical record only		
e) no description		
2. Same method of ascertainment for cases and controls		
a) yes		★
b) no		
3. Non-response rate		
a) same rate for both groups	Not applicable; claims-based registry study	★
b) non-respondents described		
c) rate different and no designation		
FUNDING/CONFLICT OF INTEREST		
This study was supported by the Fonds de la Recherche en Sante' du Que' bec (FRSQ), grant number 6263, the Re' seau Que' be' cois de Recherche sur l'Usage des Me' dicaments and the FRSQ Network for the Wellbeing of Children. E.R. is the recipient of a PhD bursary from the CHU Sainte-Justine. A.B. is the recipient of a career award from the Canadian Institutes of Health Research/Health Research Foundation, and is the Endowment Research Chair of the Famille Louis-Boivin on Medications, Pregnancy and Lactation at the Faculty of Pharmacy of the University of Montreal.		
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for case-control studies.

Simon 2002

Study type: retrospective group-model health maintenance organisation-based cohort study		Simon 2002
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The study sample was drawn from the Group Health Cooperative, a prepaid health plan serving approximately 400,000 members in Washington State. The membership is generally representative of the area's population in terms of age, sex, ethnicity, and socioeconomic status. Because of contracts between Group Health Cooperative and the state of Washington, the 1996 membership included approximately 25,000 individuals covered by Medicaid and 12,000 covered by the Basic Health Plan, a state subsidised program for low-income residents. Group Health Cooperative's computerized information systems record outpatient prescriptions, outpatient visits, and hospital discharges.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		

Study type: retrospective group-model health maintenance organisation-based cohort study		Simon 2002
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Pharmacy records were used to identify all antidepressant prescriptions filled or refilled during the 360 days before delivery. Mothers with no antidepressant prescriptions during this period were considered unexposed. Those with any antidepressant prescriptions during the 270 days before delivery were considered exposed. The remaining patients (i.e., those with antidepressant prescriptions filled in the period between 270 and 360 days before delivery) were classified as indeterminate and excluded from further analysis. Except for Medicare members, all Group Health Cooperative plans include prescription drug coverage. Previous surveys have indicated that over 95% of exposure to antidepressants is captured by computerised pharmacy records.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Matched on lifetime number of antidepressant prescriptions filled or refilled, lifetime history of outpatient psychiatric treatment, lifetime history of inpatient psychiatric treatment. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Not reported.	
c) study controlled for most other important potential confounders	Matched on the following additional characteristics: age, year of delivery, and length of Group Health Cooperative enrollment.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Malformation outcomes identified via (i) standardised physical examination records from pediatric health-monitoring ("well-baby") visits from birth to age two and (ii) records of all other outpatient visits and, where appropriate, hospital admissions. For each infant, all relevant records were photocopied after masking all identifying information and information regarding any prenatal exposures. Two chart reviewers received an initial six hours of training from the investigators, followed by approximately 40 hours of supervision during the course of the project. Reviews were conducted by using a structured abstraction form available from the first author on request. All records with any suspected abnormalities (malformation, developmental delay, etc.) were also reviewed by the investigators for diagnostic classification. Final classification of malformation diagnosis and malformation severity (major versus minor) was performed by a pediatrician specializing in diagnosis and treatment of congenital malformations. Likely underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Not specifically stated for malformations but for other outcomes (weight and head circumference) was measured up until age two.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		

Study type: retrospective group-model health maintenance organisation-based cohort study	Simon 2002
FUNDING/CONFLICT OF INTEREST	
Supported by NIMH grant MH-57811.	
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.	

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Sørensen 2013

Study type: retrospective registry-based cohort study. Substantially overlaps with Hviid 2013 cohort		Sørensen 2013
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Study conducted using prospectively collected data from national registers in Denmark including: Danish Civil Registration System, Danish National Prescription Registry, Danish Psychiatric Central Register, Danish Medical Birth registry and Danish National Hospital Register. Analyses used in review are limited to those in women with hospital-diagnosed depression and sibling analyses.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same national registers.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Recorded prospectively in the National Prescription Registry. Purchases only recorded (not actual adherence to medication). The authors note a Danish study that reported high compliance for antidepressant medication prescribed to pregnant women (80%).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Includes analyses limited to women with a hospital-based diagnosis of affective disorder, or exposed and unexposed siblings from families with at least one child diagnosed with ASD. No adjustment for maternal illness severity during or after pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Adjusted for parental psychiatric history.	
c) study controlled for most other important potential confounders	Analysis was adjusted for maternal age at conception, paternal age at conception, parental psychiatric history (except maternal affective disorder), gestational age, birth weight, sex, and parity.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	The study identified children who had been diagnosed with ASD or childhood autism (CA) by December 6, 2010 based on ICD-10 (codes F84.0, F84.1, F84.5, F84.8, and F84.9). The quality of the infantile autism diagnosis in the DPCR has been validated, with 94% of children diagnosed with childhood autism using the ICD-10 meeting the criteria for correct diagnosis.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Mean age at the end of follow-up was 8.8 years (0–14 years). Analysis not adjusted for year of birth.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		

Study type: retrospective registry-based cohort study. Substantially overlaps with Hviid 2013 cohort		Sørensen 2013
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Jakob Christensen received honoraria from giving lectures and serving on the scientific advisory board of UCB Nordic and Eisai AB, and received funding for a trip from UCB Nordic. The other authors have no conflicts to declare in this study.		
Final score: Moderate risk of bias due to lack of adjustment for maternal disease severity.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

AppD5.1.2 Antipsychotics

The 11 individual studies for which results are considered in the 'Assessment of evidence' section (**Section AppD4.1.2**) were assessed for risk of bias using the Newcastle-Ottawa Scale (low, moderate or high risk of bias).

Bodén 2012b

Study type: retrospective, linked, population-based cohort study		Bodén 2012b
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Population-based cohort of exposed singleton infants (or stillborns) identified from the Swedish Medical Birth Register, Prescribed Drug Register and National Patient Register.	★
b) somewhat representative of the average cohort in the community		★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Exposure was defined as a <u>dispensed</u> prescription for an antipsychotic on the Prescribed Drug Register. However, the register does not include drugs administered in hospitals.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Population-based, so no selection bias for outcome of interest.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	No – groups defined by exposure irrespective of diagnosis, and no adjustment for indication (captured as indirectness).	★
b) study controls for other treatment	Excluded exposure to prochlorperazine, levomepromazine, and melperone prescriptions (mainly used as antiemetics or anxiolytics). Lithium was also excluded.	★
c) study controlled for most other important potential confounders	Adjusted for birth order, maternal age, country of origin, cohabitation, smoking, and height.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	The Medical Birth Register contains data on almost all births in Sweden. The information is obtained by midwives and attending physicians in connection with visits and hospitalizations from the antenatal visit through the neonatal period.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★

Study type: retrospective, linked, population-based cohort study		Bodén 2012b
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Financial Disclosure: None reported. Funding/Support: This study was supported by unrestricted grants from the Lennander's Foundation and Gillbergska Foundation. Role of the Sponsor: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.		
Final score: Moderate risk of bias for malformation outcomes: potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis. Low risk of bias for other outcomes.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Cohen 2016

Study type: prospective hospital-based pregnancy registry for SGAs		Cohen 2016
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★
b) somewhat representative of the average cohort in the community	Pregnant women aged 18-45, recruited through provider referral, self-referral, and the Center's web site. Analysis based on live births.	★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	Same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	Participants are interviewed at three time points across pregnancy: at enrollment, at 7 months, and at 3 months postpartum.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Enrollment occurred during pregnancy.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Partially – comparator group “consisted mostly of women with a history of psychiatric illness” exposed to other psychotropic medication. The impact of diagnosis was explored using bipolar disorder as a confounder in univariate analyses, but only crude results were considered for interpretation by the authors.	★
b) study controls for other treatment	Only crude results were interpreted by authors. Each potential confounding factor was added individually to the crude logistic regression model to examine the changes in the OR estimate from the unadjusted model. A hypothetical propensity score-adjusted model was examined in a sensitivity analysis, created using a logistic regression model to predict exposure to SGAs. The score was created using a primary diagnosis of bipolar disorder and first-trimester use of FGAs, SSRIs, SNRIs, tricyclic antidepressants, atypical antidepressants (bupropion), antianxiety medications, sedatives, and stimulants (<i>this adjusted OR was extracted for the current Review</i>). An additional sensitivity analysis examined the relationship between major malformations and SGA-use excluding all participants exposed to known teratogens: valproic acid, isotretinoin, lithium, and first-trimester illicit drug use (no change to OR – no infants with malformations exposed).	★
c) study controlled for most other important potential confounders	Factors such as smoking, anticonvulsant use, maternal age and others were explored in univariate analyses, but as mentioned above, this study is far smaller than other antipsychotics studies reporting adjusted results (N = 303), and the authors note that they only interpret crude results .	★

Study type: prospective hospital-based pregnancy registry for SGAs		Cohen 2016
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage		★
c) self-report	During the final postpartum interview (3 months postpartum), information is gathered from maternal reports regarding pharmacotherapy, labor, delivery, and neonatal health outcomes. Likely underestimates malformations because the study does not capture potential excess malformations coinciding with miscarriage, abortion or stillbirth, which are not included in the study population. Potential for selection bias.	
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost	7.2% of women were lost to follow-up.	
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Supported by AstraZeneca, Bristol-Myers Squibb, Ortho-McNeil-Janssen Pharmaceuticals, Pfizer, and Sunovion Pharmaceuticals. Dr. Cohen has received research support for the National Pregnancy Registry for Atypical Antipsychotics from AstraZeneca, Bristol-Myers Squibb/Otsuka, Ortho-McNeil-Janssen Pharmaceuticals, Pfizer, and Sunovion Pharmaceuticals; he has received other research support from Abbott Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Berlex Laboratories, Cephalon, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceuticals, the National Alliance for Research on Schizophrenia and Depression, the National Institute on Aging, NIH, NIMH, Organon, Sanofi-Synthelabo, Sepracor, Stanley Medical Research Institute, Takeda/Lundbeck, van Ameringen Foundation, Wyeth-Ayerst Pharmaceuticals, and Wyeth Pharmaceuticals; he has received consulting fees from Eli Lilly, GlaxoSmithKline, Janssen Pharmaceuticals, JDS/Noven Pharmaceuticals, Novartis Pharmaceuticals, Ortho-McNeil Pharmaceuticals, PamLab, Sepracor, and Wyeth-Ayerst Pharmaceuticals; and he has received honoraria from AstraZeneca, Berlex Pharmaceuticals, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceuticals, Pfizer, and Wyeth-Ayerst Pharmaceuticals. Dr. Viguera has received research support for the National Pregnancy Registry for Atypical Antipsychotics from AstraZeneca, Bristol-Myers Squibb, Ortho-McNeil-Janssen Pharmaceuticals, Pfizer, and Sunovion Pharmaceuticals; she has received other research support from the Epilepsy Foundation and NIMH; and she has received consulting fees from Medco Health Solutions. Dr. Freeman has received research support from the Department of Defense, GlaxoSmithKline, NIMH, the Patient-Centered Outcomes Research Institute, and Takeda; she has received consulting fees from Genentech, JDS Therapeutics, Johnson & Johnson, Lundbeck, Otsuka, and Takeda; and she has received medical editing stipends from DSM Nutritional and the GOEDOmega-3 newsletter. Dr. Hernández-Díaz has received support for training grants from Bayer AG, the Pharmaceutical Research and Manufacturers of America, Pfizer, and Takeda; she has consulted for Astra-Zeneca, GlaxoSmithKline Biologicals, and UCB; and she is an investigator for the North American Antiepileptic Drug Pregnancy Registry and the National Pregnancy Registry for Atypical Antipsychotics, which are supported by multiple companies. The other authors report no financial relationships with commercial interests.		
Final score: Moderate risk of bias: potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis (malformation outcomes only are reported).		

Abbreviations: OR, odds ratio; SGA, second generation antipsychotic.

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Habermann 2013

Study type: prospective cohort study with matched controls		Habermann 2013
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★
b) somewhat representative of the average cohort in the community	Pregnant women were enrolled through the consultation process at the Teratology Information Service (TIS Berlin) offered free to pregnant women and health care providers. Study entry could have taken place at any time between conception (defined as 2 weeks of gestation) and delivery. Women or health care providers must have initiated contact with the TIS to be enrolled.	★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★

Study type: prospective cohort study with matched controls		Habermann 2013
b) structured interview	Data ascertainment was performed using 2 structured questionnaires at (1) the first contact and (2) 8 weeks after the estimated date of birth.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Enrollment occurred on query by pregnant women.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	No – groups defined by exposure irrespective of diagnosis (captured as indirectness). One comparison addressed indication: SGAs versus FGAs.	★
b) study controls for other treatment	Women exposed to teratogenic or fetotoxic agents were excluded from the main comparator group but the exposure groups were “assessed afterward”. This assessment is not described.	★
c) study controlled for most other important potential confounders	Maternal age, alcohol consumption (>1 drink/day), smoking habits (>5 cigarettes/day), number of previous spontaneous abortions, number of previous malformed children, and gestational week at delivery were considered as covariates and potential confounders when assessing embryo-/fetotoxic effects. Adjustment was achieved through logistic regression using relevant confounders identified by model selection including all potential confounders in a start model. Only alcohol consumption (>1 drink/day) was shown to have a significant influence and, therefore, was considered in the final analysis.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	A detailed history of drug use is recorded at the first contact. In addition, the interview includes demographic characteristics, previous and current obstetrical history, family history, maternal chronic diseases, and other risks and exposures. Follow up is especially focused on congenital anomalies and postnatal disorders. For this purpose, the hospital discharge summaries are asked for. Likely underestimates malformations because the study does not capture potential excess malformations coinciding with miscarriage or abortion. Potential for selection bias	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for	Yes	★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The authors declare no conflicts of interest.		
Final score: Moderate risk of bias for malformation outcomes: potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis. Low risk of bias for other outcomes.		

Abbreviations: FGA, first generation antipsychotics; SGA, second generation antipsychotic.

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Huybrechts 2016

Study type: retrospective Medicaid cohort study		Huybrechts 2016
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Nationwide insurance database the cohort consisted of all pregnancies that resulted in live births for which Medicaid covered the health care expenses.	★
b) somewhat representative of the average cohort in the community		★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		

Study type: retrospective Medicaid cohort study		Huybrechts 2016
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Exposure to antipsychotics was defined based on filling at least 1 prescription during the first 90 days of pregnancy.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Large insurance database, so no selection bias for outcome of interest.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Groups in main analysis defined by exposure irrespective of diagnosis, but main analyses adjusted for both indication ⁶⁰⁸ (first adjustment) as well as a propensity score (fully adjusted). Additional exploratory analyses adjusted for a high-dimensional propensity score. The impact of indication was also addressed in comparisons restricting both cohorts to women with psychosis, schizophrenia or bipolar disorder, or comparing continuing use with discontinuing use.	★
b) study controls for other treatment	Yes, using propensity score as described below.	★
c) study controlled for most other important potential confounders	Adjusted for a propensity score based on a broad range of potential confounders or proxies for potential confounders, including calendar year, age, race, smoking, multiple gestation, indications for APs, other maternal morbidity, concomitant medication use, and general markers of the burden of illness. Indications for AP use included schizophrenia, bipolar disorder, psychosis, depression, anxiety, attention-deficit/ hyperactivity disorder, and other psychiatric disorders. Other maternal morbidities included other psychiatric and neurologic conditions (personality disorder, adjustment disorder, delirium, sleep disorders, chronic fatigue syndrome, alcohol and other drug abuse or dependence, epilepsy or convulsions, migraine, and other headaches) and chronic maternal illness (diabetes, hypertension, renal disease, and obesity). Concomitant medications assessed included other psychotropic medications (anticonvulsants, antidepressants, anxiolytics, benzodiazepines, other hypnotics, barbiturates, and stimulants), antidiabetic medications, antihypertensives, and suspected teratogens, as well as methadone hydrochloride, naloxone hydrochloride, naltrexone hydrochloride, and opioid use as possible proxies for drug abuse or dependence. Finally, general markers of comorbid illness included the Obstetric Morbidity Index and numbers of distinct prescriptions for medications other than APs, distinct diagnoses, outpatient visits, hospitalizations, and emergency department visits. A high-dimensional propensity score based on 200 covariates was also adjusted for in exploratory analyses.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	We defined the outcomes based on infant claims only. Restricting the outcome definition to malformation codes in the infant's record only did not alter the results. Likely underestimates malformations because the study does not capture potential excess malformations coinciding with miscarriage, abortion or stillbirth, which are not included in the study population. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes – 3 months from birth.	★
b) no		

⁶⁰⁸ Medicaid database includes diagnoses from inpatient and outpatient sources.

Study type: retrospective Medicaid cohort study		Huybrechts 2016
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
<p>Conflict of Interest Disclosures: Dr Hernández-Díaz reports consulting for AstraZeneca and UCB for unrelated topics. Dr L. Cohen reports receiving grant support from AstraZeneca Pharmaceuticals, Alkermes, Bristol-Myers Squibb/Otsuka, Sunovion Pharmaceuticals, Inc, Bayer HealthCare Pharmaceuticals, Ortho-McNeil Janssen Pharmaceuticals, Inc, Pfizer, Inc, Forest Laboratories, Inc, Cephalon, Inc, GlaxoSmithKline, Takeda/Lundbeck, National Institute on Aging, National Institutes of Health, and National Institute of Mental Health (NIMH) and personal fees for consultancy from JDS Therapeutics LLC, Noven Pharmaceuticals, and PamLab LLC. No other disclosures were reported. Funding/Support: This study was supported by grant R01 MH100216 from the NIMH, career development grant K01MH099141 from the NIMH (Dr Huybrechts), career development grant K08HD075831 from the National Institute of Child Health and Human Development (Dr Bateman), and grant P3SMP3-158808/1 from the Swiss National Science Foundation (Dr Panchaud). Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.</p> <p>Final score: Moderate risk of bias: potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis (malformation outcomes only are reported).</p>		

Abbreviations: AP, antipsychotic.

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Johnson 2012

Study type: prospective, university program-based cohort study		Johnson 2012
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★
b) somewhat representative of the average cohort in the community	Women participating in a naturalistic study of the perinatal course of mental illness at the Emory Women's Mental Health Program (WMHP) were invited to participate in the current protocol. Women with varied psychiatric histories were referred to the WMHP by community providers including obstetricians, therapists, and other psychiatrists during pregnancy or prior to conception.	★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	The nonmedicated subsample of the WMHP cohort was supplemented with an additional community control group that was recruited after pregnancy via a mass mailing.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	Women in the Women's Mental Health Program cohort were followed up longitudinally across pregnancy and the postpartum period; psychometric data and maternal report of medication exposure were gathered during all visits. Prenatal psychotropic exposure data were collected retrospectively from the community cohort. We have previously reported that postpartum maternal recall of prenatal psychotropic exposure at 6 months postpartum is reliable when compared with the prospective record.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Yes – enrollment was during pregnancy or prior to conception, infant outcomes at 6 months.	★
b) no		

Study type: prospective, university program-based cohort study		Johnson 2012
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Yes – the comparator group was a mix of women with and without mental health disorders (38% had no psychiatric history ⁶⁰⁹) but psychiatric diagnoses during pregnancy were tested and found not to be significantly associated with INFANIB scores (so were not adjusted for in effect size estimates). Results were adjusted for a lifetime history of at least 1 major depressive episode or dysthymia, a lifetime diagnosis of a psychotic disorder and a severity/chronicity index (for the severity/chronicity composite variable, 1 point was given for each of the following: (1) psychiatric diagnosis lasting longer than 10 years, (2) previous hospitalization, and (3) past or present psychotropic treatment). Not adjusted for postnatal severity of disease.	★
b) study controls for other treatment	Mothers prescribed antiepileptic drugs during pregnancy were removed from the sample to isolate the potential effects of antipsychotic medications.	★
c) study controlled for most other important potential confounders	Additional covariates were adjusted for where a significant association was found (infant age at test, maternal age).	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment	Infant Neurological International Battery (INFANIB)	★
b) record linkage		★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes – clinically informative cutoff scores are provided for 3 age groups, including 4 to 8 months old (outcome at 6 months).	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Number analysed, rather than enrolled, was reported. High loss to follow up: 8.7% failed to complete the INFANIB because of fatigue or irritability (attrition was comparable between exposure groups).	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Financial Disclosure: Dr Stowe has received research support from the National Institutes of Health, GlaxoSmithKline, Pfizer, and Wyeth; served on speakers or advisory boards for Pfizer, Eli Lilly, Wyeth, Bristol-Myers Squibb, and GlaxoSmithKline; and received honoraria from Eli Lilly, GlaxoSmithKline, Pfizer, and Wyeth. Dr Newport has received research support from Eli Lilly, GlaxoSmithKline, Janssen, the National Institutes of Health, NARSAD, and Wyeth; served on speakers or advisory boards for AstraZeneca, Eli Lilly, GlaxoSmithKline, Pfizer, and Wyeth; and received honoraria from AstraZeneca, Eli Lilly, GlaxoSmithKline, Pfizer, and Wyeth. Funding/Support: This study was supported by a NARSAD Young Investigator Grant Award (Dr Brennan), Emory University Silvio O. Conte Center for the Neurobiology of Mental Disease grant MH58922, Specialized Center of Research on Sex and Gender Effects grant MH68036, and National Institute of Mental Health grant MH88609. Role of the Sponsors: The study sponsors had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.		
Final score: Moderate risk of bias: lack of adjustment for maternal disease severity.		

Abbreviations: INFANIB, Infant Neurological International Battery.

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Källén 2013

Study type: retrospective, linked, population-based cohort study		Källén 2013
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Population-based cohort of exposed live births from the Swedish Medical Birth Register linked to Register of Birth Defects, Register of Prescribed Drugs and Hospital Discharge Register.	★
b) somewhat representative of the average cohort in the community		★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		

⁶⁰⁹ No psychiatric history in 24/38 in the community cohort, nor in 8/47 of the WMHP cohort – in control group of 85, 32 (38%) had no psychiatric history.

Study type: retrospective, linked, population-based cohort study		Källén 2013
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Late pregnancy drug exposure was defined as a <u>dispensed</u> prescription for an antipsychotic on the Prescribed Drug Register. Early pregnancy drug exposure was determined at midwife interview during the first antenatal care visit (data recorded in Medical Birth Register).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Population-based, so no selection bias for outcome of interest.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	No – groups defined by exposure irrespective of diagnosis, and no adjustment for indication (captured as indirectness).	★
b) study controls for other treatment	For malformations, infants exposed to concomitantly used drugs with teratogenic properties were excluded in some analyses. Dixyrazine and prochlorperazine (used for non-psychiatric indications) were excluded from the exposed group.	★
c) study controlled for most other important potential confounders	Adjusted for year of birth, maternal age (5-year class), parity (1-4+), smoking in early pregnancy and BMI.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Information on congenital malformations was obtained from the Medical Birth Register (MBR) but was supplemented with data from the Register of Birth Defects (RCM, previously Register of Congenital Malformations) and from a Hospital Discharge Register (HDR), containing diagnoses after inpatient treatments. Likely underestimates malformations because the study does not capture potential excess malformations coinciding with miscarriage, abortion or stillbirth, which are not included in the study population. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Conflicts of interest: The authors declare no conflicts of interest.		
Final score: Moderate risk of bias for malformation outcomes: potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis. Low risk of bias for other outcomes.		

Abbreviations: BMI, Body mass index.

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Lin 2010

Study type: retrospective, population-based cohort		Lin 2010
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Population-based cohort of live-birth singleton infants of mothers with schizophrenia identified from the National Health Insurance Research Database (universal health insurance coverage) and linked to the birth certificate registry. Schizophrenia patients identified by at least three consensus diagnoses using ICD codes.	★
b) somewhat representative of the average cohort in the community		★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		

Study type: retrospective, population-based cohort		Lin 2010
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Using ICD-9-CM codes to retrieve patient profiles from the claims (database), women receiving antipsychotics during pregnancy were defined as those prescribed antipsychotics for more than 30 days while pregnant. [Somewhat limited by indirectness of prescribing as an indicator of exposure rather than reporting of actual exposure.]	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Population-based, so no selection bias for outcome of interest.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Yes – exposed and comparator populations limited to women with schizophrenia.	★
b) study controls for other treatment	Women who received antiepileptics or lithium during pregnancy were excluded.	★
c) study controlled for most other important potential confounders	Adjusted for infant gender, parity, maternal age, highest maternal and paternal educational levels (separately), hypertension, gestational diabetes, parental age difference, mother marital status, and family monthly income. The authors noted they were not able to adjust for smoking with the available data.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	The birth certificate registry provides data on birthdates for both infants and their parents, gestational week at birth, birth weight, gender, parity, place of birth, parental educational levels, and maternal marital status	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Conflict of interest: None. Role of funding source: None.		
Final score: Low risk of bias.		

Abbreviations: ICD, International Classification of Diseases; ICD-9, International Classification of Diseases, Ninth Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Petersen 2016a

Study type: retrospective linked primary care record-based cohort study		Petersen 2016a
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The Health Improvement Network and the Clinical Practice Research Datalink are two large primary care databases that provide continuous anonymised longitudinal general practice data on patients' clinical and prescribing records and include data from >10% of the UK population.	★
b) somewhat representative of the average cohort in the community		★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		

Study type: retrospective linked primary care record-based cohort study		Petersen 2016a
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Women who were prescribed antipsychotics prior to pregnancy irrespective of whether or not they had a record of psychosis in their electronic health records.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Population-based database, so no selection bias for outcome of interest.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	No – groups in main analysis defined by exposure irrespective of diagnosis, but some analyses compare groups with mental health disorders, such as patients that discontinue antipsychotics prior to pregnancy, which controls somewhat for underlying indication. No adjustments for indication were performed (captured as indirectness). No adjustment for disease severity.	★
b) study controls for other treatment	Adjusted for concomitant prescriptions (e.g. antidepressants and anticonvulsant mood stabilisers).	★
c) study controlled for most other important potential confounders	Adjusted for maternal age; 'health and lifestyle' factors (i.e. smoking, obesity, records of alcohol and illicit drug problems).	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	<p>Malformations: Read codes from database records were used to ascertain outcomes. For malformations, these Read code lists were compared with the EUROCAT guidelines and reviewed by a GP to identify whether the codes indicated a major or minor malformation occurred.</p> <p>Neurodevelopmental outcomes: This outcome includes a broad range of Read codes describing developmental delay as well as behavioural problems recorded within the first 5 years of life. Read codes for neurodevelopmental and behavioural disorders were identified as those relating to conditions listed as neurodevelopmental or behavioural disorders in Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition.</p> <p>Likely underestimates malformations because the study does not capture potential excess malformations coinciding with miscarriage, abortion or stillbirth, which are not included in the study population. Potential for selection bias. However, a sensitivity analysis explored the potential impact of various scenarios and found extreme assumptions may result in changes in relative risk estimates.</p>	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★
c) follow-up rate high and no description of those lost		
d) no statement		

Study type: retrospective linked primary care record-based cohort study	Petersen 2016a
FUNDING/CONFLICT OF INTEREST	
<p>Declared competing interest of authors: Phillip J Cowen has, in the last 3 years, been a paid member of an advisory board of Lundbeck. Nick Freemantle has received funding for research and consultancy from a variety of governmental, industrial, and charitable sources. Cormac J Sammon has received funding for research from Novartis Vaccines and Diagnostics. Irene Petersen supervises a PhD student who is sponsored by Novo Nordisk. Irwin Nazareth is currently a member of the National Institute for Health Research Health Technology Assessment commissioning board.</p> <p>The research reported in this issue of the journal was funded by the HTA programme (part of the National Institute for Health Research, UK).</p>	
<p>Final score: Moderate risk of bias for malformation outcomes due to potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis. High risk of bias for neurodevelopmental outcome due to lack of adjustment for maternal disease severity and use of a non-validated outcome assessment tool.</p>	

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Reis 2008

Study type: retrospective, linked, population-based cohort study	Reis 2008
SELECTION	
1. Representativeness of the exposed cohort	
a) truly representative of the average cohort in the community	Population-based cohort of exposed live births and stillborns identified from the Swedish Medical Birth Register linked to Register of Congenital Malformations, Register of Prescribed Drugs and Hospital Discharge Register. ★
b) somewhat representative of the average cohort in the community	★
c) selected group of users (e.g. nurses, volunteers)	
d) no description of the derivation of the cohort	
2. Selection of the non-exposed cohort	
a) Drawn from the same community as the exposed cohort	From same cohort. ★
b) drawn from a different source	
c) no description of the derivation of the non-exposed cohort	
3. Ascertainment of exposure	
a) secure record	Early pregnancy drug exposure was determined at midwife interview during the first antenatal care visit, usually before the end of the first trimester (data recorded in Medical Birth Register). ★
b) structured interview	★
c) written self-report	
d) no description	
4. Demonstration that outcome of interest was not present at start of study	
a) yes	Population-based, so no selection bias for outcome of interest. ★
b) no	
COMPARABILITY	
1. Comparability of cohorts on the basis of the design or analysis	
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	No – groups defined by exposure irrespective of diagnosis, and no adjustment for indication (captured as indirectness). ★
b) study controls for other treatment	Anticonvulsants excluded in a sensitivity analysis (resulting in the loss of significance). ★
c) study controlled for most other important potential confounders	Adjusted for year of birth, maternal age, parity, smoking, and previous miscarriages. ★
OUTCOME	
1. Assessment of outcome	
a) independent blind assessment	★
b) record linkage	<p>Ascertainment of congenital malformations was made from 3 national health registers: Medical Birth Register, Register of Congenital Malformations, and the Hospital Discharge Register. The last-mentioned register was used up to and including 2005. Linkage between registers was made using maternal and child personal identification numbers that everyone living in Sweden has and is widely used in society and in all health care.</p> <p>Likely underestimates malformations because the study does not capture potential excess malformations coinciding with miscarriage or abortion, which are not included in the study population. Potential for selection bias.</p> ★
c) self-report	
d) no description	
2. Was follow-up long enough for outcomes to occur	
a) yes	Yes ★
b) no	
3. Adequacy of follow-up of cohorts	
a) complete follow-up – all subjects accounted for	★

Study type: retrospective, linked, population-based cohort study		Reis 2008
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias. Data on 1.4% of all deliveries in Sweden are missing in the register.	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Author Disclosure Information: The authors declare no conflict of interest.		
Final score: Moderate risk of bias for malformation outcomes: potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis. Low risk of bias for other outcomes.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Sorensen 2015

Study type: retrospective, linked, population-based cohort		Sorensen 2015
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Identified all clinically recognized pregnancies in Denmark with an estimated conception date and an observed pregnancy outcome from the Danish National Prescription Register and Danish National Hospital Register and the Danish Medical Birth Register. Information about all pregnancies was obtained, except for very early miscarriages, which may be considered a late menstrual period. Information was linked through the Danish personal identification number, assigned to all citizens. We investigated all inpatient or outpatient contacts involving a diagnosis of spontaneous abortion before 22 weeks of gestation (in Denmark, a child born after 22 weeks of gestation is either stillborn or live born). We also included specific information on pregnancies ending in a molar pregnancy, ectopic pregnancy, induced abortion, stillbirth or live birth.	★
b) somewhat representative of the average cohort in the community		★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Prescription dispensed (Danish National Prescription Register). The medication exposure window was defined as the period from 30 days before the estimated conception date to one day prior to spontaneous abortion/ stillbirth/ birth.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Population-based, so no selection bias for outcome of interest.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	No – groups in main analysis defined by exposure irrespective of diagnosis, but some analyses compare groups with mental health disorders, such as patients that discontinue antipsychotics prior to pregnancy, or patients with a psychiatric diagnosis (from Danish Psychiatric Central Register, which captures hospital but not GP diagnoses), which controls somewhat for underlying indication (captured as indirectness for non-restricted comparisons).	★
b) study controls for other treatment	Adjusted for concomitant medication.	★
c) study controlled for most other important potential confounders	Adjusted for maternal age at conception, cohabitation at time of conception, income at time of conception, education level at time of conception.	★

Study type: retrospective, linked, population-based cohort		Sorensen 2015
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Abortions were identified in the Danish National Hospital Register, which contains data on all inpatient and outpatient contacts in Denmark since 1995 coded according to ICD-10. stillbirths were identified in the Danish Medical Birth Register, which holds information on all births in Denmark.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Funding: The Regional Center for Child and Adolescent Psychiatry, Aarhus University Hospital, Risskov, Denmark, contributed with funding to the study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Competing Interests: Merete Juul Sørensen, Maiken Ina Siegismund Kjaersgaard, Bodil Hammer Bech, Henrik Søndergaard Pedersen, Mogens Vestergaard, Jørn Olsen, Lars Henning Pedersen and Erik Parner have no competing interests. Jakob Christensen reported receiving honoraria for serving on the scientific advisory boards of UCB Nordic and Eisai AB; receiving lecture honoraria from UCB Nordic and Eisai AB; being involved in clinical trials initiated by UCB Nordic, Eisai, Pfizer and Novartis, and receiving travel funding from UCB Nordic. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.		
Final score: Low risk of bias.		

Abbreviations: ICD-10, International Classification of Diseases, Tenth Revision.

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Vigod 2015

Study type: retrospective, linked, population-based, hdPS-matched cohort		Vigod 2015
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Obstetric deliveries were identified using Institute for Clinical Evaluative Sciences' MOMBABY datafile. This validated datafile comprises all in-hospital deliveries in Ontario, with 98% successful linkage of maternal and newborn health records. Study population (all participants) consisted of women eligible for public drug coverage who had been hospitalised for obstetrical delivery of a live-born or stillborn infant between 1 April 2003 and 31 December 2012. These women had universal access to hospital care, physician services, and drug coverage. To ensure that all participants were covered under the provincial drug plan (Ontario Drug Benefit) during the index pregnancy, we only included those who had filled a provincially funded drug prescription within 180 days before pregnancy and one during pregnancy or within 180 days of delivery.	★
b) somewhat representative of the average cohort in the community		★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		

Study type: retrospective, linked, population-based, hdPS-matched cohort		Vigod 2015
3. Ascertainment of exposure		
a) secure record	Exposure to antipsychotic drugs and other medications were identified using the Ontario Drug Benefit database, which records prescription medication use for those receiving full drug benefits under the provincial drug programme with an error rate of <1%. Eligibility for drug coverage includes unemployment, disability, high prescription drug costs relative to net household income, and receipt of home care services. Approximately 70% of pregnant women with a psychotic disorder receive Ontario Drug Benefit coverage.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Population-based, so no selection bias for outcome of interest.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Yes – underlying indication ⁶¹⁰ addressed through matching subjects using hdPS (500 covariates).	★
b) study controls for other treatment	Adjusted for a prescribed SSRI, non-SSRI, mood stabiliser, or benzodiazepine during the index pregnancy. Exposure to teratogens not mentioned but are included as covariate in the hdPS matching (e.g. tretinoin).	★
c) study controlled for most other important potential confounders	Yes, through 500 covariates in hdPS matching.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Perinatal outcomes were based on validated ICD-10-CA diagnoses during the index birth hospitalisation (Canadian Institutes of Health Information Discharge Abstract Database).	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
<p>Funding: This study was supported by a grant from the Canadian Institutes of Health Research (CIHR). It was also supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Role of the study sponsors: The study sponsors provided the operating costs and infrastructure to support the research. No funding bodies had any role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript. Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that no authors (nor their institutions) received payments for their efforts on this project. Unrelated to this project, SNV has received a one-time consulting fee from Multi-Dimensional Health Care (MDH) consulting for the development of continuing healthcare activities related to perinatal mental health; VHT receives funding from Bristol-Myers Squibb for an investigator initiated study and has been a speaker for Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly, and Lundbeck. The remaining authors declare no competing interests: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.</p>		
Final score: Low risk of bias.		

Abbreviations: hdPS, high-dimensional propensity score; ICD-10-CA, International Classification of Diseases, Tenth Revision, Canada; SSRI, selective serotonin reuptake inhibitor.

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

⁶¹⁰ The data dimensions used were those traditionally available within health claims databases, and included our aforementioned data sources for hospital (CIHIDAD, OMHRS), emergency department (NACRS), and physician billing claim (OHIP) diagnoses and procedures, as well as for prescription drug claims (ODB).

AppD5.1.3 Anticonvulsants

Bromley 2014

Study type: systematic review and meta-analysis		Bromley 2014
INTERNAL VALIDITY		
The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper	Yes	
A comprehensive literature search is carried out	Yes	
At least two people should have selected studies	Yes	
At least two people should have extracted data	Yes	
The status of publication was not used as an inclusion criterion	Yes	
The excluded studies are listed	Yes	
The relevant characteristics of the included studies are provided	Yes	
The scientific quality of the included studies was assessed and reported	Yes	
Was the scientific quality of the included studies used appropriately?	Yes	
Appropriate methods are used to combine the individual study findings	No, combined raw data from observational studies	
The likelihood of publication bias was assessed appropriately	Yes	
Conflicts of interest are declared	Yes	
FUNDING/CONFLICT OF INTEREST		
National Institute for Health Research, UK: independent research commissioned by the National Institute for Health Research (NIHR). The views expressed in the publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. National Institute for Health Research, UK: the report is independent research supported by the National Institute for Health Research (Post-Doctoral Fellowship, Dr Rebecca Bromley, PDF-2013-06-041). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.		
OVERALL ASSESSMENT OF QUALITY		
What is your overall assessment of the methodological quality of this review?	Moderate	

Note: Quality assessment completed using the Scottish Intercollegiate Guideline Network (SIGN) checklist for systematic reviews.

NICE 2015

Study type: systematic review and meta-analysis		NICE 2015
INTERNAL VALIDITY		
The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper	Yes	
A comprehensive literature search is carried out	Yes	
At least two people should have selected studies	Yes	
At least two people should have extracted data	Yes	
The status of publication was not used as an inclusion criterion	Yes	
The excluded studies are listed	Yes	
The relevant characteristics of the included studies are provided	Yes	
The scientific quality of the included studies was assessed and reported	Yes	
Was the scientific quality of the included studies used appropriately?	Yes	
Appropriate methods are used to combine the individual study findings	No, combined raw data from observational studies	
The likelihood of publication bias was assessed appropriately	Unclear	
Conflicts of interest are declared	Yes	
FUNDING/CONFLICT OF INTEREST		
The guideline was commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). The NCCMH is a collaboration of the professional organisations involved in the field of mental health, national service user and carer organisations, a number of academic institutions and NICE. The NCCMH is funded by NICE and is led by a partnership between the Royal College of Psychiatrists and the British Psychological Society's Centre for Outcomes Research and Effectiveness, based at University College London. The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included women who have experienced a mental health problem in the pregnancy or the postnatal period, and professionals from psychiatry, clinical psychology, general practice, nursing, health visitors, obstetrics, midwifery and the private and voluntary sectors, and a mother-infant specialist. All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting.		
OVERALL ASSESSMENT OF SR		
What is your overall assessment of the methodological quality of this review?	Moderate	

Note: Quality assessment completed using the Scottish Intercollegiate Guideline Network (SIGN) checklist for systematic reviews.

Tanoshima 2015

Study type: systematic review and meta-analysis		Tanoshima 2015
INTERNAL VALIDITY		
The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper	Yes	
A comprehensive literature search is carried out	Yes	
At least two people should have selected studies	Yes	

Study type: systematic review and meta-analysis		Tanoshima 2015
At least two people should have extracted data	Yes	
The status of publication was not used as an inclusion criterion	Yes	
The excluded studies are listed	Yes	
The relevant characteristics of the included studies are provided	Yes	
The scientific quality of the included studies was assessed and reported	Yes	
Was the scientific quality of the included studies used appropriately?	Yes	
Appropriate methods are used to combine the individual study findings	No, combined raw data from observational studies	
The likelihood of publication bias was assessed appropriately	Yes	
Conflicts of interest are declared	Yes	
FUNDING/CONFLICT OF INTEREST		
T.K. was financially supported by the Japan Society of Clinical Pharmacology and Therapeutics. R.T. was financially supported by the Joseph M. West Family Memorial Fund from the Post Graduate Medical Education at University of Toronto, Toronto, Canada during the period of this study. The authors do not have any competing interest to disclose.		
OVERALL ASSESSMENT OF SR		
What is your overall assessment of the methodological quality of this review?	Moderate	

Note: Quality assessment completed using the Scottish Intercollegiate Guideline Network (SIGN) checklist for systematic reviews.

Weston 2016

Study type: systematic review and meta-analysis		Weston 2016
INTERNAL VALIDITY		
The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper	Yes	
A comprehensive literature search is carried out	Yes	
At least two people should have selected studies	Yes	
At least two people should have extracted data	Yes	
The status of publication was not used as an inclusion criterion	Yes	
The excluded studies are listed	Yes	
The relevant characteristics of the included studies are provided	Yes	
The scientific quality of the included studies was assessed and reported	Yes	
Was the scientific quality of the included studies used appropriately?	Yes	
Appropriate methods are used to combine the individual study findings	No, combined raw data from observational studies	
The likelihood of publication bias was assessed appropriately	Yes	
Conflicts of interest are declared	Yes	
FUNDING/CONFLICT OF INTEREST		
National Institute for Health Research, UK: independent research commissioned by the National Institute for Health Research (NIHR). The views expressed in the publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. National Institute for Health Research, UK: the report is independent research supported by the National Institute for Health Research (Post-Doctoral Fellowship, Dr Rebecca Bromley, PDF-2013-06-041). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.		
OVERALL ASSESSMENT OF SR		
What is your overall assessment of the methodological quality of this review?	Moderate	

Note: Quality assessment completed using the Scottish Intercollegiate Guideline Network (SIGN) checklist for systematic reviews.

AppD5.1.4 Benzodiazepines and z-drugs

Ban 2014b

Study type: retrospective linked primary care record-based cohort study		Ban 2014
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Included all singleton live births for women aged 15–45 years between 1990 and 2009 from The Health Improvement Network (THIN), in which the medical records of the mothers and the children were linked to provide prospectively recorded information throughout pregnancy and in the year before pregnancy. THIN is a nationally representative database of computerised primary care records from across the UK that has been validated for pharmacoepidemiology studies, and contains diagnoses, events, symptoms, and drug prescriptions.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★

drugs

Study type: retrospective linked primary care record-based cohort study		Ban 2014
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Antenatal exposure to SSRIs and TCAs during the first trimester of pregnancy was defined according to the presence or absence of relevant drug prescriptions in women's records from 4 weeks before to 12 weeks after the first day of the estimated last menstrual period. Using 4 weeks before the last menstrual period enabled the inclusion of drug prescriptions received immediately before pregnancy and potentially used during early pregnancy. Purchases only recorded (not actual dispensing or adherence to medication).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limited comparator population to children exposed to depression but not medicated. Also excluded women with serious mental illness (i.e. bipolar disorder, schizophrenia and other related psychotic disorders). No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Excluded women with prescriptions of antiepileptic drugs.	
c) study controlled for most other important potential confounders	Adjusted for maternal age at the end of pregnancy, year of childbirth, Townsend deprivation index, maternal smoking history, maternal body mass index before pregnancy, and maternal diabetes, hypertension, asthma, and epilepsy in the year before conception or during pregnancy.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	All diagnoses of major congenital anomalies (MCAs) were identified in the children's medical records using Read codes that we classified into 14 system-specific groups according to the European Surveillance of Congenital Anomalies (EUROCAT) subgroups, ³⁹ which are based on the codes listed in the tenth edition of the International Classification of Diseases (ICD-10, mainly in chapter Q). A comparison of prevalence estimates across all system-specific groups (and specific MCA diagnoses for the most prevalent system-specific subgroups, accounting for 77% of all MCAs) between THIN and the UK registers of the EUROCAT network has shown that THIN is a valid and complete source of data to investigate MCAs in live-born children. Likely underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Children followed up for up to 20 years	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
L.S. received grants from the Wellcome Trust and personal fees from GlaxoSmithKline. All other authors report no competing interests.		
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Diav-Citrin 1999

Study type: prospective teratogen service-based cohort study		Diav-citrin 1999
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★
b) somewhat representative of the average cohort in the community	Includes women who consulted the Motherisk Program at the Hospital for Sick Children in Toronto Canada. Motherisk is a teratogen information service.	
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	Obtained from women when they contacted the teratogen service.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	No (downgrade for indirectness)	★
b) study controls for other treatment	Control group included women not exposed to known teratogens.	
c) study controlled for most other important potential confounders	Matched on age, smoking and alcohol consumption.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	From telephone interviews with mothers following delivery, and confirmed with child's physician via letter.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for	For miscarriage	★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
d) no statement	Substantial number excluded from the analyses of preterm delivery (14%) and small for gestational age (15%).	
FUNDING/CONFLICT OF INTEREST		
Not reported		
Final score: Moderate risk of additional bias due to number of exposures excluded from analysis for preterm birth and small for gestational age. Low risk of additional bias for miscarriage.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Eros 2002

Study type: retrospective registry-based case-control study		Eros 2002
SELECTION		
1. Is the case definition adequate?		
a) yes, with independent validation		★

Study type: retrospective registry-based case-control study		Eros 2002
b) yes, e.g. record linkage or based on self-reports	The Hungarian Congenital Abnormality Registry (HCAR) is a national-based registry of cases with CA. Notification of CAs is compulsory for physicians, mainly obstetricians (practically all deliveries take place in inpatient obstetric clinics) and pediatricians (who are working in the neonatal units of inpatient obstetric clinics and various inpatient and outpatient pediatric clinics). Autopsy was obligatory for all infant deaths and usual in stillborn fetuses during the study period and pathologists sent a copy of the detailed autopsy report to the HCAR in lethal cases due to CA. The recorded total (birth þ fetal) prevalences of cases with CA was 35 per 1000 informative offspring (live-born infants, stillborn and selectively terminated malformed fetuses) and about 90% of major CAs were notified to the HCAR during 17 years of the study period. who were notified on the first three months after birth or termination of pregnancy (77% of the total dataset). Cases with isolated CAs and multiple CAs were included into the dataset of the HCCSCA. Three mild CAs (such as congenital dislocation of hip based on Ortolani click, congenital inguinal hernia, and hemangiomas), minor anomalies, (e.g. umbilical hernia), and CA-syndromes of Mendelian or chromosomal origin (such as Down syndrome) were excluded. Checked against maternal self-report and nurse interview when self-report not available.	
c) no description		
2. Representativeness of the cases		
a) Consecutive or obviously representative series of cases	Taken from population-based register	★
b) Potential for selection biases or not stated		
3. Selection of controls		
a) community controls	Also population-based – from National Birth Registry	★
b) hospital controls		
c) no description		
4. Definition of controls		
a) no history of disease (endpoint)	Two (or three between 1986 and 1992) newborn infants without CAs were matched to every case according to sex, birth week, and district of parents' residence from the National Birth Registry of the Central Statistical Office. The type of informative offspring was not matched, however, the proportion of stillborn and selectively terminated malformed fetuses was 1.7 and 0.3% in the group of cases, respectively, and the comparison of only live-born infants did not change the results considerably.	★
b) no description of source		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Included assessment of and adjustment for chronic maternal disorders, including psychiatric disorders. Data collected via maternal self-report and nurse follow-up for non-respondents. To standardise answers, mothers were asked to read a list of drugs and diseases as memory aid before they replied.	★
b) study controls for other treatment	Included assessment of and adjustment for use of drugs during pregnancy. Se above.	
c) study controlled for most other important potential confounders	Adjusted for maternal age and birth order. Matched on sex, birth week and district of parents' residence.	★
EXPOSURE		
1. Ascertainment of exposure		
a) secure record	Three sources of information on exposure were differentiated: (i) only data from the antenatal care logbook (antenatal care obstetricians are obliged to record all prescribed drugs for women concerning complications and diseases in the logbook) or other medical records; (ii) only maternal self-reported data from questionnaire (for drugs used for treatment of diseases unrelated to pregnancy are prescribed by general practitioners or other physicians, in addition drugs taken by the personal choice of pregnant women); (iii) data concordant from both medical records and questionnaire.	★
b) structured interview where blind to case/control status		★
c) interview not blinded to case/control status		
d) written self-report of medical record only		
e) no description		
2. Same method of ascertainment for cases and controls		
a) yes		★
b) no		
3. Non-response rate		
a) same rate for both groups	Not applicable; population-based registry study	★
b) non-respondents described		
c) rate different and no designation		

drugs

Study type: retrospective registry-based case-control study	Eros 2002
FUNDING/CONFLICT OF INTEREST	
This study was supported by the EuroMap concerted action in the Biomed 2Work-program, contract No. BMH4-97-2430 and the Danish Medical Research Council (grant No. 9700 677).	
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of miscarriages and stillborn from the analysis.	

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for case-control studies.

Kjær 2007

Study type: retrospective registry-based case-control study	Kjær 2007
SELECTION	
1. Is the case definition adequate?	
a) yes, with independent validation	★
b) yes, e.g. record linkage or based on self-reports	The case-crossover design was introduced as a method to avoid selection bias. In this design, only cases are considered and their exposures are measured during two different time windows: 'at risk' (Months 2-3) and 'reference' (Months 5-6). Thus, each subject is matched to herself on confounders that remain constant over that time window. The odds ratio in the case-crossover design is the ratio of cases exposed only during the 'at-risk' window to the cases exposed only during the 'reference window' (ratio of discordant pairs).
c) no description	
2. Representativeness of the cases	
a) Consecutive or obviously representative series of cases	Taken from population-based register – Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) among children born in Hungary in 1980–1996. The HCCSCA receives information from the Hungarian Congenital Abnormality Registry and from the Hungarian National Birth Registry.
b) Potential for selection biases or not stated	
3. Selection of controls	
a) community controls	From population-based birth register.
b) hospital controls	
c) no description	
4. Definition of controls	
a) no history of disease (endpoint)	No congenital abnormalities. External controls used only to estimate exposure distributions at the at-risk and reference windows.
b) no description of source	
COMPARABILITY	
1. Comparability of cohorts on the basis of the design or analysis	
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Via case-time-control study design.
b) study controls for other treatment	Via case-time-control study design.
c) study controlled for most other important potential confounders	Via case-time-control study design.
EXPOSURE	
1. Ascertainment of exposure	
a) secure record	Information on drug use was taken from antenatal logbooks, hospital discharge summaries and from structured questionnaires completed by parents of cases and controls following HCCSCA registration. Use of drugs under study was considered present if any of these three sources had a record of use.
b) structured interview where blind to case/control status	
c) interview not blinded to case/control status	
d) written self-report of medical record only	
e) no description	
2. Same method of ascertainment for cases and controls	
a) yes	★
b) no	
3. Non-response rate	
a) same rate for both groups	Not applicable; population-based registry study
b) non-respondents described	
c) rate different and no designation	
FUNDING/CONFLICT OF INTEREST	
The Danish Pharmaceutical Association (Apotekerfonden af 1991); Obel Family Foundation (Det Obelske Familiefond); Ekkert Petersens Memorial Fund; FIGO Foundation.	
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of miscarriages and stillborn from the analysis.	

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for case-control studies.

Juric 2009

Study type: prospective hospital-based cohort study		Juric 2009
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★
b) somewhat representative of the average cohort in the community	Includes pregnant women enrolled in a prospective study of the pharmacokinetics of psychotropic medications during pregnancy at the Emory Women's Mental Health Program.	
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Obtained from maternal and umbilical cord plasma collection, maternal interview and medical records.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Matched on Structured Clinical Interview for DSM-IV diagnosis. Beck Depression Inventory (BDI) scores and Pittsburgh Sleep Quality Index scales were collected at serial visits across pregnancy. Mean, peak and final visit BDI scores were higher for zolpidem-exposed women were higher than for non-exposed women and not factored into the analysis. There was no difference in sleep measurements.	★
b) study controls for other treatment	Matched on use of exposure to numerous classes of non-zolpidem psychotropic medications.	
c) study controlled for most other important potential confounders	Matched on age and race.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment	Obstetrical outcome data were obtained from the medical record and direct interview of the women within 24 hours of delivery.	★
b) record linkage		★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for	45 available zolpidem-exposed women matched with non-zolpidem-exposed women. 6 zolpidem-exposed women from the original cohort excluded (four lost-to-follow-up, one miscarried and one underwent an elective termination due to a fetal genetic syndrome).	★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Supported by NIH grant MH-68036. Drs Newport, Ritchie and Stowe have received research support and honoraria from various pharmaceutical companies and served on company advisory boards.		
Final score: Low risk of bias.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

NICE 2015

Study type: systematic review and meta-analysis		NICE 2015
INTERNAL VALIDITY		
The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper		Yes

Study type: systematic review and meta-analysis		NICE 2015
A comprehensive literature search is carried out	Yes	
At least two people should have selected studies	Yes	
At least two people should have extracted data	Yes	
The status of publication was not used as an inclusion criterion	Yes	
The excluded studies are listed	Yes	
The relevant characteristics of the included studies are provided	Yes	
The scientific quality of the included studies was assessed and reported	Yes	
Was the scientific quality of the included studies used appropriately?	Yes	
Appropriate methods are used to combine the individual study findings	No, combined raw data from observational studies	
The likelihood of publication bias was assessed appropriately	Unclear	
Conflicts of interest are declared	Yes	
FUNDING/CONFLICT OF INTEREST		
The guideline was commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). The NCCMH is a collaboration of the professional organisations involved in the field of mental health, national service user and carer organisations, a number of academic institutions and NICE. The NCCMH is funded by NICE and is led by a partnership between the Royal College of Psychiatrists and the British Psychological Society's Centre for Outcomes Research and Effectiveness, based at University College London. The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included women who have experienced a mental health problem in the pregnancy or the postnatal period, and professionals from psychiatry, clinical psychology, general practice, nursing, health visitors, obstetrics, midwifery and the private and voluntary sectors, and a mother-infant specialist. All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting.		
OVERALL ASSESSMENT OF SR		
What is your overall assessment of the methodological quality of this review?	Moderate	

Note: Quality assessment completed using a modified version of the Scottish Intercollegiate Guideline Network (SIGN) checklist for systematic reviews.

Oberlander 2008a

Study type: retrospective linked primary care record-based cohort study		Oberlander 2008a
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Data was from five administrative sources housed in the British Columbia Linked Health Database: BC registry of births, hospital separation records, Pharmacare registry of subsidised prescriptions, the Medical Services Plan physician billing records and the registry of Medical Services Plan subscribers. Following matching of datasets and accounting for data errors records for multiple births, the final cohort included 119,547 of 203,250 potentially eligible live births.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Prescriptions for SRIs (SSRIs + venlafaxine) and benzodiazepines were identified in the PharmaNet dataset. Exposure in the first trimester was determined if the dispensing period (i.e. days of dosing covered by the prescription) overlapped with the period from the LMP to LMP plus 90 days. Prescriptions only recorded (not actual dispensing or adherence to medication).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Adjusted for depression in the first trimester, times visiting a psychiatrist in the previous year, number of time receiving a diagnosis of depression in the previous year. No adjustment for maternal illness severity during pregnancy using direct measurement of severity of symptoms.	★
b) study controls for other treatment	Diagnosis of epilepsy or seizures was identified from maternal records regardless of timing of exposure.	

Study type: retrospective linked primary care record-based cohort study		Oberlander 2008a
c) study controlled for most other important potential confounders	Adjusted for maternal age, prenatal care visits, number of visits to a physician in previous year, maternal illness characteristics, diseases, and complications of pregnancy diagnosed more than 60 days before birth, and a dummy variable indicating the mother filed a prescription after she knew she was pregnant. Methadone use was used as a proxy marker for other maternal characteristics such as poor nutrition or other drug use.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Neonatal outcomes were identified using ICD-9 codes for major congenital abnormalities (740.0 to 759.9) and the subset of cardiovascular defects (745.0-747.9). Congenital anomalies considered minor were excluded. Specific codes for ventricular septal defects (745.4) and atrial septal defects (745.5) were also used. Likely underestimates malformations because miscarriages and stillborns are excluded from the analysis. Potential for selection bias.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Probably. Study notes 39 month period of data collection but not clear what the average period of time after birth data was checked at.	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
BC Ministry of Children and Family Development; The Michael Smith Foundation for Health Research. T.F.O. is supported by a HELP Senior Career Award and is the R.Howard Webster professor in Child Development (UBC, Faculty of Graduate Studies). None of the authors has a conflict of interest with these data or our findings.		
Final score: Moderate risk of bias due to potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Odsbu 2015

Study type: prospective population-based cohort study		Odsbu 2015
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★
b) somewhat representative of the average cohort in the community	The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort conducted by the Norwegian Institute of Public Health. Pregnant women were recruited from all over Norway from 1999 to 2008 around week 17–18 of pregnancy. The final cohort consisted of 90,700 women and 108,000 children. The women consented to participation in 38.5 % of the pregnancies. Some of the information in MoBa is obtained from the Medical Birth Registry of Norway (MBRN). MBRN is a nationwide registry that is based on compulsory notification of every birth or late abortion from 12 weeks of gestation onwards in Norway. The authors note that a previous study has suggested that participants in the study may have a healthier lifestyle than the total pregnant population.	
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★

drugs

Study type: prospective population-based cohort study		Odsbu 2015
b) structured interview	Anxiolytics and hypnotics were defined as benzodiazepines and benzodiazepine-related drugs classified in ATC groups N05BA (diazepam, oxazepam, and alprazolam), N05CD (nitrazepam and midazolam), N03AE01 (clonazepam), and N05CF (zopiclone and zolpidem). Mothers were asked to report on their medication use at pregnancy week 17–18, 30, and at 6 months postpartum. The questionnaires covered (i) the time period from 6 months before pregnancy to pregnancy week 17–18, (ii) the time period from pregnancy week 19–29, and (iii) the time period from pregnancy week 30 until birth. Women were defined as users of anxiolytics and hypnotics if they had reported use of any anxiolytic or hypnotic drug on at least one of the three questionnaires. The users were further classified according to whether they had reported use of the drugs before pregnancy only (6 months before pregnancy to pregnancy week 0) or during pregnancy (between pregnancy week 0 until birth). Duration of drug use was classified as (i) no use, (ii) use before pregnancy only, and (iii) use during pregnancy. The third category was further divided into use during one time period only (short-term use) if the woman reported use only on one questionnaire and use during at least two time periods (long-term use) if she reported use on more than one questionnaire. Self-reported drug use in MoBa from pregnancies starting after 2004 has been validated with prescription data from the Norwegian Prescription Database (NorPD). When self-reported drug use was compared to NorPD, lower agreement was observed for drugs often used intermittently (e.g., BZD-anxiolytics and BZD-hypnotics) as opposed to drugs used for chronic conditions (e.g., BZD antiepileptics).	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Adjusted for symptoms of depression before pregnancy, symptoms of anxiety and depression during pregnancy. Symptoms of anxiety and depression were assessed both during pregnancy and after birth. In pregnancy, the self-assessments were done in week 17–18 and week 30. After pregnancy, they were conducted at 6 months, 18 months and 3 years. The assessments were done by the 5-item version (SCL-5) of the Hopkins Symptom Checklist (SCL-25).	★
b) study controls for other treatment	Adjusted for use of other psychotropic drugs (SSRIs or opioids) and antimigraine drugs.	
c) study controlled for most other important potential confounders	Adjusted for maternal and paternal age, parity, maternal and paternal education level, marital status, information about whether the pregnancy was planned, maternal working status, maternal smoking in pregnancy, maternal alcohol intake in pregnancy, use of folic acid, pre-pregnancy body mass index (BMI) and sleeping problems.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage		★
c) self-report	Language competence at age 3 years was determined by a validated language grammar rating scale in the 3-year questionnaire. The mother classified her child's language competence according to six different categories. These categories were (1) not yet talking, (2) talking, but unintelligible, (3) talking in one-word utterances, such as "milk" or "down" (4) talking in 2–3 word phrases, such as "me got ball" or "give doll", (5) talking in fairly complete sentences, such as "I got a doll" or "Can I go outside?", and (6) talking in long and complicated sentences, such as "when I went to the park, I went on the swings" or "I saw a man standing on the corner". Categories 1 and 2 were combined in the analysis due to very small numbers. If the mother had marked several categories, the child was classified in the most advanced language category.	
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Measured at 3 years	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★

Study type: prospective population-based cohort study		Odsbu 2015
c) follow-up rate high and no description of those lost	Of the 108,000 children in the cohort at the time of the study, 58,410 had reached three years and had questionnaires returned. An additional 6662 were excluded due to multiple birth, presence of malformations and/or chromosomal abnormalities, and had missing exposure and outcome data.	
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and the Ministry of Education and Research, NIH/NIEHS (contract no. N01-ES-75558), NIH/NINDS (grant no.1 U01 NS 047537-01, and grant no.2 U01 NS 047537-06A1). The authors declare that they have no conflict of interest.		
Final score: Moderate risk of bias due to self-reported nature of exposure and outcome.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Wang 2010

Study type: Retrospective population-based cohort study		Wang 2010
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Two nationwide population-based data sets from Taiwan were linked for this study: the Taiwan National Health Insurance Research Dataset (NHIRD), which is derived from the Taiwan National Health Insurance (NHI) program (representing >98.4% of Taiwan's 22.96 million residents in 2007) and the national birth certificate registry, which contains data on the following: birth dates of infants and parents, gestational week at birth, birth weight, gender, parity, place of birth, parental educational level, and maternal marital status. The study identified 218,776 women who had live singleton births and used prenatal care services between 1 January 2005 and 31 December 2005.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Identified via the NHIRD and prescribed zolpidem.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Women with a history of a mental health disorder were excluded from the study. Therefore, the study is not likely to be confounded by the underlying mental health indication. Severity of insomnia was not captured.	★
b) study controls for other treatment	Women prescribed any other type of medication for > 30 days during pregnancy were excluded.	
c) study controlled for most other important potential confounders	Adjusted for maternal age, infant's gender, parity, maternal education level, gestational hypertension, diabetes, pre-eclampsia and anaemia. The authors note that they did not have data on smoking and alcohol use, but that adjustment for smoking in the study by Wikner 2007 did not change findings and that because women with mental health disorders were excluded they would expect smoking to be evenly distributed between exposed and non-exposed groups, and therefore is not likely to be a major confounder.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★

drugs

Study type: Retrospective population-based cohort study		Wang 2010
b) record linkage	The outcome variables were identified via the included datasets and included: LBW (<2,500 g), preterm gestation (<37 completed weeks of gestation), SGA babies (birth weight below the 10th percentile for gestational age-specific birth weight distribution), babies born with major congenital anomalies (the conditions included in this study were hydrocephaly, anencephaly, microcephaly, meningomyelocele, encephalocele, and spina bifida) and cesarean section as mode of delivery.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The authors declared no conflict of interest.		
Final score: Low risk of bias for all outcomes except for major malformations which has a moderate risk of bias; selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Wikner 2007

Study type: Retrospective population-based cohort study		Wikner 2007
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The Swedish Medical Birth Register contains information on practically all deliveries in Sweden. It is based on copies of standardised medical records completed at the maternity health care centres, the delivery units and at the paediatric examination of the newborn. Since 1st July, 1994, information on maternal drug use during pregnancy has been stored in the Medical Birth Register. This information comes from two sources. One is based on midwife interviews at the woman's first visit to the antenatal care clinic (usually before the end of the first trimester), the other on drug prescriptions made within the antenatal care system after the first visit and up to delivery.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Information regarding the exposure to benzodiazepines and/or z-drugs during pregnancy was obtained prospectively (i.e. before the outcome of the pregnancy was known) via midwife interviews and prescription data for the period 1st July, 1995 to 31st December, 2004. All agents used in clinical practice in Sweden within this time frame were included in the analysis. The most commonly used were diazepam, zopiclone, oxazepam, alprazolam and flunitrazepam.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Study does not control for underlying indication or severity of indication.	★

drugs

Study type: Retrospective population-based cohort study		Wikner 2007
b) study controls for other treatment	Infants exposed to anticonvulsants were excluded from a sensitivity analysis of malformations. Infants exposed to antidepressants were excluded from sensitivity analyses of preterm birth and respiratory difficulty.	
c) study controlled for most other important potential confounders	Adjusted for year of birth, maternal age, parity, smoking and years of involuntary childlessness. The authors note that while alcohol use was not adjusted for, it is usually associated with smoking, which was adjusted for.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Includes preterm birth (<37 completed weeks) among singleton infants; low birth weight (<2500 g) among singleton infants; small for gestational age among singleton infants (<–2 standard deviations from expected weight as determined from sex and parity specific growth curves, constructed from the Medical Birth Register); low Apgar score (<7) at 5 minutes, congenital malformations, perinatal diagnoses including: respiratory problems (ICD-9 codes 768–770, ICD-10 P20–28), jaundice (ICD-9 774, ICD-10 P59), hypoglycaemia (ICD-9 775.6, ICD-10 P70.4), convulsions (ICD-9 779.0, ICD-10 P90), CNS problems (ICD-9 779.0–779.3, ICD-10 P90, P91.3–P91.9, P92). Congenital malformations were identified from the Swedish Medical Birth Register, supplemented with information from the Register of Congenital Malformations and the Hospital Discharge Register. Congenital malformations were divided into two main groups: ‘relatively severe’ and ‘mild and variable’. The latter group contains a number of common and mild malformations (including preauricular appendix, undescended testicle, hip (sub)luxation, patent ductus arteriosus at preterm birth, tongue tie, single umbilical artery and nevus) with a highly variable registration rate. In the ‘relatively severe’ group some mild conditions are included (includes spina bifida, congenital cerebral cyst/porencephaly, cleft lip/palate, isolated cardiovascular defects, cardiovascular defects with other malformations, oesophageal atresia, ileum atresia, anal atresia, anal atresia + hypospadias, rectal/anal fistula, persistent cloaca + upper limb reduction, megacolon, malrotation of gut, renal dysplasia/unspecified renal malformation, urethra stenosis, hypospadias, pes equinovarus, polydactyly, syndactyly, upper limb reduction, skull/face malformation, spine malformation, osteogenesis imperfecta, ectodermal dysplasia, down syndrome, situs inversus + patent ductus arteriosus).	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The study was supported by grants from Knut and Alice Wallenberg Foundation and Evy and Gunnar Sandberg Foundation (BK), and the Karolinska Institute (CA). The study also received support from the EuroMaP concerted action in Biomed 2, contract no. BMH4CT97-2430(UB).		
Final score: Moderate risk of additional bias for small for gestational age and convulsions outcomes due to lack of adjustment for other treatments. Moderate risk of additional bias for malformation due to potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis. Low risk of additional bias for preterm birth and respiratory distress outcomes. No consideration of confounding by indication (has been captured as indirectness).		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Wikner 2011

Study type: Retrospective population-based cohort study		Wikner 2011
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The study used the Swedish MBR to identify women using HBRA during pregnancy and giving birth from July 1, 1995, to December 31, 2007. The Swedish MBR is based on copies of medical records and contains information on 98% to 99% of all deliveries in Sweden. Data are collected during prenatal care at the maternal health care centers, the delivery units, and the pediatric examination of the newborn.	★

drugs

Study type: Retrospective population-based cohort study		Wikner 2011
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	Information on maternal drug use during pregnancy is based on midwife interviews at the woman's first visit to the antenatal care clinic (90% of the women make their first visit before the end of week 12) and will therefore mainly refer to first-trimester exposures. The details of this interview are recorded on a standard form used throughout the country. The drug names are transferred to Anatomical Therapeutic Chemical codes for data storage. Information regarding the exposure to HBRA's during pregnancy is thus obtained prospectively (ie, before the outcome of the pregnancy is known). All HBRA's used in clinical practice in Sweden within this time frame were included (zolpidem, zopiclone, and zaleplon).	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Study does not control for underlying indication or severity of indication.	★
b) study controls for other treatment	Data collected on other treatments but does not appear to have been factored into the analysis.	
c) study controlled for most other important potential confounders	Adjusted for year of birth, maternal age, parity and smoking.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Congenital malformations were studied as outcome variable and were identified from the Swedish MBR, supplemented with information from the Register of Birth Defects (previously called the Register of Congenital Malformations) and the Hospital Discharge Register. The various registers were linked with the unique personal identification number that is assigned to everyone living in Sweden. Malformations were defined by the World Health Organization's International Classification of Disease (ICD): ICD-9 codes 740-759 or ICD-10 codes beginning with Q. Among congenital malformations a subgroup was analyzed, "relatively severe malformations." This group excludes a number of common and mild malformations (preauricular appendix, undescended testicle, unstable hip, patent ductus arteriosus in preterm infants, single umbilical artery, tongue tie, nevus) with a highly variable registration rate and with a low clinical significance. Specific types of malformation were analyzed separately, including any cardiovascular defects.	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
The study was supported by Ewy and Gunnar Sandberg Foundation, Lund (B.K.), and HKH Kronprinsessan Lovisas förbarnsjukvård/Axel Thielmans minnesfond (B.N.W.). The authors reported no conflicts of interest.		
Final score: High risk of additional bias due: potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis, and lack of adjustment for other treatments. No consideration of confounding by indication (has been captured as indirectness).		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

AppD5.1.5 Lithium

Diav-Citrin 2014

Study type: prospective observational study		Diav-Citrin 2014
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community		★
b) somewhat representative of the average cohort in the community	Pregnant women who contacted the Israeli Teratology Information Service (Jerusalem) with regard to gestational exposure to lithium (comparator groups taken from the same TIS: 1) women with bipolar disorder but no lithium exposure and 2) women exposed to known non-teratogens. ⁶¹¹	★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same plus similar cohorts.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	Details of exposure (dosage, duration and timing in pregnancy, and additional exposures) are routinely collected at the initial contact and before pregnancy outcome is known using a structured questionnaire.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	No adjusted results reported only for comparison with any non-exposed women (for miscarriage and cardiac malformations only), and adjustment for indication was inadequate (adjusting only for bipolar disorder, which made up 66% of the exposed cohort). For major malformations, only crude results presented, and although one of the comparator groups is restricted to women with bipolar disorder, this was considered inadequate to fully control for the range of indications in the exposure group.	★
b) study controls for other treatment	No adjustment for, or exclusion of other medications.	★
c) study controlled for most other important potential confounders	Major malformations: crude results only presented. Cardiovascular malformations adjusted for pregnancy order, smoking and bipolar disorder. Miscarriage adjusted for maternal age, pregnancy order, bipolar disorder, smoking, gestational age at initial contact with TIS.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment	Abnormalities detected by prenatal ultrasonography (if verified postnatally or by autopsy) were included in our study, since antenatal screening for major anomalies is routinely performed in Israel. The classification of anomalies was done by a certified pediatrician blinded to the exposure group. A certified medical geneticist was consulted in case of classification difficulty. Thus, the analysis of major congenital anomalies was performed in all live-born infants, as well as in stillbirths and in elective terminations of pregnancy as a result of prenatally diagnosed anomalies. Therefore, given miscarriage was captured in this study, outcome ascertainment was not considered not to increase the risk of bias for major malformations, nor for cardiac malformations.	★
b) record linkage		★
c) self-report		
d) no description		

⁶¹¹ In an attempt to increase the power of the study by increasing the number of exposed pregnancies, other analyses were performed after adding data collected by two additional services: MotherSafe (Sydney, Australia) and the Motherisk Program (Toronto) (multicenter design was applied). However, all adjusted risk estimates are derived from the Israeli TIS.

Study type: prospective observational study		Diav-Citrin 2014
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Adrienne Einarson has received consulting fees from Eli Lilly for a duloxetine pregnancy registry. All other authors report no financial relationships with commercial interests. The Motherisk Program has received an unrestricted educational grant from Eli Lilly to study the safety of duloxetine in pregnancy.		
Final score: Moderate risk of bias due to inadequate adjustment for indication (for both comparison adjusted for bipolar disorder and comparisons where the comparator group is limited to women with bipolar).		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Källén 2013

Study type: retrospective, linked, population-based cohort study		Källén 2013
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Population-based cohort of exposed live births from the Swedish Medical Birth Register linked to Register of Birth Defects, Register of Prescribed Drugs and Hospital Discharge Register.	★
b) somewhat representative of the average cohort in the community		★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Late pregnancy drug exposure was defined as a <u>dispensed</u> prescription for an antipsychotic on the Prescribed Drug Register. Early pregnancy drug exposure was determined at midwife interview during the first antenatal care visit (data recorded in Medical Birth Register).	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Population-based, so no selection bias for outcome of interest.	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	No – groups defined by exposure irrespective of diagnosis, and no adjustment for indication (captured as indirectness).	★
b) study controls for other treatment	For malformations, infants exposed to concomitantly used drugs with teratogenic properties were excluded in some analyses.	★
c) study controlled for most other important potential confounders	Adjusted for year of birth, maternal age (5-year class), parity (1-4+), smoking in early pregnancy and BMI.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Information on congenital malformations was obtained from the Medical Birth Register (MBR) but was supplemented with data from the Register of Birth Defects (RCM, previously Register of Congenital Malformations) and from a Hospital Discharge Register (HDR), containing diagnoses after inpatient treatments. Likely underestimates malformations because the study does not capture potential excess malformations coinciding with miscarriage, abortion or stillbirth, which are not included in the study population. Potential for selection bias.	★
c) self-report		
d) no description		

Study type: retrospective, linked, population-based cohort study		Källén 2013
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
<u>Conflicts of interest:</u> The authors declare no conflicts of interest.		
Final score: Moderate risk of bias for malformation outcomes: potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis. Low risk of bias for other outcomes.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

Källén 1983

Study type: retrospective cohort study		Källén 1983
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	Infants born to women who had been treated as inpatients for manic-depressive disease, identified from central registries (Swedish Discharge Registry for Inpatient Psychiatric Wards database) and information from hospital charts.	★
b) somewhat representative of the average cohort in the community		★
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record	Medical Birth Registry includes medical items and information on drug use during pregnancy.	★
b) structured interview		★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes	Yes	★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Yes – all participants had a diagnosis of manic depression.	★
b) study controls for other treatment	Yes cohorts taking other psychotropic drugs were separated from those not taking other psychotropic drugs, from both the lithium-exposed and lithium-non-exposed groups.	★
c) study controlled for most other important potential confounders	No	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage	Medical Birth Registry and Registry of Congenital Malformations	★
c) self-report		
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes	Yes	★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost	Unclear but unlikely to be sufficient to introduce bias.	★
c) follow-up rate high and no description of those lost		
d) no statement		

Study type: retrospective cohort study	Källén 1983
FUNDING/CONFLICT OF INTEREST	
This study was supported by a grant from Expressens Prenatalfond.	
Final score: Moderate risk of bias for malformation outcomes: potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis. Low risk of bias for neonatal death.	

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

AppD5.2 COMPLEMENTARY

AppD5.2.1 Omega-3 fatty acids

Gould 2013

Study type: systematic review and meta-analysis	Gould 2013
INTERNAL VALIDITY	
The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper	Yes
A comprehensive literature search is carried out	Yes
At least two people should have selected studies	Yes
At least two people should have extracted data	Yes
The status of publication was not used as an inclusion criterion	Yes
The excluded studies are listed	No
The relevant characteristics of the included studies are provided	Yes
The scientific quality of the included studies was assessed and reported	Yes
Was the scientific quality of the included studies used appropriately?	Yes
Appropriate methods are used to combine the individual study findings	Yes
The likelihood of publication bias was assessed appropriately	Yes
Conflicts of interest are declared	Yes
FUNDING/CONFLICT OF INTEREST	
Supported by a Doctorate of Philosophy Health Sciences Faculty Scholarship from the University of Adelaide (to JFG) and Senior Research Fellowship from the National Health and Medical Research Council of Australia (to MM). Associated honoraria are paid to the Women's and Children's Health Research Institute to support conference travel and continuing education for postgraduate student and early career researchers.	
OVERALL ASSESSMENT OF QUALITY	
What is your overall assessment of the methodological quality of this review?	High

Note: Quality assessment completed using the Scottish Intercollegiate Guideline Network (SIGN) checklist for systematic reviews.

Kar 2016

Study type: systematic review and meta-analysis	Kar 2016
INTERNAL VALIDITY	
The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper	Yes
A comprehensive literature search is carried out	Yes
At least two people should have selected studies	Yes
At least two people should have extracted data	Yes
The status of publication was not used as an inclusion criterion	Yes
The excluded studies are listed	No
The relevant characteristics of the included studies are provided	Yes
The scientific quality of the included studies was assessed and reported	Yes
Was the scientific quality of the included studies used appropriately?	Yes; authors note that the majority of studies were of adequate methodological quality
Appropriate methods are used to combine the individual study findings	Yes
The likelihood of publication bias was assessed appropriately	Yes
Conflicts of interest are declared	Yes
FUNDING/CONFLICT OF INTEREST	
The authors have no support or funding to report. The authors have declared that no competing interests exist.	
OVERALL ASSESSMENT OF QUALITY	
What is your overall assessment of the methodological quality of this review?	High

Note: Quality assessment completed using the Scottish Intercollegiate Guideline Network (SIGN) checklist for systematic reviews.

Saccone 2016b

Study type: systematic review and meta-analysis	Saccone 2016b
INTERNAL VALIDITY	
The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper	Yes
A comprehensive literature search is carried out	Yes
At least two people should have selected studies	Yes

Study type: systematic review and meta-analysis		Saccone 2016b
At least two people should have extracted data	Yes	
The status of publication was not used as an inclusion criterion	Yes	
The excluded studies are listed	No	
The relevant characteristics of the included studies are provided	Yes	
The scientific quality of the included studies was assessed and reported	Yes	
Was the scientific quality of the included studies used appropriately?	Yes; the majority of studies included for the relevant outcomes had a low risk of bias	
Appropriate methods are used to combine the individual study findings	Yes	
The likelihood of publication bias was assessed appropriately	Yes	
Conflicts of interest are declared	No	
FUNDING/CONFLICT OF INTEREST		
The authors report no conflict of interest. The study has no funding source.		
OVERALL ASSESSMENT OF QUALITY		
What is your overall assessment of the methodological quality of this review?	High	

Note: Quality assessment completed using the Scottish Intercollegiate Guideline Network (SIGN) checklist for systematic reviews.

AppD5.2.2 St John's wort

Moretti 2009

Study type: prospective cohort study		Moretti 2009
SELECTION		
1. Representativeness of the exposed cohort		
a) truly representative of the average cohort in the community	The sample group, both exposed and unexposed subjects, was drawn from women who contacted the Motherisk Program, a teratogen information service in Canada. The exposed index group consisted of women who used St. John's wort at any time during their pregnancy.	★
b) somewhat representative of the average cohort in the community		
c) selected group of users (e.g. nurses, volunteers)		
d) no description of the derivation of the cohort		
2. Selection of the non-exposed cohort		
a) Drawn from the same community as the exposed cohort	From same cohort. Two cohorts included: (i) depressed women on standard pharmacologic treatments and (ii) healthy women not exposed to known teratogens.	★
b) drawn from a different source		
c) no description of the derivation of the non-exposed cohort		
3. Ascertainment of exposure		
a) secure record		★
b) structured interview	At initial contact with the patient, during pregnancy, detailed information on the use of medications, medical and obstetric history and other exposures was recorded. A second contact with the patient was made after the expected date of delivery to collect further information about additional exposures, medical conditions and details about delivery and infant outcomes. All interviews were conducted systematically and data recorded on structured standardised collection forms. Interviews were conducted in the same manner for both exposed and unexposed subjects. Subjects were recruited and followed over a 5–7-year time interval. Patients were excluded if they were unable or unwilling to complete the interviews in English.	★
c) written self-report		
d) no description		
4. Demonstration that outcome of interest was not present at start of study		
a) yes		★
b) no		
COMPARABILITY		
1. Comparability of cohorts on the basis of the design or analysis		
a) study controls for underlying indication (+ illness severity for neurodevelopmental outcomes)	Limited comparator population of interest to women with depression on standard pharmacological treatment for depression.	★
b) study controls for other treatment	Not reported. Main comparison of interest for this is between St John's wort and standard pharmacological therapy for depression.	
c) study controlled for most other important potential confounders	Matched on gestational age at intake (± 2 weeks), maternal age (± 2 years) and gravidity.	★
OUTCOME		
1. Assessment of outcome		
a) independent blind assessment		★
b) record linkage		★

Study type: prospective cohort study		Moretti 2009
c) self-report	From structured interview after delivery date.	
d) no description		
2. Was follow-up long enough for outcomes to occur		
a) yes		★
b) no		
3. Adequacy of follow-up of cohorts		
a) complete follow-up – all subjects accounted for		★
b) subjects lost to follow-up unlikely to introduce bias – small number lost or description provided of those lost		★
c) follow-up rate high and no description of those lost		
d) no statement		
FUNDING/CONFLICT OF INTEREST		
Supported by The Complementary and Alternative Therapies and Child and Youth Health Research Grant No. CAM03-327, The Hospital For Sick Children. GK is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation (Toronto), and the Ivey Chair in Molecular Toxicology, Department of Medicine, University of Western Ontario. The authors declare that there are no conflicts of interest.		
Final score: High risk of bias for malformation outcome due to potential exclusion of planned abortions, miscarriages and still born from the analysis, self-report ascertainment of outcome and inadequate follow-up. High risk of bias for other outcomes due to self-report ascertainment of outcome and inadequate follow-up.		

Note: Quality assessment completed using a modified version of the Newcastle-Ottawa Scale for cohort studies.

AppD5.3 PHYSICAL

AppD5.3.1 Electroconvulsive therapy

No quality assessment was undertaken due to the very low evidence provided by the investigated studies.

AppD5.3.2 Transcranial magnetic stimulation

No quality assessment was conducted due to the very low evidence provided by the investigated studies.

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