Australian Perinatal Mental Health Guideline Evidence Review

Technical Report Part D

Harms of treatment and prevention interventions

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clinical evidence for the real world

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TABLE OF CONTENTS

TABLE OF TABLES

ABBREVIATIONS

AD	antidepressant
ADHD	attention deficit hyperactivity disorder
ADSI	Ankara Developmental Screening Inventory
AOR	adjusted odds ratio
ARR	adjusted relative risk
ASD	autism spectrum disorder
Benzo	benzodiazepine
BSID	Bayley Scales of Infant Development
CI	confidence interval
ECT	electroconvulsive therapy
FGA	first generation antipsychotics
GMDS	Griffiths Mental Development Scales
IQ	intelligence quotient
IUGR	intrauterine growth restriction
K-ABC	Kaufman Assessment Battery for Children
LFGA	large for gestational age
MD	mean difference
meds	medication
NA	not available
NaSSA	noradrenergic and specific serotonergic antidepressants
NE	not estimable
NR	not reported
OBS	observational studies
OR	odds ratio
P & L	pregnancy and lactation
P	pregnancy
PNAS	poor neonatal adaptation syndrome
PPH	persistent pulmonary hypertension
PPVT	Peabody Picture Vocabulary Test
PS	propensity score
RCT	randomised controlled trial
RD	risk difference
RE	risk estimate
RR	relative risk
RR	risk ratio
Rx	prescription
SFGA	small for gestational age
SGA	second generation antipsychotic
SMD	standardised mean difference
SNRI	serotonin and noradrenalin reuptake inhibitor
SR	systematic review
SRI	selective reuptake inhibitor
SRS	social responsiveness scale
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

D1 INTRODUCTION

The aim of this Evidence Review is to assess the evidence relating to the identification and treatment or prevention of mental health problems in women during pregnancy or the postnatal period. The following Technical Reports and associated Appendices are related to this assessment:

- Part B Technical Report and Part B Appendix – Psychosocial Assessment and Screening
- Part C Technical Report and Part C Appendix – Treatment and Prevention
- Part D Technical Report and Part D Appendix – Harms.

This Technical Report and associated Appendix (Part D) present the findings of the assessment of evidence of the harms of *interventions* used for the treatment and prevention of mental health problems in women during the antenatal or postnatal period.

D2 METHODOLOGY

D2.1 CLINICAL QUESTIONS

The four main questions relating to the harms associated with interventions for the treatment of mental health problems in pregnant or postpartum women, or prevention of mental health problems in pregnant or postpartum women identified as being at risk of developing mental health problems, were each broken down into four sub-questions based on the different populations that may potentially experience harm. It should be noted that each sub-question is broken down further into individual interventions and outcomes. The detailed definitions associated with these interventions and outcomes can be found in **Section D2.2**. All questions were addressed via systematic review.

Harms to the fetus, infant or child include any direct harms (e.g. malformations, miscarriage, perinatal mortality, neurodevelopmental disorders) and any birth outcomes that may cause subsequent harm (e.g. prenatal birth, small for gestational age, convulsions). Harm to the mother has been limited to postpartum haemorrhage; maternal side effects of treatment have been assessed in **Part C** of the **Technical Report**.

D2.1.1.1 Pharmacological interventions

Main question:

6. What are the harms that occur as a result of perinatal exposure to pharmacological interventions used for the treatment of mental health problems?

Sub-questions:

6a. What are the harms that occur to the fetus as a result of perinatal exposure to a pharmacological intervention used for the treatment of mental health problems?

6b. What are the harms that occur to the infant as a result of perinatal exposure to a pharmacological intervention used for the treatment of mental health problems?

6c. What are the harms that occur to the child as a result of perinatal exposure to a pharmacological intervention used for the treatment of mental health problems?

6d. What are the harms that occur to the mother as a result of perinatal exposure to a pharmacological intervention used for the treatment of mental health problems?

D2.1.1.2 Complementary interventions

Main question:

7. What are the harms that occur as a result of perinatal exposure to a complementary intervention used for the treatment of mental health problems?

Sub-questions:

7a. What are the harms that occur to the fetus as a result of perinatal exposure to a complementary intervention used for the treatment of mental health problems?

7b. What are the harms that occur to the infant as a result of perinatal exposure to a complementary intervention used for the treatment of mental health problems?

7c. What are the harms that occur to the child as a result of perinatal exposure to a complementary intervention used for the treatment of mental health problems?

7d. What are the harms that occur to the mother as a result of perinatal exposure to a complementary intervention used for the treatment of mental health problems?

D2.1.1.3 Physical interventions

Main question:

8. What are the harms that occur as a result of perinatal exposure to a physical intervention used for the treatment of mental health problems?

Sub-questions:

8a. What are the harms that occur to the fetus as a result of perinatal exposure to a physical intervention used for the treatment of mental health problems?

8b. What are the harms that occur to the infant as a result of perinatal exposure to a physical intervention used for the treatment of mental health problems?

8c. What are the harms that occur to the child as a result of perinatal exposure to a physical intervention used for the treatment of mental health problems?

8d. What are the harms that occur to the mother as a result of perinatal exposure to a physical intervention used for the treatment of mental health problems?

D2.2 CRITERIA FOR DETERMINING STUDY ELIGIBILITY

To determine whether an intervention causes harm, a systematic review (SR) of randomised controlled trials (RCTs) provides the highest level of evidence, as shown in the evidence hierarchy for examination of intervention questions (**Table D 2-1**). However, in cases where it is not possible or ethical to perform a RCT (as is the case when examining harms to the fetus, infant or child following maternal exposure), observational evidence should be used. The highest level of evidence in this case is a SR of prospective cohort studies, as shown in the hierarchy for examination of aetiology questions. Thus, where available, RCT evidence was used, although the majority evidence came from observational studies. Wherever possible, only observational studies with concurrent control groups were included.

For each of the intervention-based questions to be assessed by the Evidence Review (effectiveness of treatment and prevention, and harms), the EWG agreed to the appropriate level of evidence for inclusion. For the review of the harms of pharmacological, complementary and physical interventions, the EWG agreed that SRs of observational studies should be used as the basis of the review where available, with individual observational studies and SRs of case series/reports to be assessed only where higher level evidence was unavailable or inadequate. There were exceptions to this: (i) fetal, infant and child harms associated with the use of anticonvulsants during pregnancy, and postpartum haemorrhage were limited to SRs of observational studies; and (ii) the assessment of evidence for harms related to omega-3 fatty acids were limited to SRs of RCTs.

Table D 2-1 NHMRC Evidence Hierarchy: designation of levels of evidence according to type of research question[1]

Level	Intervention	Aetiology
I	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A prospective cohort study
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	All or none[2]
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial[3] • Cohort study • Case-control study • Interrupted time series with a control group	A retrospective cohort study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm studies[4] • Interrupted time series without a parallel control group	A case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	A cross-sectional study or case series

Table D2-2 summarises the criteria used to determine study eligibility. The population of interest varies depending on the outcome being measured: (i) for outcomes that are identified at or occur around birth, pregnant women and/or neonates are the appropriate population; (ii) for outcomes that occur around the time of breast feeding, post-partum women and/or infants are the appropriate population, and (iii) for neurodevelopmental outcomes that are measured in the years after birth, infants/children are the appropriate population. For fetal, infant or child harm, the exposure status of the mother is coupled with the outcome status of the fetus, infant or child. It should be noted that because the outcome was harm to the fetus, infant, child or mother (and the effect of the intervention on the fetus, infant or child independent of the mother's mental health status is under investigation) the maternal population for inclusion was not always specifically limited to women with mental health disorders, although that population was used preferentially where available.

Pharmacological, complementary and physical interventions that are known to be used in pregnant and postnatal women with mental health disorders were selected for assessment. For anticonvulsants, this was limited to the three drugs most commonly used as mood stabilisers: sodium valproate, carbamazepine and lamotrigine. While classified as physical therapies with exercise, yoga and acupuncture in Part C of the Technical Report, electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) have been included in the assessment of harms to the fetus, infant and child due to their direct impact on maternal systemic physiology.

Two types of comparator were included: (i) comparison to no intervention and (ii) comparison to other interventions. Comparison to no intervention provides a measure of whether an intervention may cause a harm, whereas comparison to another intervention provides a measure of whether the intervention of interest causes more or less harm than the comparator intervention.

The included outcomes were grouped into three categories:

- Malformations – which occur as a result of antenatal exposure, generally in the first trimester.

[1] NHRMC (2009) NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Accessed on 12 May 2017 from https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.

[2] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[3] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

[4] Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

- Pregnancy and birth outcomes – featl, infant or child harms which can occur as a result of antenatal exposure both early in pregnancy (e.g. miscarriage) and later in pregnancy (e.g. poor neonatal adaptation syndrome [PNAS] and respiratory distress), and maternal harm which can occur as a result of antenatal exposure.
- Neurodevelopmental outcomes – which may potentially occur as a result of antenatal or postnatal exposure.

Table D2-2 PICO criteria used to inform the literature search

Population	Exposure	Comparator	Outcomes
Pregnant women Post-partum women Infants or children exposed during pregnancy or postnatally	Pharmacological therapies Antidepressants Antipsychotics Mood stabilisers (including anticonvulsants,[5] benzodiazepines and z-drugs) Lithium Complementary therapies Omega-3 fatty acids St John's wort Gingko biloba Physical therapies Electroconvulsive therapy Transcranial magnetic stimulation	No exposure Exposure to an active comparator	**Fetal, infant or child harms** Malformations Major malformations Cardiac malformations Septal malformations Pregnancy and birth outcomes Neonatal mortality/still birth Miscarriage Preterm birth SFGA/IUGR PNAS Persistent pulmonary hypertension Respiratory distress Tremors Convulsions Neurodevelopmental outcomes Autism spectrum disorder ADHD Other neurodevelopmental disorders measured with validated instruments Intelligence quotient Behavioural problems Depression Anxiety **Maternal harm** Postpartum haemorrhage

Abbreviations: ADHD, attention deficit hyperactivity disorder; IUGR, intrauterine growth restriction; PNAS, poor neonatal adaptation syndrome; SFGA, small for gestational age.

D2.3 LITERATURE SEARCH

D2.3.1 Search strategy

A two-tiered search strategy was undertaken. An initial search was undertaken to identify SRs that assessed various treatments for the main mental health disorders seen during the perinatal period; these included depression, anxiety, schizophrenia and bipolar disorder. Full details of the SR search can be found in **Appendix D1.1.1** and **Appendix D1.2.1**. It should be noted that this search was conducted to identify studies not only for the assessment of harms, but also for screening interventions, and the efficacy of treatment and prevention for psychosocial and psychologic interventions, as well as additional physical interventions.

From this search, an initial list was assembled of SRs that assessed the harms to the infant associated with the pharmacological, complementary and physical therapies outlined in **Table D2-2**.The individual studies included in each SR were identified and, where possible, a 'foundation review' was identified. The process for identifying the foundation reviews is outlined in **Appendix D2**. The foundation review was defined as

[5] Sodium valproate, carbamazepine and lamotrigine only.

the SR that included the most recent and comprehensive set of data for a particular intervention and outcome, and if suitable could be included in the Evidence Review; if not suitable for inclusion, the foundation review could be used to identify relevant individual studies. Further details on the criteria for determining the suitability for inclusion of foundation SRs is provided in **Section D2.3.2**.

Based on the findings of the SR search, a second series of literature searches were carried out. These 'updated' searches aimed to identify additional SRs, and individual RCTs and observational studies, and were based on the interventions of interest as follows:

- Where a suitable foundation review was identified, the search was limited from the year of the foundation review's literature search up to October 2016. Date-limited searches were conducted for all pharmacological agents except z-drugs, and the complementary therapy omega-3 fatty acids.
- Where no suitable foundation review was identified, no initial date limit was set, and the search was conducted up to October 2016. Extended date searches were conducted for z-drugs, the complementary therapies St John's wort and Gingko biloba, and the physical therapies electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS).

Full details of the updated searches can be found in **Appendix D1.1.2** and **Appendix D1.2.2**. It should be noted that these updated searches also aimed to identify evidence of efficacy for the pharmacologic, complementary and selected physical interventions.

Searches were conducted in the MEDLINE, Embase and PsychINFO databases (via the OVID and/or Embase.com interfaces), the Cochrane Library, and included examination of the reference lists of included SRs and individual studies.

D2.3.2 Study eligibility

The aim of the literature search was to identify the highest possible quality evidence for each intervention/outcome. As noted previously, SRs of RCTs provide the highest level of evidence for assessment of the effects of interventions; however, it may not be feasible or ethical to conduct an RCT to examine harms to offspring or women exposed to interventions used for treating or preventing mental health disorders in pregnant or postnatal women. In this case, a SR of observational studies provides an alternative. For each intervention/outcome assessed, a hierarchy of evidence was applied (see **Table D 2-3**). Starting from SRs of RCTs, evidence at each level in the hierarchy were searched, until relevant evidence was found.

The level of evidence identified for each intervention/outcome pairing had a direct impact on the grading of the quality of the evidence, as will be described in **Section D2.5.1**.

Table D 2-3 Hierarchy of evidence for the literature review

SR of RCTs
Individual RCT
SR of comparative observational studies
Individual comparative observational studies
SR of case series/single-arm studies
SR of case reports
Individual case series/report

Abbreviations: RCT, randomised controlled trial; SR, systematic review.

Citations identified in the literature searches were reviewed and evidence selection criteria were applied hierarchically. As shown in **Table D 2-4**, there was a set of standard evidence selection criteria that applied to both the SR search for all interventions, and the updated searches for pharmacological, complementary and the physical interventions ECT and TMS.

In addition, due to the volume and types of evidence available for certain interventions, additional intervention-specific criteria were applied. A large volume of evidence was identified for fetal, infant and child outcomes for antidepressants and so strict inclusion criteria were applied in order to identify 'higher quality' evidence. In order to be included in the assessment of antidepressant harms, studies had to have attempted to match or adjust the analysis for most of the main known confounders, which included maternal age, parity, smoking and alcohol. In addition, studies had to have specifically addressed confounding by indication by (i) limiting the analysis to women with a psychiatric condition, (ii) adjusting for psychiatric condition-related variables (e.g. psychiatric diagnosis, presence/number of psychiatric visits), or (iii) performing sibling analyses, in which outcomes in exposed/unexposed pairs of siblings are compared (with the assumption being that confounding by indication should be minimised because each discordant pair has the same mother). Similar criteria were applied for antipsychotics and benzodiazepines/z-drugs; however, these criteria could be relaxed for individual treatments where the 'higher quality' evidence wasn't available.

The assessment of evidence for anticonvulsants was limited to SRs of observational studies only. This is because there is a large volume of SR evidence available regarding the fetal, infant and child harms associated with anticonvulsants. This evidence is limited to a maternal population with epilepsy, and so the high level of confounding by indication known to be associated with psychiatric disorders is not present.

The assessment of evidence for omega-3 fatty acids was also limited to SRs due to the large volume available. There is a large amount of RCT evidence available for the use of omega-3 fatty acids in pregnancy, as there are no known harms, and it is believed that omega-3 fatty acids are beneficial to the mother and offspring when taken during pregnancy. For this reason, examination of the evidence for omega-3 fatty acids was limited to SRs of RCTs.

No additional evidence selection criteria were applied for St John's wort, Gingko biloba, ECT and TMS.

The ultimate aim of the evidence selection criteria was to limit the assessment of evidence to the 'highest quality' studies for each intervention grouping and type. All evidence selection criteria were applied in two stages: first to the titles/abstracts and then to the full publications/reports of potentially included studies. Full details of the exclusion of studies are provided in **Appendix D1.3**.

Table D 2-4 Evidence selection criteria - general

Criterion	Description
SR search	
Not a SR	Excludes individual clinical studies, narrative reviews, editorials, animal studies and in vitro studies
Wrong population	Excludes studies that are not conducted in pregnant or postnatal women, or children exposed to intervention antenatally or postnatally
Wrong intervention/exposure	Excludes studies that do not examine one of the exposures included in Table D2-2 (as well as other psychosocial, psychological and physical interventions defined in Part C of the Technical Report)
Wrong outcome	Excludes studies that do not examine one of the outcomes included in Table D2-2 (as well as other efficacy/safety/harm outcomes defined in Part C of the Technical Report)
Not in English	Excludes SRs not available in English.
Updated searches - all	
Not a clinical study	Excludes narrative reviews, editorials, animal studies and in vitro studies
Not a SR	Excludes reviews described as systematic that are not, or that limit identification of evidence to MEDLINE /PubMed only.
Wrong population	Excludes studies that are not conducted in pregnant or postnatal women, or children exposed to intervention antenatally or postnatally
Wrong intervention/exposure	Excludes studies that do not examine one of the exposures included in Table D2-2
Wrong/no comparator	Excludes studies that do not compare the exposure with no exposure or a relevant active exposure
Wrong study type	Excludes individual studies (assessment of postpartum haemorrhage [see Part C of the Technical Report] limited to SRs only)
Protocol only	Excludes publications describing a study protocol only
Duplicate data	Excludes studies that include data that has already been included from another publication
Not in English	Excludes studies not available in English
Abstract only	Excludes studies available as a conference abstract only. Where identified, an additional search will be conducted to see if the study has subsequently published.

Table D 2-5 Evidence selection criteria – intervention-specific

Criterion	Description
Updated searches - antidepressants	
Not adjusted for potential confounders	Excludes individual studies that have not attempted to minimise confounding either by study design or statistical methods
Not limited to/adjusted for maternal mental health disorder	Excludes studies that have not specifically attempted to minimise confounding by indication by limiting the included population, or matching or adjusting for disorder-related variables
Updated searches - antipsychotics	
Not adjusted for potential confounders	Excludes individual studies that have not attempted to minimise confounding either by study design or statistical methods
Not limited to/adjusted for maternal mental health disorder	Excludes studies that have not specifically attempted to minimise confounding by indication by limiting the included population, matching on disorder-related variable, or adjusting for disorder-related variables. However, where no such information was available for a specific antipsychotic, this criterion was relaxed.
Updated searches - anticonvulsants	
Wrong study type	Excludes individual studies (assessment of anticonvulsants limited to SRs only)
Updated searches -benzodiazepine and z-drugs	
Not adjusted for potential confounders	Excludes individual studies that have not attempted to minimise confounding either by study design or statistical methods
Not limited to/adjusted for maternal mental health disorder	Excludes studies that have not specifically attempted to minimise confounding by indication by limiting the included population, matching on disorder-related variable, or adjusting for disorder-related variables. However, where no such information was available for a specific antipsychotic, this criterion was relaxed.
Updated searches – omega-3 fatty acids	
Wrong study type	Excludes SRs of observational studies, and individual RCTs or observational studies (assessment of omega-3 fatty acids limited to SRs of RCTs only)

Abbreviations: RCT, randomised controlled trial; SR, systematic review.

D2.4 ASSESSMENT OF THE EVIDENCE

The highest quality evidence for each intervention/outcome was selected from the available body of evidence. Where there were no existing SR/meta-analyses appropriate for inclusion, and multiple individual studies were identified, it was necessary to perform a meta-analysis de novo for this literature review. Meta-analyses were performed using Review Manager 5.3. The results most completely adjusted for potential confounding were used preferentially where available, and the inverse variance method with a random effects model (REM) was used; meta-analyses were not performed using raw, unadjusted data from observational studies.

The full assessment of the evidence for harms for each intervention can be found in **Appendix D4**.

D2.5 EVIDENCE TO RECOMMENDATIONS PROCESS

The aim of the Evidence Review process was to identify the highest quality evidence of the harms of maternal exposure to various pharmacological, complementary and physical mental health disorder interventions. This evidence was then described and graded, and recommendations developed.

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology was used to grade the quality of the evidence for each intervention and outcome and translate this into recommendations and practice points. For further details about GRADE see http://www.gradeworkinggroup.org/.

According to the GRADE process, the body of evidence is summarised in either an Evidence Profile (EP), or Summary of Findings (SoF) table. For the purpose of the assessment of infant and maternal harm, the evidence was presented in EP tables, because they provide greater transparency regarding the decisions that have gone into grading the evidence. An EP table explicitly provides the following information:

- Quality assessment – this section provides information on the size of the evidence base, as well as the assessment of the quality of the evidence. The evidence is assessed according to five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. The aim of this section is to generate a 'score' for the overall quality of the evidence for each intervention/outcome.
- Summary of findings – this section provides details on the study event rates for the intervention and comparator groups in the study, the risk estimate, and the anticipated absolute effects.

It should be noted that modifications to these were required in order to accommodate the evidence base for harms, which largely consisted of observational studies. Each of these will be described in detail below. The EP tables for each intervention can be found in **Section D3**.

D2.5.1 Grading of the certainty of the evidence

The certainty of evidence assessment for GRADE involves consideration of the following five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. For an evidence base drawn from RCTs, the grading of the certainty of the evidence starts at 'high' (⬤⬤⬤⬤). However, for an evidence base drawn from observational studies (which mostly form the basis for the assessment of harms in this guideline), the grading of the certainty of the evidence starts at 'low' (⬤⬤◯◯). For the purpose of this Evidence Review, it is assumed that this 'low' grading already takes into account the general biases associated with observational study design. The certainty of the evidence is then downgraded depending on whether there is any *additional* risk of bias, and how it scores on the other four domains. There is also the opportunity to upgrade the certainty of the evidence in specific circumstances (see below).

A number of 'general rules' for handling the assessment of the certaimty of the evidence were agreed *a priori* with the EWG and Harms Expert Committee. These included:

- The certainty of the evidence could be downgraded for one or more of the five domains examined in GRADE: risk of bias, inconsistency, indirectness, imprecision, and publication bias.
- An additional downgrading by one or two levels for risk of bias could be undertaken if there were specific study-, exposure- or outcome-related concerns.
- The certainty of the evidence was downgraded one level for inconsistency where there was moderate heterogeneity within a meta-analysis (I^2 between 25% and 59%). The certainty of the evidence was downgraded two levels for inconsistency where there was substantial heterogeneity within a meta-analysis ($I^2 \geq 60\%$).
- The certainty of the evidence was downgraded one level for indirectness where the exposed population (with a mental health disorder) was compared with a non-exposed population without a mental health disorder, except in the case where the underlying condition was accounted for in the analysis using statistical methods.
- The certainty of the evidence was downgraded one level for imprecision for any one of the following reasons: (i) where the 95% confidence interval (CI) of the relative risk (RR) crossed 1.00, and where either or both the lower and upper 95% CI crossed 0.75 or 1.25; this indicated that the results included a measure of appreciable benefit and/or harm; (ii) where only a p value was provided; and (iii) where there were no events for the analysis.
- The certainty of the evidence was never downgraded due to publication bias as a comprehensive literature search was conducted to identify all relevant studies and few of the studies were identified as having been commercially funded.[6]
- The certainty of the evidence could potentially be upgraded for the following reasons, as long as it had not already been downgraded for one of the domains above: (i) large magnitude of effect, (ii) dose-response gradient, or (iii) effect of plausible residual confounding.

A number of additional 'intervention-specific rules' were also agreed with the EWG and Harms Expert Committee due to the different evidence base identified for some of the intervention types. These will be outlined in the results section where appropriate.

In some cases, downgrading resulted in the evidence base being considered as lower than 'very low' (●○○○), the lowest certainty category used by GRADE. For the purpose of this Evidence Review, an additional category was added – inadequate (○○○○). This circumstance is distinct from situations where there is no evidence. It was agreed by the EWG that evidence-based recommendations could not be made based on evidence that is inadequate; however, it was acknowledged there may be cases where it is appropriate to use this evidence to make consensus-based recommendations or practice points.

D2.5.2 Determining the absolute increase in risk

This section of the EP table generally includes the event rates seen in the intervention and comparator groups. As this is an assessment of harms, and the body of evidence is largely based on observational studies, it was not considered appropriate to include event rates. Instead, for evidence based on observational studies, the size of the exposed and unexposed/active comparator populations was included instead.

The absolute increase in risk could be calculated for dichotomous outcomes that were reported as RRs or risk differences (RD). As the evidence is based largely on data from cohort and case-control studies, in many cases the results were presented as odds ratios (ORs) instead of RRs. Where the baseline risk was <7% (identified by the risk in an unexposed group with a mental health disorder, where available), it was assumed that the OR approximates the RR and the results were interpreted as RRs. The absolute increase in risk was calculated by determining the baseline (unexposed or active treatment) risk, and multiplying by

[6] The following studies were commercially funded: Cole 2007a (GlaxoSmithKline), Cole 2007b (Genzyme) and Nulman 2015 (Wyeth-Ayerst Canada and Shopper Drug Mart, Canada). See the individual risk of bias assessments for further details.

the RR. Where the certainty of the evidence base was considered inadequate (◯◯◯◯), the absolute additional risk associated with the intervention was not calculated as the results are highly uncertain.

D2.5.3 Drafting of Evidence Statements

Whilst not a requirement of GRADE, Evidence Statements (ES) for each PICO have been developed for the purpose of the current Guideline. This has been done to facilitate the explicit weighing of benefits and harms across multiple outcomes, for the mother versus the infant, in the antenatal versus the postnatal periods.

It should be noted that evidence from RCTs can be used to infer that an intervention *causes* an outcome/harm, while observational studies provide evidence only of an *association* between an intervention and an outcome, which is not sufficient alone to prove causality. Causal inference in epidemiology requires consideration of a number of criteria including the following which, if present, may strengthen the possibility of a causal relationship, although it should be noted there are counterarguments against most of them:[7]

- A temporal relationship – exposure to the intervention precedes the condition.
- Strength of the association – the stronger the association, the more likely it is causal.
- Dose response – increasing the amount of exposure increases the risk proportionally.
- Consistency – the association is consistent when results are replicated in studies using different methods.
- Biologic plausibility – the association agrees with currently accepted understanding of biologic processes.
- Experimentation – the condition can be altered (prevented or ameliorated) by an appropriate experimental intervention.
- Specificity – a single putative cause produces a specific effect.
- Biologic coherence – the association is consistent with the natural history of the disease.
- Analogy – there are similar associations in other populations or under different settings.

The wording of the ES has thus been chosen carefully to avoid undue use of double negatives, and to convey the confidence of the findings, keeping in mind that the findings relate to the presence or absence of *associations* between exposure and the outcomes (most of which are pre-specified as 'harms' not benefits). The specific rules around the wording of the ES are as follows:

- If the effect estimate and CI include 1.00 (relative measures; RR, OR) or 0 (absolute measures; RD, mean difference [MD], standardised mean difference [SMD]):
    - and moderate or high certainty evidence is available: the phrasing "is no association between [exposure] and an increased risk of [outcome]" is used.
    - and low or very low certainty evidence is available: the phrasing "does not appear to be an association between [exposure] and an increased risk of [outcome]" is used
    - and inadequate certainty evidence is available: the phrasing "any association between [exposure] and an increased risk of [outcome] is uncertain" is used.
- If the effect estimate and CI do not include 1.00 (relative measures; RR, OR) or 0 (absolute measures; RD, MD, SMD):
    - and moderate or high certainty evidence is available: the phrasing "is an association between [exposure] and an increased risk of [outcome]" is used.
    - a low or very low quality evidence is available: the phrasing "may be an association between [exposure] and an increased risk of [outcome]" is used and the absolute risk estimates cited.

[7] See Kovesdy and Kalantar-Zadeh (2012) Observational studies vs. randomized controlled trials: avenues to causal inference in nephrology. Adv Chronic Kidney Dis 19(1): 11-18.

  - Where low quality evidence is available, but the evidence shows a large magnitude of effect:[8] the phrasing "is an association between [exposure] and an increased risk of [outcome] is used.
  - and inadequate quality evidence is available: the phrasing "appears to be an association between [exposure] and an increased risk of [outcome], but due to the inadequate quality of the evidence this association is uncertain" with no citing of the absolute risk estimates.
- Where there 'is' or 'may be' an association, and where an absolute increase or decrease in risk is available, this is also captured in the ES.

[8] 95% exceeds the minimum level of appreciable harm (RR > 1.25 or SMD < -0.5).

D3 RESULTS

The results of the assessment of evidence are presented in the following sections:

- Pharmacological therapies:
  - Antidepressants: Section D3.1.1
  - Antipsychotics: Section D3.1.2
  - Anticonvulsants: Section D3.1.3
  - Benzodiazepines and z-drugs: Section D3.1.4
  - Lithium: Section D3.1.5
- Complementary therapies:
  - Omega-3 fatty acids: Section D3.2.1
  - St John's wort: Section D3.2.2
  - Gingko biloba: Section D3.2.3
- Physical therapies:
  - Electroconvulsive therapy: Section D3.3.1
  - Transcranial magnetic stimulation: Section D3.3.2.

The following sections of the Appendix to Part provide detailed information on how this evidence was selected and evaluated:

- Included studies: **Appendix D2**
- Data extraction: **Appendix D3**
- Assessment of evidence: **Appendix D4**
- Risk of bias assessment: **Appendix D5**.

D3.1 PHARMACOLOGICAL

D3.1.1 Antidepressants

The following section presents the Evidence Profile tables for the specific antidepressant classes and individual medications examined. Due to the large amount of evidence available for the assessment of antidepressants, only evidence from studies that adjusted for confounding and attempted to minimise the effect of confounding by indication have been included here. A summary of the characteristics of the individual included studies can be found in **Table AppD2-5** in **Appendix D2.1.1.2**. A detailed discussion of the evidence for each group or individual intervention type and outcome can be found in **Appendix D4.1.1**.

It should be noted that no certainty assessments based on assessment of individual studies were downgraded due to indirectness, because all included studies had been selected to minimise indirectness: they either limited the comparison to a population with depression/psychiatric disorder, or adjusted the analysis for depression/psychiatric disorder, thus attempting to minimise confounding by indication.

Table D 3-1 presents a summary of the results of the Evidence Review of antidepressants as well as the location of the detailed assessment of the certainty of evidence in the evidence profile tables. Due to the unsuitability of the identified SRs, relevant individual studies were identified and de novo meta-analyses were performed where appropriate. While evidence was identified for a number of groupings of antidepressants, only groupings with a pharmacological or chemical basis (i.e. groups based on similar modes of action such as receptor type [eg, SSRIs, SNRIs] or similar chemical structure [eg, TCAs]) were assessed in the EP tables. However, the evidence base for excluded groupings such as any antidepressants, non-SSRIs and co-exposures) is presented and discussed in **Appendix D4.1.1**.

The most evidence was available for SSRIs as a class, as demonstrated by the number of outcomes that were able to be assessed. The results suggest that antidepressants are, or may be, associated with adverse pregnancy and birth outcomes. There appeared to be no effect of SSRIs as a group, fluvoxamine, SNRIs and TCAs on malformations, although septal malformations may be associated with use of fluoxetine. For other individual SSRIs and antidepressants, the evidence on malformations was imprecise due to the low numbers available for the analysis. Where evidence was available on malformations, the certainty was considered very low. With the exception of no effect on IQ for SSRIs as a group, all available evidence for neurodevelopmental outcomes was uncertain, the main reason being that studies did not adequately account for confounding by indication due to depression severity both during pregnancy, and in the period following birth, which for some of the neurodevelopmental outcomes was up to 14 years. The evidence for the maternal harm postpartum haemorrhage was considered to be inadequate for SSRIs (although the finding was statistically significant), while for SNRIs the evidence was of very low certainty, and suggested SNRIs may be associated with postpartum haemorrhage.

A number of comparisons were made against other treatments; however, most of these were based on inadequate evidence. The exception was the risk of poor neonatal adaptation syndrome (PNAS) associated with the use of SSRIs compared with SNRIs, which showed that the risk may be greater for SSRIs.

Table D 3-1 Summary of results of the Evidence Review for antidepressants

Intervention	Increased/may be increased risk of harm Outcome Certainty of evidence	Appears to be no increased risk of harm Outcome Certainty of evidence	Decreased/may be decreased risk of harm Outcome Certainty of evidence	Uncertain Outcome ○○○○	Evidence profile table
SSRIs[9]	Miscarriage ●●○○ Preterm birth ●●○○ PNAS ●●○○ PNAS (SSRI vs SNRI) ●○○○ PPH ●○○○ Respiratory distress ●○○○ Convulsions ●●○○	Major malformation ●○○○ Cardiac malformation ●○○○ Neonatal mortality ●○○○ IQ ●○○○ Behavioural problems[10] ●○○○		Cardiac malformation (vs non-SSRI) Septal malformation ASD ADHD Other disorders[11] Depression Anxiety Postpartum haemorrhage	**Table D3-2**
Paroxetine	Miscarriage ●●○○			Major malformation Cardiac malformation Cardiac malformation (vs other ADs) ASD	**Table D3-3**
Fluoxetine	Septal malformation ●○○○	Miscarriage ●○○○		Major malformation Cardiac malformation ASD	**Table D3-4**
Sertraline		Miscarriage ●○○○		Major malformation Cardiac malformation ASD	**Table D3-5**
Citalopram		Miscarriage ●○○○		Major malformation Cardiac malformation ASD	**Table D3-6**
Escitalopram				Major malformation Cardiac malformation	**Table D3-7**
Fluvoxamine		Major malformation ●○○○ Cardiac malformation ●○○○ Miscarriage ●○○○		ASD	**Table D3-8**
SNRIs/ venlafaxine	Miscarriage ●●○○ Postpartum haemorrhage ●○○○	Major malformation ●○○○		Cardiac malformation ASD ADHD	**Table D3-9**
NaSSA/ mirtazapine				Major malformation (vs other ADS) Stillbirth (vs other ADS) Miscarriage (vs other ADS) Preterm birth (vs other ADS)	**Table D3-10**
TCAs	Miscarriage ●○○○	Major malformation ●○○○ Neonatal mortality ●○○○		Cardiac malformation ASD ADHD	**Table D3-11**
Bupropion				Cardiac malformation Cardiac malformation (vs other ADs) ADHD	**Table D3-12**

Abbreviations: AD, antidepressant; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; IQ, intelligence quotient; NaSSA, noradrenergic and specific serotonergic antidepressants; PNAS, poor neonatal adaptation syndrome; PPH, persistent pulmonary hypertension; SNRI, serotonin and noradrenalin reuptake inhibitor; SRI, selective reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor, TCA, tricyclic antidepressant.

Note: All comparisons are against non-exposure, unless otherwise stated. Certainty of evidence gradings are as follows: ●●●● – high certainty; ●●●○ – moderate certainty; ●●○○ – low certainty; ●○○○ – very low certainty; ○○○○ – inadequate certainty.

[9] Also includes some data on SRIs (SSRIs and SNRIs)

[10] Includes internalising and externalising behaviours.

[11] Includes speech/language, scholastic and motor disorders.

Table D3-2 Evidence Profile table: SSRI harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[12]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)** **Unexposed**	**Exposed**	**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects** **Risk with control**[13]	**Risk with intervention**[14]
Major malformations: see Section AppD4.1.1.3.2											
48,717 (3 – OBS)[15]	Serious(a)	None	None	None	None	●○○○ Very low	**Unexposed** NA	**SSRIs**[16] **(first trimester)** NA	RR 1.02 (0.91, 1.14)	28 per 1000[17]	29 per 1000 (25, 32)
Evidence Statement: *Maternal use of SSRIs during the first trimester of pregnancy does not appear to be associated with an increased risk of major malformation in the newborn (very low certainty evidence)*											
Cardiac malformations: see Section AppD4.1.1.4.2											
286,647 (6 – OBS)[18]	Serious(a)	None	None	None	None	●○○○ Very low	**Unexposed** NA	**SSRIs (first trimester)** NA	RR 1.04 (0.94, 1.15)	6 per 1000[19]	6 per 1000 (6, 7)
3,768 (1 – OBS)[20]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Non-SSRIs** 992	**SSRIs (first trimester)** 2,776	RR 1.48 (0.58, 3.73)	Unknown	-
Evidence Statements: *Maternal use of SSRIs during the first trimester of pregnancy does not appear to be associated with an increased risk of cardiac malformation in the newborn (very low certainty evidence)* *Due to the inadequate certainty of the evidence, any additional risk of cardiac malformations in the newborn associated with maternal use of SSRIs during the first trimester of pregnancy, compared with maternal use of non-SSRIs during the same period, is uncertain.*											
Septal malformations: see Section AppD4.1.1.5.2											
16,831 (1 – OBS)[21]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** 1,651	**Non-sertraline SSRIs** 236	RR 1.13 (0.81, 1.58)	3 per 1000[22]	3 per 1000 (2, 5)
Evidence Statements: *Due to the inadequate certainty of the evidence, any association between maternal use of non-sertraline SSRIs during the first trimester of pregnancy and septal malformation in the newborn is uncertain.*											

[12] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[13] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[14] Calculated by multiplying relative effect by control risk; it is not considered appropriate to calculate the risk with intervention where the quality of the evidence is inadequate.
[15] Based on a de novo meta-analysis of data from Ban 2014a, Bérard 2015 and Simon 2002.
[16] One study included non-sertraline studies only (Bérard 2015).
[17] Ban 2014a.
[18] Based on a de novo meta-analysis of data from Ban 2014a, Bérard 2015, Furu 2015, Huybrechts 2014a, Margulis 2013 and Petersen 2016.
[19] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[20] Petersen 2016.
[21] Bérard 2015.
[22] The Bérard 2015 study used an insured population and as such the prevalence of septal malformations in this study (1.83%) is not likely to be representative of the general population with depression. To estimate the prevalence, it is assumed that 50% of cardiac malformations are septal, resulting in an estimate of 0.3%.

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
Neonatal mortality:[23] see Section AppD4.1.1.6.2											
NR (1 – OBS)[24]	None	NA	None	Serious (b)	None	⊕◯◯◯ Very low	**Unexposed** NA	**SSRIs** **(first trimester)** NA	RR 1.2 (0.6, 2.3)	5 per 1000[25]	6 per 1000 (3, 12)
Evidence Statement: *Maternal use of SSRIs during the first trimester of pregnancy does not appear to be associated with an increased risk of neonatal mortality (very low certainty evidence).*											
Miscarriage: see Section AppD4.1.1.7.2											
NR (2 – OBS)[26]	None	NA	None	None	None	⊕⊕◯◯ Low	**Unexposed** NA	**SSRIs** **(first trimester)** NA	**RR 1.34** **(1.16, 1.54)**	81 per 1000[27]	109 per 1000 (94, 125)
5,001 (1 – OBS)[28]	None	NA	None	None	None	⊕⊕◯◯ Low	**Unexposed** NA	**SSRIs** **(up to 20 weeks)** NA	**OR 1.61** **(1.28, 2.04)**	81 per 1000[29]	Not estimable
Evidence Statement: *Maternal use of SSRIs during the first 20 weeks of pregnancy is associated with an increased risk of miscarriage, from an absolute risk of 8% to 11% (low certainty evidence).*											
Pre-term birth: see Section AppD4.1.1.8.2											
< 37 weeks *1,787* (1 – OBS)[30]	None	NA	None	None	None	⊕⊕◯◯ Low	**Unexposed** 1,566	**SSRIs** **(late gestation)** 221	**RR 2.68** **(1.83, 3.93)**	60 per 1000[31]	161 per 1000 (110, 236)

[23] Includes stillbirth and neonatal death up to 28 days.
[24] Ban 2012.
[25] Ban 2012.
[26] Based on a de novo meta-analysis of data from Almeida 2016 and Ban 2012.
[27] Almeida 2016 and Ban 2012.
[28] Nakhai-Pour 2010; population likely overlaps with that of Almeida 2016.
[29] Almeida 2016 and Ban 2012.
[30] Grzeskowiak 2012.
[31] Malm 2015.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
< 37 weeks *1,622* (1 – OBS)[32]	None	NA	None	None	None	●●○○ Low	**Unexposed** 805	**SSRI (any time)** 817	RD 0.007 (-0.018, 0.034)	60 per 1000[33]	-
Evidence Statement: *Maternal use of SSRIs during late pregnancy is associated with an increased risk of preterm birth, from an absolute risk of 6% to 16% (low certainty evidence).*											
Small for gestational age: see Section AppD4.1.1.9.2											
1,787 (1 – OBS)[34]	None	NA	None	Serious(b)	None	●○○○ Very low	**Unexposed** 1,566	**SSRI (any time)** 221	OR 1.13 (0.65, 1.94)	Unknown	-
1,622 (1 – OBS)[35]	None	NA	None	None	None	●●○○ Low	**Unexposed** 805	**SSRI (any time)** 817	**RD 0.033 (0.007, 0.059)**	Unknown	-
Evidence Statement: *Maternal use of SSRIs at any time during pregnancy does not appear to be associated with an increased risk of the newborn being small for gestational age (low certainty evidence).*											
Poor neonatal adaptation syndrome: see Section AppD4.1.1.10.1 and AppD4.1.1.10.2											
312 (2 – OBS)[36]	Unknown[37]	Serious (c)	Serious (d)	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	**RR 4.74 (2.14, 10.5)**	Unknown	-
247 *(1 – OBS)[38]*	Serious(e)	NA	None	None	None	●○○○ Very low	**SNRI** 24	**SSRI (third trimester)** 188	**OR 2.75 (1.13, 6.71)**	Unknown	-
Evidence Statement: *Maternal use of SSRIs at any time during pregnancy appears to be associated with an increased risk of poor neonatal adaptation syndrome in the newborn, but due to the inadequate certainty of the evidence this association is uncertain.* *Maternal use of SSRIs during the third trimester of pregnancy may be associated with an increased risk of poor neonatal adaptation syndrome compared with maternal use of SNRIs during the same period (increase in absolute risk not estimable) (very low certainty)*											

[32] Oberlander 2006.
[33] Malm 2015.
[34] Grzeskowiak 2012.
[35] Oberlander 2006.
[36] Based on an existing meta-analysis by Grigoriadis 2013b. No individual studies comparing exposure to non-exposure met the 'higher quality' criteria.
[37] Individual included studies not reported.
[38] Kieviet 2015.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
Persistent pulmonary hypertension: see Section AppD4.1.1.11.1 and AppD4.1.1.11.2											
NR (3 – OBS)[39]	None[40]	None	Serious(d)	None	None	●○○○ Very low	**Unexposed** NA	**SSRI (any time)** NA	**RR 2.41 (1.35, 3.95)**	3 per 1000[41]	7 per 1000 (4, 12)
NR (3 – OBS)[42]	None[43]	Very serious(f)	Serious(d)	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (early pregnancy)[44]** NA	RR 1.45 (0.84, 2.49)	3 per 1000[45]	-
NR (4 – OBS)[46]	None[47]	Serious(c)	Serious(d)	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (late pregnancy)[48]** NA	**RR 2.72 (1.63, 4.54)**	3 per 1000[49]	
786,446 (2 – OBS)[50]	None	Very serious(f)	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (late exposure)[51]** NA	RR 1.80 (0.65, 4.95)	3 per 1000[52]	-
Full-term deliveries only *621,399* (1 – OBS)[53]	None	NA	None	None	None	●●○○ Low	**Unexposed** 567,118	**SSRI (late exposure)[54]** 54,281	**RR 1.27 (1.00, 1.61)**	3 per 1000[55]	4 per 1000 (3, 5)

[39] Based on an existing meta-analysis by McDonagh 2014. Included because the individual studies comparing exposure to non-exposure did not adjust for a major potential confounder, caesarean birth.
[40] Based on the description provided by McDonagh 2014.
[41] Huybrechts 2015.
[42] Based on an existing meta-analysis by McDonagh 2014. Included because the individual studies comparing exposure to non-exposure did not adjust for a major potential confounder, caesarean birth.
[43] Based on the description provided by McDonagh 2014.
[44] Not defined.
[45] Huybrechts 2015.
[46] Based on an existing meta-analysis by McDonagh 2014. Included because the individual studies comparing exposure to non-exposure did not adjust for a major potential confounder, caesarean birth.
[47] Based on the description provided by McDonagh 2014.
[48] Mostly > 20 weeks.
[49] Huybrechts 2015.
[50] Based on a de novo meta-analysis of data from Huybrechts 2015 and Kieler 2012.
[51] Defined as 90 days before delivery for Huybrechts 2015 and from 140 days after start of pregnancy for Kieler 2012.
[52] Huybrechts 2015.
[53] Huybrechts 2015.
[54] Defined as 90 days before delivery.
[55] Huybrechts 2015.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
Without cardiac malformation or lung hypoplasia *722,830* (1 – OBS)[56]	None	NA	None	Serious(b)	None	●○○○ Very low	**Unexposed** 657,515	**SSRI (late exposure)[54]** 65,316	RR 1.08 (0.92, 1.27)	3 per 1000[57]	3 per 1000 (3, 4)
Full-term deliveries and excluding cardiac malformation or lung hypoplasia 621,399 (1 – OBS)[58]	None	NA	None	None	None	●●○○ Low	**Unexposed** 567,118	**SSRI (late exposure)[54]** 54,281	**RR 1.28 (1.01, 1.64)**	3 per 1000[59]	4 per 1000 (3, 5)
No meconium aspiration *NR* (1 – OBS)[60]	None	NA	None	None	None	●●○○ Low	**Unexposed** NA	**SSRI (early exposure)[61]** NA	**RR 1.3 (1.1, 1.7)**	-[62]	-
Evidence Statement: *Maternal use of SSRIs during late pregnancy may be associated with an increased risk of persistent pulmonary hypertension in the newborn, from an absolute risk of 0.3% to 0.4% (low certainty evidence)*											
Respiratory distress: see Section AppD4.1.1.12.2											
25,381 (1 – OBS)[63]	Serious(g)	NA	None	None	None	●○○○ Very low	**Unexposed** 9,652	**SSRI (any time)** 15,729	**RR 1.40 (1.20, 1.62)**	32 per 1000[64]	45 per 1000 (38, 52)
1,622 (1 – OBS)[65]	None	NA	None	None	None	●●○○ Low	**Unexposed** NR	**SSRI (any time)** NR	**RD 0.044 (0.013, 0.077)**	32 per 1000[64]	33 per 1000 (32, 34)
Evidence Statement: *Maternal use of SSRIs at any time during pregnancy may be associated with an increased risk of respiratory distress in neonates, from an absolute risk of 3% to 5% (very low certainty evidence)*											

[56] Huybrechts 2015.
[57] Huybrechts 2015.
[58] Huybrechts 2015.
[59] Huybrechts 2015.
[60] Kieler 2012.
[61] Defined as from 140 days after start of pregnancy for Kieler 2012.
[62] Limited to population of women with previous psychiatric hospitalisation. No data available for baseline risk in this population.
[63] Malm 2015.
[64] Malm 2015.
[65] Oberlander 2006.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
Convulsions: see Section AppD4.1.1.14.2											
228,876 (1 – OBS)[66]	None	NA	None	Serious(b)	None	●○○○ Very low	**Unexposed** NA	**SSRI (third-trimester and 1 filled prescription)** NA	RR 1.4 (0.7, 2.8)	3 per 1000[67]	4 per 1000 (2, 8)
228,876 (1 – OBS)[68]	None	NA	None	None	None	●●○○ Low	**Unexposed** NA	**SSRI (third-trimester and 2 filled prescriptions)** NA	**RR 2.8 (1.4, 5.5)**	3 per 1000[69]	8 per 1000 (6, 17)
228,876 (1 – OBS)[70]	None	NA	None	None	None	●●○○ Low	**Unexposed** NA	**SSRI (third-trimester and 3+ filled prescriptions)** NA	**RR 4.9 (2.6, 9.5)**	3 per 1000[71]	15 per 1000 (8, 29)
Note: Hayes 2012 also show (without presenting risk estimates) that these same analyses conducted for first and second trimester exposure to SSRIs did not result in significant associations with convulsions.											
1,622 (1 – OBS)[72]	None	NA	None	None	None	●●○○ Low	**Unexposed** NA	**SSRI (any time)** NA	RD 0.00077 (-0.0010, 0.0036)	3 per 1000[73]	-
Evidence Statement: *Maternal use of SSRIs during the third trimester of pregnancy is associated with an increased risk of convulsions in the newborn, and the risk increases with increasing exposure, from an absolute risk of 0.3% up to 0.4% for one prescription filled, and up to 1.5% for three prescriptions filled (low certainty evidence).*											
Autism spectrum disorder: see Section AppD4.1.1.15.2											
29,737 (3 – OBS)[74]	Very serious(h)	None	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	**RR 1.38 (1.02, 1.87)**	9 per 1000[75]	12 (9, 17)

[66] Hayes 2012.
[67] Hayes 2012.
[68] Hayes 2012.
[69] Hayes 2012.
[70] Hayes 2012.
[71] Hayes 2012.
[72] Oberlander 2006.
[73] Hayes 2012.
[74] Based on a de novo meta-analysis of data from Malm 2016, Harrington 2014 and Sørensen 2013.
[75] Sørensen 2013 and Malm 2016.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
229 (1 – OBS)[76]	Very serious(h)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (first trimester)** NA	RR 1.70 (0.66, 4.38)	9 per 1000[75]	-
229 (1 – OBS)[77]	Very serious(h)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (second trimester)** NA	RR 1.12 (0.40, 3.14)	9 per 1000[75]	-
229 (1 – OBS)[78]	Very serious(h)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (third trimester)** NA	RR 1.43 (0.52, 3.93)	9 per 1000[75]	-
144,507 (1 – OBS)[79]	Very serious(h)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (second or third trimester)** NA	**RR 2.17 (1.20, 3.93)**	9 per 1000[75]	20 per 1000 (11, 35)
Childhood autism											
5,799 (1 – OBS)[80]	Very serious(h)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	RR 1.0 (0.4, 2.6)	Unknown	-
Pervasive developmental disorder											
623 (2 – OBS)[81]	Very serious (i)	None	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	**RR 1.05 (1.01, 1.09)**	Unknown	-
178 (1 – OBS)[82]	Very serious (i)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	RR 1.01 (0.98, 1.05)	Unknown	-

[76] Harrington 2014.
[77] Harrington 2014.
[78] Harrington 2014.
[79] Boukhris 2016.
[80] Sørensen 2013.
[81] Based on a de nova meta-analysis of data from Johnson 2016 and El Marroun 2014.
[82] Johnson 2016.

Certainty assessment							**Summary of findings**				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
Autistic traits – SRS											
445 (1 – OBS)[83]	Very serious (i)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	**β 0.10 (0.02, 0.18)**	NA	-
Social cognition – SRS											
445 (1 – OBS)[84]	Very serious (i)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	β 0.10 (-0.02, 0.22)	NA	-
Social communication – SRS											
445 (1 – OBS)[85]	Very serious (i)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	**β 0.12 (0.03, 0.21)**	NA	-
Autistic mannerism – SRS											
445 (1 – OBS)[86]	Very serious (i)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	**β 0.09 (0.01, 0.17)**	NA	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs at any time during pregnancy and autism spectrum disorder in the child, is uncertain.*											
Attention deficit hyperactivity disorder: see Section AppD4.1.1.16.2											
23,709 (1 – OBS)[87]	Very serious(h)	None	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	RR 0.98 (0.75, 1.28)	10 per 1000[88]	-
NR (1 – OBS)[89]	Very serious(h)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (first trimester)** NA	RR 1.62 (0.79, 3.32)	10 per 1000[88]	-

[83] El Marroun 2014.
[84] El Marroun 2014.
[85] El Marroun 2014.
[86] El Marroun 2014.
[87] Malm 2016.
[88] Based on Malm 2016.
[89] Figueroa 2010.

Certainty assessment							**Summary of findings**				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
NR (1 – OBS)[90]	Very serious(h)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (second trimester)** NA	RR 1.59 (0.58, 4.35)	10 per 1000[88]	-
NR (1 – OBS)[91]	Very serious(h)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (third trimester)** NA	RR 0.38 (0.14, 1.03)	10 per 1000[88]	-
NR (1 – OBS)[92]	Very serious(h)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (after pregnancy)** NA	**RR 2.04 (1.43, 2.91)**	10 per 1000[88]	20 per 1000 (14, 29)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs at any time during or after pregnancy and attention deficit hyperactivity disorder in the child, is uncertain.*											
Other disorders: see Section AppD4.1.1.17.2											
Speech/ language disorder *25,133* (1 – OBS)[93]	Very serious(j)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	RR 1.20 (0.97, 1.49)	Unknown	-
Speech/ language disorder *NR* (1 – OBS)[94]	Very serious(j)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI – 1 purchase (any time)** NA	RR 0.86 (0.67, 1.10)	Unknown	-
Speech/ language disorder *NR* (1 – OBS)[95]	Very serious(j)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI – 2+ purchases (any time)** NA	**RR 1.37 (1.11, 1.70)**	Unknown	-
Speech/ language disorder *NR* (1 – OBS)[96]	Very serious(j)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI monotherapy only – 2+ purchases (any time)** NA	**RR 1.34 (1.07, 1.68)**	Unknown	-

[90] Figueroa 2010.
[91] Figueroa 2010.
[92] Figueroa 2010.
[93] Brown 2016.
[94] Brown 2016.
[95] Brown 2016.
[96] Brown 2016.

Certainty assessment							**Summary of findings**				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
Speech/ language disorder *NR* (1 – OBS)[97]	Very serious(j)	NA	None	None	None	○○○○ Inadequate	**Unexposed/ <u>additional adjustment for suicidal behaviour</u>** NA	**SSRI – 2+ purchases (any time)** NA	**RR 1.34 (1.07, 1.68)**	Unknown	-
Scholastic disorder *25,133* (1 – OBS)[98]	Very serious(j)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	RR 1.00 (0.63, 1.59)	Unknown	-
Scholastic disorder *NR* (1 – OBS)[99]	Very serious(j)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI – 1 purchase (any time)** NA	RR 0.86 (0.52, 1.42)	Unknown	-
Scholastic disorder *NR* (1 – OBS)[100]	Very serious(j)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI – 2+ purchases (any time)** NA	RR 1.15 (0.72, 1.84)	Unknown	-
Motor disorder *25,133* (1 – OBS)[101]	Very serious(j)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI (any time)** NA	RR 1.18 (0.81, 1.72)	Unknown	-
Motor disorder *NR* (1 – OBS)[102]	Very serious(j)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI – 1 purchase (any time)** NA	RR 0.86 (0.57, 1.30)	Unknown	-
Motor disorder *NR* (1 – OBS)[103]	Very serious(j)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI – 2+ purchases (any time)** NA	RR 1.33 (0.93, 1.91)	Unknown	-
<u>Evidence Statement:</u> *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs at any time during pregnancy and speech/language, scholastic or motor disorders in the child, is uncertain.*											

[97] Brown 2016.
[98] Brown 2016.
[99] Brown 2016.
[100] Brown 2016.
[101] Brown 2016.
[102] Brown 2016.
[103] Brown 2016.

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
Intelligence Quotient: see Section AppD4.1.1.18.2											
Total IQ 90 (1 – OBS)[104]	None	NA	None	Unknown(b)	None	●○○○ Very Low	**Unexposed** NA	**SRIs[105]** **(any time)** NA	P ≥ 0.05	NA	-
Verbal IQ 90 (1 – OBS)[106]	None	NA	None	Unknown(b)	None	●○○○ Very Low	**Unexposed** NA	**SRIs** **(any time)** NA	P ≥ 0.05	NA	-
Performance IQ 90 (1 – OBS)[107]	None	NA	None	Unknown(b)	None	●○○○ Very Low	**Unexposed** NA	**SRIs** **(any time)** NA	P ≥ 0.05	NA	-
Evidence Statement: *Maternal use of SRIs at any time during pregnancy does not appear to be associated with a reduction in IQ in children aged 3 to 6 years (very low certainty evidence)*											
Behavioural problems: see Section AppD4.1.1.19.2											
Total problems (CBCL) 90 (1 – OBS)[108]	None	NA	None	Unknown(b)	None	●○○○ Very low	**Unexposed** NA	**SRIs[109]** **(any time)** NA	P ≥ 0.05	NA	-
Internalising behaviours											
90 (1 – OBS)[110]	None	NA	None	Unknown(b)	None	●○○○ Very low	**Unexposed** NA	**SRIs** **(any time)** NA	P ≥ 0.05	NA	-

[104] Nulman 2015
[105] Includes SSRIs and SNRIs.
[106] Nulman 2015
[107] Nulman 2015
[108] Nulman 2015
[109] Includes SSRIs and SNRIs.
[110] Nulman 2015

Certainty assessment							**Summary of findings**				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
Externalising behaviours											
90 (1 – OBS)[111]	None	NA	None	Unknown(b)	None	●○○○ Very low	**Unexposed** NA	**SRIs** **(any time)** NA	P ≥ 0.05	NA	-
Evidence Statement: *Maternal use of SRIs at any time during pregnancy does not appear to be associated with an increased risk of behavioural problems in children aged 3 to 6 years (very low certainty evidence)*											
Depression: see Section AppD4.1.1.20.2											
NR (1 – OBS)[112]	Very serious(k)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**SSRI mono- or polytherapy** **(any time)** NA	**HR 1.84** **(1.14, 2.97)**	3 per 1000[113]	6 per 1000 (3, 9)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs at any time during pregnancy and depression in children aged up to 14 years, is uncertain.*											
Anxiety: see Section AppD4.1.1.21.2											
NR (1 – OBS)[114]	Very serious(k)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SSRI mono- or polytherapy** **(any time)** NA	RR 1.30 (0.84, 2.01)	3 per 1000[115]	4 per 1000 (3, 6)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SSRI mono- or polytherapy during pregnancy and an increased risk of anxiety in children aged up to 14 years is uncertain.*											
Postpartum haemorrhage: see Section AppD4.1.1.15.1											
NR (4/10 – OBS)[116]	None	Very serious(f)	None	None	None	○○○○ Inadequate	**Unexposed** NR	**SRIs** **(any time)** NR	**OR 1.23** **(1.06, 1.44)**	Unknown	-
NR (3/7 – OBS)[117]	None	Very serious(f)	None	None	None	○○○○ Inadequate	**Unexposed** NR	**SRIs** **(recent users)** NR	**OR 1.30** **(1.06, 1.60)**	Unknown	-

[111] Nulman 2015
[112] Malm 2016.
[113] Malm 2016.
[114] Malm 2016.
[115] Malm 2016.
[116] Represents studies/estimates. Included studies not specified.
[117] Represents studies/estimates. Included studies not specified.

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[12]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[13]**	**Risk with intervention[14]**
NR (2/4 – OBS)[118]	None	Very serious(f)	None	None	None	○○○○ Inadequate	**Unexposed** NR	**SRIs** **(current users)** NR	OR 1.39 (0.96, 1.61)	Unknown	-
Evidence Statements: *There appears to be an association between maternal use of SRIs at any time during pregnancy and an increased risk of postpartum haemorrhage, but due to the inadequate certainty of the evidence, this association is uncertain.*											
Footnotes: a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis. b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events. c. Downgraded one level due to moderate heterogeneity (I^2 = 25% to 59%). d. Downgraded one level due to indirectness caused by use of non-depressed control group. e. Downgraded one level due to moderate risk of bias; use of a non-validated outcome assessment tool. f. Downgraded two levels due to substantial heterogeneity (I^2 > 60%). g. Downgraded one level due to moderate risk of bias; potential for selection bias between exposed and psychiatric disorder/unexposed populations. h. Downgraded two levels due to high risk of bias; lack of adjustment for potential confounding by maternal disease severity in the antenatal and postnatal period. i. Downgraded two levels due to high risk of bias; self-rated outcomes that were inconsistent and lack of/inadequate adjustment for maternal disease severity in the postnatal period. j. Downgraded two levels due to high risk of bias; potential for selection bias between exposed and psychiatric disorder/unexposed populations and lack of adjustment for potential confounding by maternal disease severity in the postnatal period. k. Downgraded two levels due to high risk of bias; potential for selection bias due to age unbalanced populations and lack of adjustment for potential confounding by maternal disease severity in the antenatal or postnatal period.											

Abbreviations: AD, antidepressant; CI, confidence interval; NA, not available; NE, not estimable; NR, not reported; OBS, observational studies; OR, odds ratio; RD, risk difference; RR, relative risk; SRS, social responsiveness scale; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

[118] Represents studies/estimates. Included studies not specified.

Table D3-3 Evidence Profile table: paroxetine harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[119]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[120]**	**Risk with intervention[121]**
Major malformations: see Section AppD4.1.1.3.2											
27,362 (2–OBS)[122]	Serious(a)	None	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Paroxetine (first trimester)** NA	RR 1.09 (0.82, 1.45)	28 per 1000[123]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of paroxetine during the first trimester of pregnancy and major malformation in the newborn, is uncertain.*											
Cardiac malformations: see Section AppD4.1.1.4.2											
214,345 (2 – OBS)[124]	Serious (a)	Serious (c)	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Paroxetine** NA	RR 1.20 (0.69, 2.09)	6 per 1000[125]	-
5,013 (1 – OBS)[126]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Other AD monotherapy (first trimester)** NA	**Paroxetine monotherapy (first trimester)** NA	RR 1.46 (0.74, 2.88)	Unknown	-
5,956 (1 – OBS)[127]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Other AD mono- or polytherapy** NA	**Paroxetine mono- or polytherapy (first trimester)** NA	RR 1.68 (0.95, 2.97)	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of paroxetine during the first trimester of pregnancy and cardiac malformation in the newborn, is uncertain.* *Due to the inadequate certainty of the evidence, any additional risk of cardiac malformation in the newborn that may be associated with maternal use of paroxetine in the first trimester, compared with maternal use of other antidepressant mono- or polytherapy during the same period, is uncertain.*											

[119] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[120] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[121] Calculated by multiplying relative effect by control risk.
[122] Based on a de novo meta-analysis of data from Ban 2014a and Ramos 2008.
[123] Ban 2014a.
[124] Based on a de novo meta-analysis of data from Ban 2014a and Huybrechts 2014a.
[125] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[126] Cole 2007b.
[127] Cole 2007b.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[119]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[120]**	**Risk with intervention[121]**
Miscarriage: see Section AppD4.1.1.7.2											
4,924 (1 – OBS)[128]	None	NA	None	None	None	●●○○ Low	**Unexposed** NA	**Paroxetine (up to 20 weeks)** NA	**OR 1.75 (1.31, 2.34)**	81 per 1000[129]	NE
Evidence Statement: *Maternal use of paroxetine up to the first 20 weeks of pregnancy is associated with an increased risk of miscarriage (increase in absolute risk not estimable) (low certainty evidence)*											
Autism spectrum disorder: see Section AppD4.1.1.15.2											
143,460 (1 – OBS)[130]	Very serious(d)	NA	None	None	None	○○○○ Inadequate	**Unexposed** 142,716	**Paroxetine (second or third trimester)** 744	**RR 1.99 (1.00, 3.96)**	9 per 1000[131]	18 per 1000 (9, 36)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of paroxetine during the second or third trimester of pregnancy and autism spectrum disorder is uncertain.*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.
b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events.
c. Downgraded two levels due to substantial heterogeneity (I^2 > 60%).
d. Downgraded two levels due to high risk of bias; lack of adjustment for confounding for maternal disease severity in the antenatal and postnatal period.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.
Abbreviations: AD, antidepressant; CI, confidence interval; NA, not available; NE, not estimable; NR, not reported; OBS, observational studies; OR, odds ratio; RR, relative risk.

[128] Nakhai-Pour 2010; population likely overlaps with that of Almeida 2016.
[129] Almeida 2016 and Ban 2012.
[130] Bérard 2016.
[131] Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

Table D3-4 Evidence Profile table: fluoxetine harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[132]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[133]**	**Risk with intervention[134]**
Major malformations: see Section AppD4.1.1.3.2											
27,022 (1 – OBS)[135]	Serious(a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Fluoxetine (first trimester)** NA	RR 0.85 (0.66, 1.09)	28 per 1000[136]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of fluoxetine during the first trimester of pregnancy and major malformation in the newborn, is uncertain.*											
Cardiac malformations: see Section AppD4.1.1.4.2											
216,249 (2 – OBS)[137]	Serious(a)	Serious(c)	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Fluoxetine (first trimester)** NA	RR 1.01 (0.72, 1.42)	6 per 1000[138]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of fluoxetine during the first trimester of pregnancy and cardiac malformation in the newborn, is uncertain.*											
Miscarriage: see Section AppD4.1.1.7.2											
4,862 (1 – OBS)[139]	None	NA	None	Serious (b)	None	●○○○ Very low	**Unexposed** NA	**Fluoxetine (up to 20 weeks)** NA	OR 1.44 (0.86, 2.43)	81 per 1000[140]	Not estimable
Evidence Statement: *Maternal use of fluoxetine up to the first 20 weeks of pregnancy does not appear to be associated with an increased risk of miscarriage (very low certainty).*											

[132] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[133] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[134] Calculated by multiplying relative effect by control risk.
[135] Ban 2014a.
[136] Ban 2014a.
[137] Based on a de novo meta-analysis of data from Ban 2014a and Huybrechts 2014a.
[138] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[139] Nakhai-Pour 2010; population likely overlaps with that of Almeida 2016.
[140] Almeida 2016 and Ban 2012.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[132]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[133]**	**Risk with intervention[134]**
Autism spectrum disorder: see Section AppD4.1.1.15.2											
142,887 (1 – OBS)[141]	Very serious(d)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**Fluoxetine (second or third trimester)** NA	**RR 4.99 (1.45, 17.2)**	9 per 1000[142]	45 per 1000 (13, 155)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of fluoxetine during the second or third trimester of pregnancy and autism spectrum disorder is uncertain.*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.
b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events.
c. Downgraded one level due to moderate heterogeneity (I^2 = 25% to 59%).
d. Downgraded two levels due to high risk of bias; lack of adjustment for confounding for maternal disease severity in the antenatal and postnatal period.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.
Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; OR, odds ratio; RR, relative risk.

[141] Bérard 2016.
[142] Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

Table D3-5 Evidence Profile table: sertraline harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[143]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control**[144]	**Risk with intervention**[145]
Major malformations: See AppD4.1.1.3.2											
39,824 (2 – OBS)[146]	Serious (a)	None	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Sertraline (first trimester)** NA	RR 1.13 (0.88, 1.45)	28 per 1000[147]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of sertraline during the first trimester of pregnancy and major malformation in the newborn, is uncertain.*											
Cardiac malformations: see Section AppD4.1.1.4.2											
231,444 (3 – OBS)[148]	Serious (a)	None	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Sertraline (first trimester)** NA	RR 1.12 (0.92, 1.36)	6 per 1000[149]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of sertraline during the first trimester of pregnancy and cardiac malformation in the newborn, is uncertain.*											
Septal malformations: see Section AppD4.1.1.5.2											
15,234 (1 – OBS)[150]	Serious (a)	None	None	None	None	●○○○ Very low	**Unexposed** NA	**Sertraline** NA	**RR 1.34 (1.02, 1.76)**	3 per 1000[151]	4 per 1000 (3, 5)
Evidence Statement: *Maternal use of sertraline during the first trimester of pregnancy may be associated with an increased risk of septal malformation in the newborn, from an absolute risk of 0.3% to 0.4% (very low certainty evidence)*											

[143] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[144] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[145] Calculated by multiplying relative effect by control risk.
[146] Based on a de novo meta-analysis of data from Ban 2014a and Bérard 2015.
[147] Ban 2014a.
[148] Based on a de novo meta-analysis of data from Ban 2014a, Bérard 2015 and Huybrechts 2014a.
[149] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[150] Bérard 2015.
[151] The Bérard 2015 study used an insured population and as such the prevalence of septal malformations in this study (1.83%) is not likely to be representative of the general population with depression. To estimate the prevalence, it is assumed that 50% of cardiac malformations are septal, resulting in an estimate of 0.3%.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[143]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[144]**	**Risk with intervention[145]**
Miscarriage: see Section AppD4.1.1.7.2											
4,868 (1 – OBS)[152]	None	NA	None	Serious (b)	None	●○○○ Very low	**Unexposed** NA	**Sertraline (up to 20 weeks)** NA	OR 1.33 (0.85, 2.08)	81 per 1000[153]	Not estimable
Evidence Statement: *Maternal use of sertraline during the first 20 weeks of pregnancy does not appear to be associated with an increased risk of miscarriage (very low certainty evidence)*											
Autism spectrum disorder: see Section AppD4.1.1.15.2											
143,008 (1 – OBS)[154]	Very serious(c)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** 142,716	**Sertraline (second or third trimester)** 292	RR 0.45 (0.05, 4.05)	9 per 1000[155]	4 per 1000 (<1, 36)
Evidence Statement: Due to the inadequate certainty of the evidence, any association between maternal use of sertraline during the second or third trimester of pregnancy and autism spectrum disorder in the child is uncertain.											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis.
b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events.
c. Downgraded two levels due to high risk of bias; lack of adjustment for potential confounding by maternal disease severity in the antenatal and postnatal period.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: AD, antidepressant; CI, confidence interval; NA, not available; NE, not estimable; NR, not reported; OBS, observational studies; OR, odds ratio; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[152] Nakhai-Pour 2010; population likely overlaps with that of Almeida 2016.
[153] Almeida 2016 and Ban 2012.
[154] Bérard 2016.
[155] Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

Table D3-6 Evidence Profile table: citalopram harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[156]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control**[157]	**Risk with intervention**[158]
Major malformations: see Section AppD4.1.1.3.2											
25,779 (1 – OBS)[159]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Citalopram (first trimester)** NA	RR 0.97 (0.71, 1.31)	28 per 1000[160]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of citalopram during the first trimester of pregnancy and major malformation in the newborn, is uncertain.*											
Cardiac malformations: see Section AppD4.1.1.4.2											
25,779 (1 – OBS)[161]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Citalopram (first trimester)** NA	RR 1.02 (0.61, 1.71)	6 per 1000[162]	-
Evidence Statement: *Due to the inadequate certainty of the evidence any association between maternal use of citalopram during the first trimester of pregnancy and cardiac malformation in the newborn, is uncertain.*											
Miscarriage: see Section AppD4.1.1.7.2											
4,859 (1 – OBS)[163]	None	NA	None	Serious (b)	None	●○○○ Very low	**Unexposed** NA	**Citalopram (up to 20 weeks)** NA	OR 1.55 (0.89, 2.69)	81 per 1000[164]	Not estimable
Evidence Statement: *Maternal use of citalopram during the first 20 weeks of pregnancy does not appear to be associated with an increased risk of miscarriage (very low certainty evidence)*											

[156] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[157] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[158] Calculated by multiplying relative effect by control risk.
[159] Ban 2014a.
[160] Ban 2014a.
[161] Ban 2014a.
[162] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[163] Nakhai-Pour 2010; population likely overlaps with that of Almeida 2016.
[164] Almeida 2016 and Ban 2012.

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[156]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[157]**	**Risk with intervention[158]**
Autism spectrum disorder: see Section AppD4.1.1.15.2											
143,137 (1 – OBS)[165]	Very serious(c)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**Citalopram (second or third trimester)** NA	**RR 2.23 (1.01, 4.92)**	9 per 1000[166]	20 per 1000 (9, 44)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of citalopram during the second or third trimester of pregnancy and autism spectrum disorder in the child is uncertain.*											
Footnotes: a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis. b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events. c. Downgraded two levels due to high risk of bias; lack of adjustment for potential confounding by maternal disease severity in the antenatal and postnatal period.										

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; OR, odds ratio; RR, relative risk.

[165] Bérard 2016.

[166] Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

Table D3-7 Evidence Profile table: escitalopram harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* (No. studies)	Additional risk of bias[167]	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Population (N)		Risk estimate (95% CI)	Anticipated absolute effects	
							Unexposed	Exposed		Risk with control[168]	Risk with intervention[169]
Major malformations: see Section AppD4.1.1.3.2											
24,166 (1 – OBS)[170]	Serious(a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Escitalopram (first trimester)** NA	RR 0.77 (0.36, 1.66)	28 per 1000[171]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of escitalopram during the first trimester of pregnancy and major malformation in the newborn, is uncertain.*											
Cardiac malformations: see Section AppD4.1.1.4.2											
24,166 (1 – OBS)[172]	Serious(a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Escitalopram (first trimester)** NA	RR 1.09 (0.34, 3.50)	6 per 1000[173]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of escitalopram during the first trimester of pregnancy and cardiac malformation in the newborn, is uncertain.*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis.
b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RR, relative risk.

[167] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[168] Based on average risk from unexposed, depressed control groups of population-based cohort studies providing data for that outcome.
[169] Calculated by multiplying relative effect by control risk.
[170] Ban 2014a.
[171] Ban 2014a.
[172] Ban 2014a.
[173] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.

Table D3-8 Evidence Profile table: fluvoxamine harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* (No. studies)	Additional risk of bias[174]	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Population (N)		Risk estimate (95% CI)	Anticipated absolute effects	
							Unexposed	Exposed		Risk with control[175]	Risk with intervention[176]
Major malformations: see Section AppD4.1.1.3.2											
107,439 (1 – OBS)[177]	Serious(a)	NA	None	None	None	●○○○ Very low	**Unexposed** NA	**Fluvoxamine (first trimester)** NA	RD -0.0152 (-0.0402, 0.0098)	28 per 1000[178]	28 per 1000 (27, 28)
Evidence Statement: *Maternal use of fluvoxamine during the first trimester of pregnancy does not appear to be associated with an increased risk of major malformation in the newborn (very low certainty evidence)*											
Cardiac malformations: see Section AppD4.1.1.4.2											
107,439 (1 – OBS)[179]	Serious(a)	NA	None	None	None	●○○○ Very low	**Unexposed** NA	**Fluvoxamine (first trimester)** NA	RD -0.0055 (-0.0145, 0.0036)	6 per 1000[180]	6 per 1000 (6, 6)
Evidence Statement: *Maternal use of fluvoxamine during the first trimester of pregnancy does not appear to be associated with an increased risk of cardiac malformation in the newborn (very low certainty evidence)*											
Miscarriage: see Section AppD4.1.1.7.2											
4,845 (1 – OBS)[181]	None	NA	None	Serious (b)	None	●○○○ Very low	**Unexposed** NA	**Fluvoxamine (up to 20 weeks)** NA	OR 2.19 (0.79, 6.08)	81 per 1000[182]	Not estimable
Evidence Statement: *Maternal use of fluvoxamine during the first 20 weeks of pregnancy does not appear to be associated with an increased risk of miscarriage (very low certainty evidence)*											

[174] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[175] Based on average risk from unexposed, depressed control groups of population-based cohort studies providing data for that outcome.
[176] Calculated by multiplying relative effect by control risk.
[177] Oberlander 2008a.
[178] Ban 2014a.
[179] Oberlander 2008a.
[180] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[181] Nakhai-Pour 2010; population likely overlaps with that of Almeida 2016.
[182] Almeida 2016 and Ban 2012.

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[174]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[175]**	**Risk with intervention[176]**
Autism spectrum disorder: see Section AppD4.1.1.15.2											
142,751 (1 – OBS)[183]	Very serious(d)	NA	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Fluvoxamine (second or third trimester)** NA	RR 7.30 (0.30, 178)	10 per 1000[184]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of fluvoxamine during the second or third trimester of pregnancy and autism spectrum disorder in the child is uncertain.*											
Footnotes: a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis. b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events. c. Downgraded two levels due to high risk of bias; lack of adjustment for potential confounding by maternal disease severity in the antenatal and postnatal period.											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: AD, antidepressant; CI, confidence interval; NA, not available; NE, not estimable; NR, not reported; OBS, observational studies; OR, odds ratio; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[183] Bérard 2016.

[184] Based on the pooled prevalence from Sørensen 2013 and Malm 2016.

Table D3-9 Evidence Profile table: SNRI/venlafaxine harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[185]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[186]**	**Risk with intervention[187]**
Major malformations: see Section AppD4.1.1.3.2											
107,570 (1 – OBS)[188]	Serious(a)	NA	None	None	None	●○○○ Very low	**Unexposed** NA	**Venlafaxine (first trimester)** NA	RD -0.0118 (-0.0320, 0.0084)	28 per 1000[189]	28 per 1000 (27, 28)
Evidence Statement: *Maternal use of venlafaxine during the first trimester of pregnancy does not appear to be associated with an increased risk of major malformation in the newborn (very low certainty evidence)*											
Cardiac malformations: see Section AppD4.1.1.4.2											
186,574 (1 – OBS)[190]	Serious(a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**SNRIs (first trimester)** NA	RR 1.20 (0.91, 1.57)	6 per 1000[191]	-
107,570 (1 – OBS)[192]	Serious(a)	NA	None	None	None	●○○○ Very low	**Unexposed** NA	**Venlafaxine (first trimester)** NA	RD 0.0001 (-0.0077, 0.0079)	6 per 1000[193]	6 per 1000 (6, 6)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SNRIs during the first trimester of pregnancy and cardiac malformation in the newborn, is uncertain.*											
Miscarriage: see Section AppD4.1.1.7.2											
9,014 (1 – OBS)[194]	None	NA	None	None	None	●●○○ Low	**Unexposed** NA	**SNRIs (first trimester)** NA	**RR 1.7 (1.2, 2.6)**	81 per 1000[195]	138 per 1000 (97, 211)

[185] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[186] Based on average risk from unexposed, depressed control groups of population-based cohort studies providing data for that outcome.
[187] Calculated by multiplying relative effect by control risk.
[188] Oberlander 2008a.
[189] Ban 2014a.
[190] Huybrechts 2014a.
[191] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[192] Oberlander 2008a.
[193] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[194] Almeida 2016.
[195] Almeida 2016 and Ban 2012.

Certainty assessment							**Summary of findings**				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[185]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[186]**	**Risk with intervention[187]**
4,873 (1 – OBS)[196]	None	NA	None	None	None	●●○○ Low	**Unexposed** NA	**SNRIs (up to 20 weeks)** NA	**OR 2.11 (1.34, 3.30)**	81 per 1000[197]	Not estimable
Evidence Statement: *Maternal use of SNRIs during the first 20 weeks of pregnancy is associated with an increased risk of miscarriage, from an absolute risk of 8% to 14% (low certainty evidence)*											
Autism spectrum disorder: see Section AppD4.1.1.15.2											
143,371 (1 – OBS)[198]	Very serious(c)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SNRIs (second or third trimester)** NA	RR 1.04 (0.20, 5.46)	9 per 1000[199]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SNRIs during the second or third trimester of pregnancy and autism spectrum disorder in the child is uncertain.*											
ADHD: see Section AppD4.1.1.16.2											
863,533 (1 – OBS)[200]	Very serious(c)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**SNRIs (any time)** NA	RR 1.0 (0.4, 2.5)	10 per 1000[201]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SNRIs at any time during pregnancy and attention deficit hyperactivity disorder in the child is uncertain.*											
Footnotes: a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis. b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events. c. Downgraded two levels due to high risk of bias; lack of adjustment for potential confounding by maternal disease severity in the antenatal and postnatal period.											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: AD, antidepressant; CI, confidence interval; NA, not available; NE, not estimable; NR, not reported; OBS, observational studies; OR, odds ratio; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[196] Nakhai-Pour 2010; population likely overlaps with that of Almeida 2016.
[197] Almeida 2016 and Ban 2012.
[198] Boukhris 2016.
[199] Based on the pooled prevalence from Sørensen 2013 and Malm 2016.
[200] Laugesen 2013.
[201] Based on Malm 2016.

Table D3-10 Evidence Profile table: NaSSA/mirtazapine harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[202]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[203]**	**Risk with intervention[204]**
Major malformations: see Section AppD4.1.1.3.2											
208 (1 – OBS)[205]	Serious(a)	NA	None	Unknown(b)	None	○○○○ Inadequate	**Other ADs** 104	**Mirtazapine (any time)** 104	*P=0.50*	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any additional risk of major malformation in the newborn that may be associated with maternal use of mirtazapine at any time during pregnancy, compared with maternal use of other antidepressants at any time during pregnancy, is uncertain.*											
Stillbirth: see Section AppD4.1.1.6.2											
208 (1 – OBS)[206]	Serious(a)	NA	None	Unknown(b)	None	○○○○ Inadequate	**Other ADs** NA	**Mirtazapine (any time)** NA	*P=0.50*	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any additional risk of stillbirth that may be associated with maternal use of mirtazapine at any time during pregnancy, compared with maternal use of other antidepressants at any time during pregnancy, is uncertain.*											
Miscarriage: see Section AppD4.1.1.7.2											
208 (1 – OBS)[207]	Serious(a)	NA	None	Unknown(b)	None	○○○○ Inadequate	**Other ADs** NA	**Mirtazapine (any time)** NA	*P=0.86*	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any additional risk of miscarriage that may be associated with maternal use of mirtazapine at any time during pregnancy, compared with maternal use of other antidepressants at any time during pregnancy, is uncertain.*											

[202] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[203] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[204] Calculated by multiplying relative effect by control risk.
[205] Djulus 2006.
[206] Djulus 2006.
[207] Djulus 2006.

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[202]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[203]**	**Risk with intervention[204]**
Preterm birth: see Section AppD4.1.1.8.2											
208 (1 – OBS)[208]	Serious(a)	NA	None	Unknown(b)	None	○○○○ Inadequate	**Other ADs** NA	**Mirtazapine (any time)** NA	*P=0.61*	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any additional risk of preterm birth in the newborn that may be associated with maternal use of mirtazapine at any time during pregnancy, compared with maternal use of other antidepressants at any time during pregnancy, is uncertain.*											
Footnotes: a. Downgraded one level due to moderate risk of bias; no information on extent of follow-up. b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events.											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: AD, antidepressant; CI, confidence interval; NA, not available; NE, not estimable; NR, not reported; OBS, observational studies; OR, odds ratio; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[208] Djulus 2006.

Table D3-11 Evidence Profile table: TCA harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[209]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control**[210]	**Risk with intervention**[211]
Major malformations: see Section AppD4.1.1.3.2											
29,008 (3 – OBS)[212]	Serious(a)	None	None	None	None	●○○○ Very low	**Unexposed** NA	**TCAs (first trimester)** NA	RR 0.99 (0.78, 1.25)	28 per 1000[213]	28 per 1000 (22, 35)
Evidence Statement: *Maternal use of TCAs during the first trimester of pregnancy does not appear to be associated with major malformation in the newborn (very low certainty evidence)*											
Cardiac malformations: see Section AppD4.1.1.4.2											
210,555 (3 – OBS)[214]	Serious(a)	None	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**TCAs (any time)** NA	RR 0.81 (0.59, 1.10)	6 per 1000[215]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of TCAs during the first trimester of pregnancy and cardiac malformation in the newborn, is uncertain.*											
Neonatal mortality:[216] **see Section AppD4.1.1.6.2**											
NR (1 – OBS)[217]	None	NA	None	Serious(b)	None	●○○○ Very low	**Unexposed** NA	**TCAs (first trimester)** NA	RR 1.2 (0.5, 2.7)	5 per 1000[218]	6 per 1000 (3, 14)
Evidence Statement: *Maternal use of TCAs during the first trimester of pregnancy does not appear to be associated with neonatal mortality (very low certainty evidence)*											

[209] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[210] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[211] Calculated by multiplying relative effect by control risk.
[212] Based on a de novo meta-analysis of data from Ban 2014a, Ramos 2008 and Simon 2002.
[213] Ban 2014a.
[214] Based on a de novo meta-analysis of data from Ban 2014a, Huybrechts 2014a and Simon 2002.
[215] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[216] Includes stillbirth and neonatal death up to 28 days.
[217] Ban 2012.
[218] Ban 2012.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[209]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[210]**	**Risk with intervention[211]**
Miscarriage: see Section AppD4.1.1.7.2											
NR (2 – OBS)[219]	None	None	None	None	None	●●○○ Low	**Unexposed** NA	**TCAs (first trimester)** NA	**RR 1.32 (1.13, 1.55)**	81 per 1000[220]	**107 per 1000 (92, 126)**
4,876 (1 – OBS)[221]	None	NA	None	Serious(b)	None	●○○○ Very low	**Unexposed** NA	**TCAs (up to 20 weeks)** NA	OR 1.27 (0.85, 1.91)	81 per 1000[222]	Not estimable
Evidence Statement: *Maternal use of TCAs during the first trimester of pregnancy may be associated with an increased risk of miscarriage, from an absolute risk of 8% to 11% (low certainty evidence)*											
Autism spectrum disorder: see Section AppD4.1.1.15.2											
18,524 (1 – OBS)[223]	Very serious(c)	NA	None	None	None	○○○○ Inadequate	**Unexposed** NA	**TCAs (any time)** NA	**RR 2.69 (1.04, 6.96)**	9 per 1000[224]	24 per 1000 (9, 63)
143,153 (1 – OBS)[225]	Very serious(c)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**TCAs (second or third trimester)** NA	RR 1.03 (0.23, 4.61)	9 per 1000[224]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of TCAs at any time during pregnancy and autism spectrum disorder in the child is uncertain.*											

[219] Based on a de novo meta-analysis of data from Almeida 2016 and Ban 2012.
[220] Almeida 2016 and Ban 2012.
[221] Nakhai-Pour 2010; population likely overlaps with that of Almeida 2016.
[222] Almeida 2016 and Ban 2012.
[223] Rai 2013.
[224] Based on the pooled prevalence from Sørensen 2013 and Malm 2016.
[225] Boukhris 2016.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[209]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[210]**	**Risk with intervention[211]**
ADHD: see Section AppD4.1.1.16.2											
863,533 (1 – OBS)[226]	Very serious(d)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**TCAs (any time)** NA	RR 1.1 (0.6, 2.0)	10 per 1000[227]	-
Evidence Statement: Due to the inadequate certainty of the evidence, any association between maternal use of TCAs at any time during pregnancy and attention deficit hyperactivity disorder in the child is uncertain.											

Footnotes:

a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and stillborns from the analysis.

b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events.

c. Downgraded two levels due to high risk of bias; lack of adjustment for potential confounding by maternal disease severity in the antenatal and postnatal period.

d. Downgraded two levels due to high risk of bias; inadequate adjustment for potential confounding by indication and lack of adjustment for potential confounding by maternal disease severity in the antenatal and postnatal period.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: AD, antidepressant; CI, confidence interval; NA, not available; NE, not estimable; NR, not reported; OBS, observational studies; OR, odds ratio; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[226] Laugesen 2013.

[227] Based on Malm 2016.

Table D3-12 Evidence Profile table: bupropion harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[228]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[229]**	**Risk with intervention[230]**
Cardiac malformations: see Section AppD4.1.1.4.2											
187,254 (1 – OBS)[231]	Serious(a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed** NA	**Bupropion (first trimester)** NA	RR 0.92 (0.69, 1.22)	6 per 1000[232]	6 per 1000 (4, 7)
5,381 (1 – OBS)[233]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Bupropion (first trimester)** NA	**Other AD (first trimester)** NA	RR 0.54 (0.19, 1.51)[234]	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of bupropion during the first trimester of pregnancy and cardiac malformation in the newborn, is uncertain.* *Due to the inadequate certainty of the evidence, any additional risk of cardiac malformation associated with maternal use of bupropion during the first trimester of pregnancy, compared with maternal used of other antidepressants during the same period, is uncertain.*											
ADHD: see Section AppD4.1.1.16.2											
38,074 (1 – OBS)[235]	Very serious(c)	NA	None	None	None	○○○○ Inadequate	**Unexposed** 37,960	**Bupropion (any time)** 114	**RR 3.63 (1.20, 11.0)**	10 per 1000[236]	36 per 1000 (12, 110)
38,074 (1 – OBS)[237]	Very serious(c)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** 37,995	**Bupropion (first trimester)** 79	RR 2.06 (0.35, 12.2)	10 per 1000[236]	21 per 1000 (4, 122)

[228] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[229] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[230] Calculated by multiplying relative effect by control risk.
[231] Huybrechts 2014a.
[232] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013.
[233] Cole 2007a.
[234] In the analysis, bupropion is used as the reference group.
[235] Figueroa 2010.
[236] Based on Malm 2016.
[237] Figueroa 2010.

Certainty assessment							**Summary of findings**				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[228]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[229]**	**Risk with intervention[230]**
38,074 (1 – OBS)[238]	Very serious(c)	NA	None	None	None	○○○○ Inadequate	**Unexposed** 38,036	**Bupropion (second trimester)** 46	**RR 14.7 (3.27, 65.7)**	10 per 1000[236]	147 per 1000 (33, 657)
38,074 (1 – OBS)[239]	Very serious(c)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** 38,037	**Bupropion (third trimester)** 37	NE[240]	10 per 1000[236]	-
38,074 (1 – OBS)[241]	Very serious(c)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** 37,889	**Bupropion (after pregnancy)** 185	RR 0.90 (0.32, 2.53)	10 per 1000[236]	9 per 1000 (3, 25)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of bupropion at any time during or after pregnancy and attention deficit hyperactivity disorder in the child is uncertain.*											
Footnotes: a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis. b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events. c. Downgraded two levels due to high risk of bias; lack of adjustment for potential confounding by maternal disease severity in the antenatal and postnatal period.											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: AD, antidepressant; CI, confidence interval; NA, not available; NE, not estimable; NR, not reported; OBS, observational study/studies; RR, relative risk.

[238] Figueroa 2010.
[239] Figueroa 2010.
[240] No events.
[241] Figueroa 2010.

D3.1.2 Antipsychotics

The following section presents the Evidence Profile tables for any antipsychotics use, the specific antipsychotics classes, and individual medications examined. The quantity of evidence available for the assessment of antipsychotics was sufficient to limit the evidence to studies that adjusted risk estimates for confounding. A summary of the characteristics of the individual included studies can be found in **Table AppD2-11** in **Appendix D2.1.2.2**. A detailed discussion of the evidence for each group or individual intervention type and outcome can be found in **Appendix D4.1.2**.

The following observations were made regarding the body of evidence for antipsychotic harms:

- No meta-analyses were feasible for any outcome, so the body of evidence for each outcome comprised collections of studies or single studies.
- Three studies included an unexposed comparator group with a mental health diagnosis[242].

As the evidence was based on data from cohort and case-control studies, in many cases the results were presented as odds ratios instead of relative risks. Where the baseline risk was < 7%, it was assumed that the odds ratio approximates the relative risk and the results were interpreted as relative risks.

Table D 3-13 presents a summary of the results of the Evidence Review of antipsychotics and the location of the detailed assessment of the certainty of evidence in the evidence profile tables. Unlike antidepressants, groupings of antipsychotics were not pharmacologically-based, but instead grouped as any antipsychotics, second-generation antipsychotics (SGAs) and first-generation antipsychotics (FGAs). These groupings have been included here, although it is unclear how useful the grouped findings are, with the increased risks of harm associated with a number of the individual antipsychotics examined suggesting these may be masked when they are grouped together.

Maternal exposure to any antipsychotics and SGAs as a group appear to not be associated with the majority of outcomes assessed, although the available evidence for malformations, and neurodevelopmental outcomes were uncertain for any antipsychotics as a group. Exposure to the SGAs risperidone and quetiapine, FGAs as a group, and the long-acting agent flupentixol, are or may be associated with an increased risk of harm, including major and cardiac malformations (risperidone), miscarriage (quetiapine and flupentixol) and preterm birth (FGAs). For most outcomes assessed for individual antipsychotics, the certainty of the evidence was inadequate.

[242] Huybrechts 2016, Sorensen 2015, Lin 2010.

Table D 3-13 Summary of results of the Evidence Review for antipsychotics

Intervention	**Increased/may be increased risk of harm** Outcome Certainty of evidence	**Appears to be no increased risk of harm** Outcome Certainty of evidence	**Decreased/may be decreased risk of harm** Outcome Certainty of evidence	**Uncertain** Outcome ○○○○	**Evidence profile table**
Any antipsychotics		Neonatal mortality ●○○○ Stillbirth ●○○○ Miscarriage ●●○○ Preterm birth ●○○○ SFGA ●○○○ LFGA ●○○○ Seizures ●○○○ Respiratory distress ●○○○ PNAS ●○○○		Major malformation Cardiac malformation Neurodevelopment/ behavioural disorders Neuromotor performance	**Table D3-14**
SGAs		Major malformation ●○○○ Cardiac malformation ●○○○ Preterm birth ●○○○ SFGA ●○○○ LFGA ●○○○		Major malformations (vs FGAs)	**Table D3-15**
Aripiprazole		Major malformation ●○○○		Cardiac malformation	**Table D3-17**
Risperidone	Major malformation ●●○○ Cardiac malformation ●●○○				**Table D3-23**
Ziprasidone				Major malformation Cardiac malformation	**Table D3-24**
Olanzapine				Major malformation Cardiac malformation Miscarriage	**Table D3-20**
Quetiapine	Miscarriage ●○○○	Major malformation ●○○○		Cardiac malformation	**Table D3-22**
FGAs	Preterm birth ●●○○	SFGA ●○○○ LFGA ●○○○		Major malformation Cardiac malformation	**Table D3-16**
Haloperidol				Major malformation	**Table D3-19**
Perphenazine				Miscarriage	**Table D3-21**
Zuclopenthixol				Miscarriage	**Table D3-25**
Flupenthixol (long-acting)	Miscarriage ●○○○			Major malformation	**Table D3-18**

Abbreviations: FGA, first-generation antipsychotic; LFGA, large for gestational age; PNAS, poor neonatal adaptation syndrome; SFGA, small for gestational age; SGA, second-generation antipsychotics.

Note: All comparisons are against non-exposure, unless otherwise stated. Certainty of evidence gradings are as follows: ●●●● – high certainty; ●●●○ – moderate certainty; ●●○○ – low certainty; ●○○○ – very low certainty; ○○○○ – inadequate certainty.

Table D3-14 Evidence Profile table: any antipsychotics

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[243]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[244]**	**Risk with intervention[245]**
Major malformations: see Section AppD4.1.2.3.2											
(2 – OBS)[246]	Serious (a)	None	Serious (b)	None	None	○○○○ Inadequate	**Unexposed – no adjustment for indication** (N = 1,184733)	**Any antipsychotics (early pregnancy)** (N = 848)	**RR 1.49 (1.07, 2.06)**	41 per 1000[247]	-
(1 – OBS)[248]	Serious (a)	NA	None	Serious (c)	None	○○○○ Inadequate	**Discontinued ≥4 months before pregnancy – no further adjustment for indication** (N = 492)	**Any antipsychotics (early pregnancy)** (N = 290)	RR 1.79 (0.72, 4.47)	41 per 1000[249]	-
Evidence Statement: *Maternal use of any antipsychotic medication during early pregnancy may be associated with an increased risk of major malformation in the newborn, but due to the inadequate certainty of the evidence any such association is uncertain.*											
Cardiac malformations: see Section AppD4.1.2.4.2											
(1 – OBS)[250]	Serious (a)	NA	Serious (b)	Serious (c)	None	○○○○ Inadequate	**Unexposed – no adjustment for indication** (N = 1,575,847)	**Any antipsychotics or lithium[251] (early pregnancy)** (N = ~1,344)	OR 0.83 (0.48, 1.41)	15 per 1000[252]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of any antipsychotic medication during early pregnancy and cardiac malformation in the newborn is uncertain.*											

[243] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[244] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[245] Calculated by multiplying relative effect by control risk.
[246] Petersen 2016a, Reis 2008.
[247] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[248] Petersen 2016a
[249] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[250] Källén 2013
[251] Lithium is the most commonly used (17% of neuroleptic-exposed women in the database), confounding the data for antipsychotics.
[252] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

Certainty assessment							**Summary of findings**				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[243]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[244]**	**Risk with intervention[245]**
Neonatal mortality: see Section AppD4.1.2.5.2											
(1 – OBS)[254]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication)** (N = 1,021)	**Any antipsychotics (≥2 consecutive scripts, one in 1st or 2nd trimester)** (N = 1,021)	RR 1.50 (0.53, 4.21)	6 per 1000[253]	9 per 1000 (3, 25)
Evidence Statement: *Maternal use of any antipsychotics during pregnancy does not appear to be associated with an increased risk of neonatal mortality (very low certainty evidence).*											
Stillbirth: see Section AppD4.1.2.5.2											
(1 – OBS)[254]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication)** (N = 1,021)	**Any antipsychotics (≥2 consecutive scripts, one in 1st or 2nd trimester)** (N = 1,021)	RR 0.56 (0.25, 1.27)	16 per 1000[255]	9 per 1000 (4, 20)
Evidence Statement: *Maternal use of any antipsychotics during pregnancy does not appear to be associated with an increased risk of stillbirth (very low certainty evidence).*											
Miscarriage: see Section AppD4.1.2.6.2											
(1 – OBS)[256]	None	NA	None	None	None	●●○○ Low	**Discontinued ≥30 days before pregnancy – no further adjustment for indication** (N = 2,745)	**Any antipsychotics (any time from 30 days before, to end of pregnancy)** (N = 1,181)	RR 1.04 (0.93, 1.17)	197 per 1000[257]	205 per 1000 (183, 230)

[253] From hdPS-matched, unexposed cohort, Vigod 2015.
[254] Vigod 2015
[255] Vigod 2015 hdPS-matched, unexposed cohort.
[256] Sorensen 2015
[257] Sorensen 2015 unexposed patients with hospital diagnosis of severe mental disorder.

Certainty assessment							**Summary of findings**				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[243]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[244]**	**Risk with intervention[245]**
(1 – OBS)[256]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed patients with hospital diagnosis of severe mental disorder – no further adjustment for indication** (N = 1,337)	**Any antipsychotics, in patients with hospital diagnosis of severe mental disorder (any time from 30 days before, to end of pregnancy)** (N = 461)	RR 1.14 (0.94, 1.39)	197 per 1000[257]	225 per 1000 (185, 274)
Evidence Statement: *Maternal use of any antipsychotics during pregnancy does not appear to be associated with an increased risk of miscarriage (low certainty evidence).*											
Preterm birth: see Section AppD4.1.2.7.2											
(1 – OBS)[258]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 1,021)	**Any antipsychotics (≥2 consecutive scripts, one in 1st or 2nd trimester)** (N = 1,021)	RR 0.99 (0.78, 1.26)	82 per 1000[259]	81 per 1000 (64, 103)
(1 – OBS)[258]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 893)	**Any antipsychotics (1st trimester)** (N = 893)	RR 0.99 (0.77, 1.27)	82 per 1000[259]	81 per 1000 (63, 104)
(1 – OBS)[258]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 758)	**Any antipsychotics (2nd trimester)** (N = 758)	RR 1.00 (0.75, 1.35)	82 per 1000[259]	82 per 1000 (62, 111)
(1 – OBS)[258]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 614)	**Any antipsychotics (3rd trimester)** (N = 614)	RR 0.83 (0.59, 1.16)	82 per 1000[259]	68 per 1000 (48, 95)
Evidence Statement: *Maternal use of any antipsychotics during pregnancy (either first, second or third trimester) does not appear to be associated with an increased risk of preterm birth (very low certainty evidence).*											

[258] Vigod 2015
[259] Lin 2010 unexposed patients with schizophrenia.

Certainty assessment							**Summary of findings**				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[243]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[244]**	**Risk with intervention[245]**
Small for gestational age (<3rd centile): see Section AppD4.1.2.8.2											
(1 – OBS)[260]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 1,021)	**Any antipsychotics (≥2 consecutive scripts, one in 1st or 2nd trimester)** (N = 1,021)	RR 1.21 (0.81, 1.82)	203 per 1000[261]	246 per 1000 (164, 369)
(1 – OBS)[260]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 893)	**Any antipsychotics (1st trimester)** (N = 893)	RR 1.33 (0.88, 2.02)	203 per 1000[261]	270 per 1000 (179, 410)
(1 – OBS)[260]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 758)	**Any antipsychotics (2nd trimester)** (N = 758)	RR 1.21 (0.74, 1.96)	203 per 1000[261]	246 per 1000 (150, 398)
(1 – OBS)[260]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 614)	**Any antipsychotics (3rd trimester)** (N = 614)	RR 1.24 (0.73, 2.10)	203 per 1000[261]	252 per 1000 (148, 426)
Evidence Statement: *Maternal use of any antipsychotics during pregnancy (either first, second or third trimester) does not appear to be associated with an increased risk of the newborn being small for gestational age (very low certainty evidence).*											
Large for gestational age (>97th centile): see Section AppD4.1.2.9.2											
(1 – OBS)[262]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 1,021)	**Any antipsychotics (≥2 consecutive scripts, one in 1st or 2nd trimester)** (N = 1,021)	RR 1.26 (0.69, 2.29)	97 per 1000[263]	122 per 1000 (67, 222)

[260] Vigod 2015
[261] Lin 2010 unexposed patients with schizophrenia.
[262] Vigod 2015
[263] Lin 2010 unexposed patients with schizophrenia.

Certainty assessment							**Summary of findings**				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[243]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[244]**	**Risk with intervention[245]**
(1 – OBS)[262]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 893)	**Any antipsychotics (1st trimester)** (N = 893)	RR 0.94 (0.46, 1.93)	97 per 1000[263]	91 per 1000 (45, 187)
(1 – OBS)[262]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 758)	**Any antipsychotics (2nd trimester)** (N = 758)	RR 1.83 (0.89, 3.77)	97 per 1000[263]	178 per 1000 (86, 366)
Evidence Statement: *Maternal use of any antipsychotics during pregnancy (either first or second trimester) does not appear to be associated with an increased risk of the newborn being large for gestational age (very low certainty evidence).*											
(1 – OBS)[262]	None	NA	None	None	None	●●○○ Low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 614)	**Any antipsychotics (3rd trimester)** (N = 614)	**RR 2.39 (1.00, 5.75)**	97 per 1000[263]	232 per 1000 (97, 558)
Evidence Statement: *Maternal use of any antipsychotics during the third trimester may be associated with an increased risk of the newborn being large for gestational age, from an absolute risk of 10% to 23% (low certainty evidence).*											
Seizures: see Section AppD4.1.2.10.2											
(1 – OBS)[262]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication)** (N = 1,021)	**Any antipsychotics (≥2 consecutive scripts, one in 1st or 2nd trimester)** (N = 1,021)	RR 1.29 (0.48, 3.45)	7 per 1000[264]	9 per 1000 (3, 24)
Evidence Statement: *Maternal use of any antipsychotics during pregnancy does not appear to be associated with an increased risk of seizures in the newborn (very low certainty evidence).*											

[264] Vigod 2015 hdPS-matched, unexposed cohort.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[243]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[244]**	**Risk with intervention[245]**
Respiratory distress: see Section AppD4.1.2.11.2											
(1 – OBS)[265]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 1,021)	**Any antipsychotics (≥2 consecutive scripts, one in 1st or 2nd trimester)** (N = 1,021)	RR 0.82 (0.46, 1.43)	29 per 1000[266]	24 per 1000 (13, 41)
Evidence Statement: *Maternal use of any antipsychotics during pregnancy does not appear to be associated with an increased risk of respiratory distress in newborns (very low certainty evidence).*											
Poor neonatal adaptation syndrome: see Section AppD4.1.2.12.2											
(1 – OBS)[265]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 1,021)	**Any antipsychotics (≥2 consecutive scripts, one in 1st or 2nd trimester)** (N = 1,021)	RR 1.15 (0.88, 1.50)	109 per 1000[266]	125 per 1000 (96, 164)
(1 – OBS)[265]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication)** (N = 151)	**Any antipsychotics (only in 1st or 2nd trimester)** (N = 151)	RR 1.50 (0.72, 3.11)	109 per 1000[266]	164 per 1000 (78, 339)
(1 – OBS)[265]	None	NA	None	Serious (c)	None	●○○○ Very low	**Unexposed – hdPS-matched (includes indication) and adjusted for other psychotropic medication** (N = 614)	**Any antipsychotics (only in 3rd trimester)** (N = 614)	RR 1.31 (0.91, 1.90)	109 per 1000[266]	164 per 1000 (78, 339)
Evidence Statement: *Maternal use of any antipsychotics during pregnancy does not appear to be associated with an increased risk of PNAS in newborns (very low certainty evidence).*											
Neurodevelopmental outcomes: see Section AppD4.1.2.13.2											
Neurodevelopment/behavioural disorders											
(1 – OBS)[267]	Very serious (d)	NA	Serious (b)	Serious (c)	None	○○○○ Inadequate	**Unexposed – no adjustment for indication** (N = 210,966)	**Any antipsychotics (early; 31-105 days)** (N = 290)	RR 1.22 (0.80, 1.84)	102 per 1000[268]	-

[265] Vigod 2015
[266] Vigod 2015 hdPS-matched, unexposed cohort.
[267] Petersen 2016a
[268] Petersen 2016a women who discontinued antipsychotics.

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[243]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[244]**	**Risk with intervention[245]**
(1 – OBS)[269]	Very serious (d)	NA	None	Serious (c)	None	○○○○ Inadequate	**Discontinued ≥4 months before pregnancy – no further accounting for indication** (N = 492)	**Any antipsychotics (early; 31-105 days)** (N = 290)	RR 0.83 (0.49, 1.39)	102 per 1000[268]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of any antipsychotics during pregnancy and an increased risk of neurodevelopment or behavioural disorders in the child is uncertain.*											
Neuromotor performance (INFANIB)											
(1 – OBS)[270]	Very serious (e)	NA	None	None	None	○○○○ Inadequate	**Unexposed –adjusted for lifetime history of psychiatric illness[271]** (N = 85)	**Any antipsychotic (pregnancy)** (N = 22)	**OR 5.41[272] (1.22, 24.09)**	unknown	-
(1 – OBS)[270]	Very serious (e)	NA	None	None	None	○○○○ Inadequate	**Antidepressants –adjusted for lifetime history of psychiatric illness[273]** (N = 202)	**Any antipsychotic (pregnancy)** (N = 22)	**OR 4.11[272] (1.05, 15.99)**	unknown	-
Evidence Statement: *Maternal use of any antipsychotics during pregnancy may be associated with an increased risk of poor neuromotor performance in the child, but due to the inadequate certainty of the evidence any such association is uncertain.*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth.
b. Downgraded one level due to indirectness caused by use of control group without a mental health disorder diagnosis, with no adjustment for indication.
c. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).
d. Downgraded two levels due to high risk of bias: neurodevelopmental outcome without adjustment for maternal disease severity and use of a non-validated outcome assessment tool.
e. Downgraded two levels due to high risk of bias: neurodevelopmental outcome without adjustment for maternal disease severity and use of a non-validated output from an outcome assessment tool.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.
Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; OR, odds ratio; RR, risk ratio.

[269] Petersen 2016a
[270] Johnson 2012
[271] No data reported regarding psychiatric status at pregnancy or at infant assessment psychiatric status, but 62% of comparator group had experienced psychiatric illness in their lifetime.
[272] This is the adjusted odds ratio for the likelihood of a normal score in the unexposed group. This indicates a significantly higher likelihood of a 'not normal' score in the exposed group (categories condensed into two for increased power in statistical analysis).
[273] No data reported regarding psychiatric status at pregnancy or at infant assessment psychiatric status, but 62% of comparator group had experienced psychiatric illness in their lifetime.

Table D3-15 Evidence Profile table: SGAs

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[274]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[275]**	**Risk Exposed[276]**
Major malformations: see Section AppD4.1.2.3.2											
(1 – OBS)[277]	Serious (a)	None	None	None	None	●○○○ Very low	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,289,826)	**SGAs (1st trimester)** (N = 9,237)	RR 1.05 (0.96, 1.16)	41 per 1000[278]	43 per 1000 (39, 48)
(1 – OBS)[277]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to schizophrenia, bipolar disorder, psychosis – fully adjusted (indication, medication, propensity score)** (N = 11,606)	**SGAs, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 3,995)	RR 1.16 (0.99, 1.35)	41 per 1000[278]	-
(1 – OBS)[279]	Serious (a)	N/A	None	Serious (b)	None	○○○○ Inadequate	**FGAs – no further adjustment for indication (pregnancy)** (N = 284)	**SGAs (pregnancy)** (N = 561)	OR 1.27 (0.57, 2.82)	41 per 1000[278]	-
Evidence Statement: *Maternal use of SGAs during the first trimester of pregnancy does not appear to be associated with an increased risk of major malformation in the newborn (very low certainty evidence).* *Due to the inadequate certainty of the evidence, any additional risk of major malformations in the newborn associated with maternal use of SGAs at any time during pregnancy, compared with maternal use of FGAs during the same period, is uncertain.*											
Cardiac malformations: See AppD4.1.2.4.2											
(1 – OBS)[277]	Serious (a)	NA	None	None	None	●○○○ Very low	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,289,826)	**SGAs (1st trimester)** (N = 9,237)	RR 1.06 (0.90, 1.24)	15 per 1000[280]	16 per 1000 (14, 19)

[274] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[275] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[276] Calculated by multiplying relative effect by control risk.
[277] Huybrechts 2016
[278] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[279] Habermann 2013
[280] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

Certainty assessment							**Summary of findings**				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[274]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[275]**	**Risk Exposed[276]**
(1 – OBS)[277]	Serious (a)	N/A	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to schizophrenia, bipolar disorder, psychosis – fully adjusted (indication, medication, propensity score)** (N = 11,606)	**SGA s, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 3,995)	RR 1.21 (0.93, 1.57)	15 per 1000[280]	-
Evidence Statement: *Maternal use of SGAs during the first trimester of pregnancy does not appear to be associated with an increased risk of cardiac malformation in the newborn (very low certainty evidence).*											
Preterm birth (<37 weeks): see Section AppD4.1.2.7.2											
(1 – OBS)[281]	None	NA	None	Serious (b)	None	●○○○ Very low	**Unexposed to FGAs or SGAs, schizophrenia[282]** (N = 454)	**SGAs, schizophrenia (pregnancy)** (N = 48)	OR 1.61 (0.63, 4.12)	82 per 1000[283]	not estimable (OR ≠ RR when assumed risk >5%)
Evidence Statement: *Maternal use of SGAs during pregnancy does not appear to be associated with an increased risk of preterm birth (very low certainty evidence).*											
Small for gestation age (<10rd centile): see Section AppD4.1.2.8.2											
(1 – OBS)[281]	None	NA	None	Serious (b)	None	●○○○ Very low	**Unexposed to FGAs or SGAs, schizophrenia[282]** (N = 454)	**SGAs, schizophrenia (pregnancy)** (N = 48)	OR 1.15 (0.55, 2.41)	203 per 1000[284]	not estimable (OR ≠ RR when assumed risk >5%)
Evidence Statement: *Maternal use of SGAs during pregnancy does not appear to be associated with an increased risk of the newborn being small for gestational age (very low certainty evidence).*											
Large for gestation age (>90th centile): see Section AppD4.1.2.9.2											
(1 – OBS)[281]	None	NA	None	Serious (b)	None	●○○○ Very low	**Unexposed to FGAs or SGAs, schizophrenia[282]** (N = 454)	**SGAs, schizophrenia (pregnancy)** (N = 48)	OR 0.55 (0.16, 1.85)	97 per 1000[285]	not estimable (OR ≠ RR when assumed risk >5%)
Evidence Statement: *Maternal use of SGAs during pregnancy does not appear to be associated with an increased risk of the newborn being large for gestational age (very low certainty evidence).*											

[281] Lin 2010
[282] 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.
[283] Lin 2010 unexposed patients with schizophrenia.
[284] Lin 2010 unexposed patients with schizophrenia.
[285] Lin 2010 unexposed patients with schizophrenia.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[274]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[275]**	**Risk Exposed[276]**
Footnotes: a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth. b. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; FGA, first generation antipsychotics; NA, not available; OBS, observational studies; OR, odds ratio; RR, risk ratio; SGA, second generation antipsychotic.

Table D3-16 Evidence Profile table: FGAs

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[286]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[287]**	**Risk Exposed[288]**
Major malformations: see Section AppD4.1.2.3.2											
(1 – OBS)[289]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,297,638)	**FGAs (1st trimester)** (N = 727)	RR 0.90 (0.62, 1.31)	41 per 1000[290]	-
(1 – OBS)[289]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder– fully adjusted (indication, meds, propensity score)** (N = 10,418)	**FGAs, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 381)	RR 0.93 (0.57, 1.51)	41 per 1000[291]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of FGAs during the first trimester of pregnancy and an increased risk of major malformation in the newborn is uncertain.*											
Cardiac malformations: see Section AppD4.1.2.4.2											
(1 – OBS)[289]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,297,638)	**FGAs (1st trimester)** (N = 727)	RR 0.75 (0.39, 1.43)	15 per 1000[292]	-

[286] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[287] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[288] Calculated by multiplying relative effect by control risk.
[289] Huybrechts 2016
[290] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[291] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[292] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

Certainty assessment							**Summary of findings**				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[286]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[287]**	**Risk Exposed[288]**
(1 – OBS)[289]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, medication, propensity score)** (N = 10,418)	**FGAs, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 381)	RR 0.91 (0.43, 1.91)	15 per 1000[293]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of FGAs during the first trimester of pregnancy and an increased risk of cardiac malformation in the newborn is uncertain*											
Preterm birth (<37 weeks): see Section AppD4.1.2.7.2											
(1 – OBS)[294]	None	NA	None	None	None	●●○○ Low	**Unexposed to FGAs or SGAs, schizophrenia[295]** (N = 454)	**FGAs, schizophrenia (pregnancy)** (N = 194)	**OR 2.46 (1.50, 4.11)**	82 per 1000[296]	not estimable (OR ≠ RR when assumed risk >5%)
Evidence Statement: *Maternal use of FGAs during pregnancy is associated with an increased risk of preterm birth, with a 2.5-fold increase of an absolute risk of 8% (low certainty evidence).*											
Small for gestational age (<10th centile): see Section AppD4.1.2.8.2											
(1 – OBS)[294]	None	NA	None	Serious (b)	None	●○○○ Very low	**Unexposed to FGAs or SGAs, schizophrenia[295]** (N = 454)	**FGAs, schizophrenia (pregnancy)** (N = 194)	OR 1.39 (0.93, 2.08)	203 per 1000[297]	not estimable (OR ≠ RR when assumed risk >5%)
Evidence Statement: *Maternal use of FGAs during pregnancy does not appear to be associated with an increased risk of the newborn being small for gestational age (very low certainty evidence).*											
Large for gestational age (>90th centile): see Section AppD4.1.2.9.2											
(1 – OBS)[294]	None	NA	None	Serious (b)	None	●○○○ Very low	**Unexposed to FGAs or SGAs, schizophrenia[295]** (N = 454)	**FGAs, schizophrenia (pregnancy)** (N = 194)	OR 0.72 (0.39, 1.34)	97 per 1000[298]	not estimable (OR ≠ RR when assumed risk >5%)
Evidence Statement: *Maternal use of FGAs during pregnancy does not appear to be associated with an increased risk of the newborn being large for gestational age (very low certainty evidence).*											

[293] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[294] Lin 2010
[295] 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.
[296] Lin 2010 unexposed patients with schizophrenia.
[297] Lin 2010 unexposed patients with schizophrenia.
[298] Lin 2010 unexposed patients with schizophrenia.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[286]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[287]**	**Risk Exposed[288]**
Footnotes: a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth. b. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; FGA, first generation antipsychotics; meds, medication; NA, not available; OBS, observational studies; OR, odds ratio; RR, risk ratio; SGA, second generation antipsychotic.

Table D3-17 Evidence Profile table: aripiprazole

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**[299]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed**[300]	**Risk Exposed**[301]
Major malformations: see Section AppD4.1.2.3.2											
(1 – OBS)[302]	Serious (a)	NA	None	None	None	●○○○ Very low	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 957,012)	**Aripiprazole (1st trimester)** (N = 1,752)	RR 0.95 (0.76, 1.19)	41 per 1000[303]	39 per 1000 (31, 49)
(1 – OBS)[302]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, meds, propensity score)** (N = 10,174)	**Aripiprazole, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 949)	RR 1.13 (0.86, 1.50)	41 per 1000[303]	-
Evidence Statement: *Maternal use of aripiprazole during the first trimester of pregnancy does not appear to be associated with an increased risk of major malformation in the newborn (very low certainty evidence).*											
Cardiac malformations: see Section AppD4.1.2.4.2											
(1 – OBS)[302]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 957,012)	**Aripiprazole (1st trimester)** (N = 1,752)	RR 0.93 (0.64, 1.37)	15 per 1000[304]	-
(1 – OBS)[302]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, meds, propensity score)** (N = 10,174)	**Aripiprazole, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 949)	RR 1.13 (0.71, 1.80)	15 per 1000[305]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of aripiprazole during the first trimester of pregnancy and an increased risk of cardiac malformation in the newborn is uncertain.*											

[299] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[300] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[301] Calculated by multiplying relative effect by control risk.
[302] Huybrechts 2016
[303] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[304] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[305] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[299]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[300]**	**Risk Exposed[301]**
Footnotes: a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth. b. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RR, risk ratio.

Table D3-18 Evidence Profile table: flupenthixol

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[306]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed**[307]	**Risk Exposed**[308]
Major malformations: see Section AppD4.1.2.3.2											
(1 – OBS)[309]	Serious (a)	NA	Serious (b)	Serious (c)	None	○○○○ Inadequate	**Unexposed – no adjustment for indication** (N = 1,575,847)	**Flupenthixol (early pregnancy)** (N = 154)	RR 1.94 (1.00, 3.40)[310]	41 per 1000[311]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of flupenthixol during early pregnancy and an increased risk of major malformation in the newborn is uncertain.*											
Miscarriage: see Section AppD4.1.2.6.2											
(1 – OBS)[312]	None	NA	Serious (b)	None	None	●○○○ Very low	**Unexposed – no adjustment for indication** (N = 841,183)	**Flupenthixol (any time from 30 days before, to the end of pregnancy)** (N = 233)	**RR 1.55 (1.22, 1.97)**	197 per 1000[313]	305 per 1000 (240, 388)
Evidence Statement: *Maternal use of flupenthixol during or just prior to pregnancy may be associated with an increased risk of miscarriage, from an absolute risk of 20% to 30% (very low certainty evidence).*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth.
b. Downgraded one level due to indirectness caused by use of control group without a mental health disorder diagnosis, with no adjustment for indication.
c. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.
No distinction was made between long-acting versus oral flupenthixol for either of the included studies.
Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RR, risk ratio.

[306] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[307] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[308] Calculated by multiplying relative effect by control risk.
[309] Källén 2013
[310] 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.
[311] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[312] Sorensen 2015
[313] Sorensen 2015 unexposed patients with hospital diagnosis of severe mental disorder.

Table D3-19 Evidence Profile table: haloperidol, infant harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[314]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed**[315]	**Risk Exposed**[316]
Major malformations: see Section AppD4.1.2.3.2											
(1 – OBS)[317]	Serious (a)	NA	Serious (b)	Serious (c)	None	○○○○ Inadequate	**Unexposed – no adjustment for indication** (N = 1,575,847)	**Haloperidol (early pregnancy)** (N = 115)	RR 1.21 (0.39, 2.83)[318]	41 per 1000[319]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of haloperidol during early pregnancy and an increased risk of major malformation in the newborn is uncertain.*											
Footnotes: a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth b. Downgraded one level due to indirectness caused by use of control group without a mental health disorder diagnosis, with no adjustment for indication. c. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RR, risk ratio.

[314] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.

[315] Based on average risk from unexposed, depressed control groups of population-based cohort studies.

[316] Calculated by multiplying relative effect by control risk.

[317] Källén 2013

[318] 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

[319] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

Table D3-20 Evidence Profile table: olanzapine, infant harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**[320]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed**[321]	**Risk Exposed**[322]
Major malformations: see Section AppD4.1.2.3.2											
(1 – OBS)[323]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,231,441)	**Olanzapine (1st trimester)** (N = 1,392)	RR 1.09 (0.85, 1.41)	41 per 1000[324]	-
(1 – OBS)[323]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, medication, propensity score)** (N = 10,949)	**Olanzapine, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 648)	RR 1.19 (0.84, 1.67)	41 per 1000[325]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of olanzapine during the first trimester of pregnancy and an increased risk of major malformation in the newborn is uncertain.*											
Cardiac malformations: see Section AppD4.1.2.4.2											
(1 – OBS)[323]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,231,441)	**Olanzapine (1st trimester)** (N = 1,392)	RR 0.99 (0.64, 1.53)	15 per 1000[326]	-

[320] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[321] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[322] Calculated by multiplying relative effect by control risk.
[323] Huybrechts 2016
[324] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[325] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[326] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

Certainty assessment							**Summary of findings**				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[320]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[321]**	**Risk Exposed[322]**
(1 – OBS)[323]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, medication, propensity score)** (N = 10,949)	**Olanzapine, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 648)	RR 1.23 (0.69, 2.19)	15 per 1000[327]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of olanzapine during the first trimester of pregnancy and an increased risk of cardiac malformation in the newborn is uncertain.*											
Miscarriage: see Section AppD4.1.2.6.2											
(1 – OBS)[328]	None	NA	Serious (c)	Serious (b)	None	○○○○ Inadequate	**Unexposed – no adjustment for indication** (N = 841,183)	**Olanzapine (any time from 30 days before, to the end of pregnancy)** (N = 223)	RR 1.10 (0.83, 1.46)	197 per 1000[329]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of olanzapine during or just prior to pregnancy and an increased risk of miscarriage is uncertain*											
Footnotes: a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth. b. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25). c. Downgraded one level due to indirectness caused by use of control group without a mental health disorder diagnosis, with no adjustment for indication.											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RR, risk ratio.

[327] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

[328] Sorensen 2015

[329] Sorensen 2015 unexposed patients with hospital diagnosis of severe mental disorder.

Table D3-21 Evidence Profile table: perphenazine, infant harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**[330]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed**[331]	**Risk Exposed**[332]
Miscarriage: see Section AppD4.1.2.6.2											
(1 – OBS)[333]	None	NA	Serious (a)	Serious (b)	None	○○○○ Inadequate	**Unexposed – no adjustment for indication** (N = 841,183)	**Perphenazine (any time from 30 days before, to end of pregnancy)** (N = 229)	RR 1.25 (0.95 1.64)	197 per 1000[334]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of perphenazine during or just prior to pregnancy and an increased risk of miscarriage is uncertain.*											
Footnotes: a. Downgraded one level due to high risk of bias; not limiting control group to women with a mental health disorder and not controlling for indication. b. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RR, risk ratio.

[330] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.

[331] Based on average risk from unexposed, depressed control groups of population-based cohort studies.

[332] Calculated by multiplying relative effect by control risk.

[333] Sorensen 2015

[334] Sorensen 2015 unexposed patients with hospital diagnosis of severe mental disorder.

Table D3-22 Evidence Profile table: quetiapine, infant harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[335]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed**[336]	**Risk Exposed**[337]
Major malformations: See AppD4.1.2.3.2											
Exposed: 4,213 Unexposed: 1,161,955 (1 – OBS)[338]	Serious (a)	NA	None	None	None	●○○○ Very low	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,161,955)	**Quetiapine (1st trimester)** (N = 4,213)	RR 1.01 (0.88, 1.17)	41 per 1000[339]	41 per 1000 (36, 48)
Exposed: 1,747 Unexposed: 11,440 (1 – OBS)[338]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, medication, propensity score)** (N = 11,440)	**Quetiapine, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 1,747)	RR 1.13 (0.92, 1.41)	41 per 1000[340]	-
Evidence Statement: *Maternal use of quetiapine during the first trimester of pregnancy does not appear to be associated with an increased risk of major malformation in the newborn (very low certainty evidence).*											
Cardiac malformations: See AppD4.1.2.4.2											
Exposed: 4,213 Unexposed: 1,161,955 (1 – OBS)[338]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,161,955)	**Quetiapine (1st trimester)** (N = 4,213)	RR 1.07 (0.85, 1.35)	15 per 1000[341]	-

[335] [335] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[336] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[337] Calculated by multiplying relative effect by control risk.
[338] Huybrechts 2016
[339] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[340] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[341] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

Certainty assessment							**Summary of findings**				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[335]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[336]**	**Risk Exposed[337]**
Exposed: 1,747 Unexposed: 11,440 (1 – OBS)[338]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, medication, propensity score)** (N = 11,440)	**Quetiapine, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 1,747)	RR 1.17 (0.81, 1.67)	15 per 1000[342]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of quetiapine during the first trimester of pregnancy and an increased risk of cardiac malformation in the newborn is uncertain.*											
Miscarriage: see Section AppD4.1.2.6.2											
Exposed: 174 Unexposed: 841,183 (1 – OBS)[343]	None	NA	Serious (c)	No serious	None	●○○○ Very low	**Unexposed – no adjustment for indication** (N = 841,183)	**Quetiapine (any time from 30 days before, to end of pregnancy)** (N = 174)	**RR 1.65 (1.28, 2.15)**	197 per 1000[344]	325 per 1000 (252, 424)
Evidence Statement: *Maternal use of quetiapine during or just prior to pregnancy may be associated with an increased risk of miscarriage, from an absolute risk of 20% to 33% (very low certainty evidence).*											
Footnotes: a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth. b. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25). c. Downgraded one level due to high risk of bias; not limiting control group to women with a mental health disorder and not controlling for indication.											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RR, risk ratio.

[342] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

[343] Sorensen 2015

[344] Sorensen 2015 unexposed patients with hospital diagnosis of severe mental disorder.

Table D3-23 Evidence Profile table: risperidone, infant harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**[345]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed**[346]	**Risk Exposed**[347]
Major malformations: See AppD4.1.2.3.2											
(1 – OBS)[348]	None[349]	NA	None	None	None	●●○○ Low	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,290,485)	**Risperidone (1st trimester)** (N = 1,565)	**RR 1.26 (1.02, 1.56)**	41 per 1000[350]	52 per 1000 (42, 64)
(1 – OBS)[348]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, medication, propensity score)** (N = 11,497)	**Risperidone, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 740)	RR 1.19 (0.86, 1.64)	41 per 1000[351]	-
(1 – OBS)[348]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Discontinued: no Rx from 8 weeks before pregnancy – no further adjustment for indication (PS adjusted)** (N = 496)	**Risperidone, continued use from 3 months prior (1st trimester)** (N = 866)	RR 1.64 (0.90, 2.98)	41 per 1000[352]	-
Evidence Statement: *Maternal use of risperidone during the first trimester of pregnancy may be associated with an increased risk of major malformation in the newborn, from an absolute risk of 4% to 5% (low certainty evidence).*											

[345] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[346] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[347] Calculated by multiplying relative effect by control risk.
[348] Huybrechts 2016
[349] This outcome normally carries an increased risk of bias is due to the possibility of missing malformations in the exposed group and thereby not detecting any increased risk associated with exposure. As a statistically significant increase in risk is reported, the only remaining risk of bias associated with this risk estimate is an underestimation of magnitude. Therefore, in this instance, it seems reasonable not to apportion additional risk of bias to the major malformations outcome in this analysis.
[350] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[351] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[352] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[345]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[346]**	**Risk Exposed[347]**
Cardiac malformations: see Section AppD4.1.2.4.2											
(1 – OBS)[348]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,290,485)	**Risperidone (1st trimester)** (N = 1,565)	RR 1.26 (0.88, 1.81)	15 per 1000[353]	-
(1 – OBS)[348]	None[354]	NA	None	None	None	●●○○ Low	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, medication, propensity score)** (N = 11,497)	**Risperidone, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 740)	**RR 1.64 (1.03, 2.62)**	15 per 1000[353]	25 per 1000 (15, 39)
(1 – OBS)[348]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Discontinued: no Rx from 8 weeks before pregnancy – no further adjustment for indication (PS adjusted)** (N = 496)	**Risperidone, continued use from 3 months prior (1st trimester)** (N = 866)	RR 2.46 (0.77, 7.87)	15 per 1000[353]	-
(1 – OBS)[348]	None[354]	NA	None	None	None	●●○○ Low	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 1,094,959)	**Risperidone, ≥2mg/day[355] (1st trimester)** (N = 609)	**RR 2.08 (1.32, 3.28)**	15 per 1000[353]	19 per 1000 (13, 27)
Evidence Statement: *Maternal use of risperidone during the first trimester of pregnancy may be associated with an increased risk of cardiac malformation in the newborn, from an absolute risk of 1.5% to 2.5% (low certainty evidence).*											
Footnotes: a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth. b. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; PS, propensity score; RR, risk ratio; Rx, prescription.

[353] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

[354] This outcome normally carries and increased risk of bias is due to the possibility of missing malformations in the exposed group and thereby not detecting any increased risk associated with exposure. As a statistically significant increase in risk is reported, the only remaining risk of bias associated with this risk estimate is an underestimation of magnitude. Therefore, in this instance, it seems reasonable not to apportion additional risk of bias to the cardiac malformations outcome in this analysis.

[355] Doses less than 1 mg and doses from 1-2 mg were also analysed, and neither group showed a statistically significant increase in risk of cardiac malformations.

Table D3-24 Evidence Profile table: ziprasidone, infant harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[356]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed[357]**	**Risk Exposed[358]**
Major malformations: see Section AppD4.1.2.3.2											
(1 – OBS)[359]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 979,614)	**Ziprasidone (1st trimester)** (N = 696)	RR 0.88 (0.60, 1.28)	41 per 1000[360]	-
(1 – OBS)[359]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, meds, propensity score)** (N = 10,971)	**Ziprasidone, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 425)	RR 0.84 (0.51, 1.39)	41 per 1000[361]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of ziprasidone during the first trimester of pregnancy and an increased risk of major malformation in the newborn is uncertain.*											
Cardiac malformations: see Section AppD4.1.2.4.2											
(1 – OBS)[359]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed – fully adjusted (indication, medication, propensity score)** (N = 979,614)	**Ziprasidone (1st trimester)** (N = 696)	RR 0.85 (0.44, 1.63)	15 per 1000[353]	-
(1 – OBS)[359]	Serious (a)	NA	None	Serious (b)	None	○○○○ Inadequate	**Unexposed, restricted to psychosis, schizophrenia, bipolar disorder – fully adjusted (indication, meds, propensity score)** (N = 10,971)	**Ziprasidone, restricted to schizophrenia, bipolar disorder, psychosis (1st trimester)** (N = 425)	RR 0.75 (0.31, 1.81)	15 per 1000[353]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of ziprasidone during the first trimester of pregnancy and increased risk of cardiac malformation in the newborn is uncertain.*											

[356] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[357] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[358] Calculated by multiplying relative effect by control risk.
[359] Huybrechts 2016
[360] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.
[361] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**[356]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed**[357]	**Risk Exposed**[358]
Footnotes: a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth. b. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control.
Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RR, risk ratio.

Table D3-25 Evidence Profile table: zuclopenthixol, infant harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[362]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk Unexposed**[363]	**Risk Exposed**[364]
Miscarriage: see Section AppD4.1.2.6.2											
(1 – OBS)[365]	None	NA	Serious (a)	Serious (b)	None	○○○○ Inadequate	**Unexposed – no adjustment for indication** (N = 841,183)	**Zuclopenthixol (any time from 30 days before, to end of pregnancy)** (N = 229)	RR 1.26 (0.95, 1.66)	41 per 1000[366]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of zuclopenthixol during or just prior to pregnancy and an increased risk of miscarriage is uncertain.*											
Footnotes: a. Downgraded one level due to high risk of bias; not limiting control group to women with a mental health disorder and not controlling for indication. b. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RR, risk ratio.

[362] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.

[363] Based on average risk from unexposed, depressed control groups of population-based cohort studies.

[364] Calculated by multiplying relative effect by control risk.

[365] Sorensen 2015

[366] Huybrechts 2016 unexposed patients with psychosis, schizophrenia, bipolar disorder.

D3.1.3 Anticonvulsants

The following section presents the Evidence Profile tables for the specific anticonvulsant medications examined. The consideration of these medications was limited to those used as mood stabilisers in women with mood disorders, and included sodium valproate, carbamazepine and lamotrigine. This is in line with the consideration of anticonvulsants by NICE 2015.

Extensive research on the effects of maternal use of anticonvulsants during pregnancy on infants has been carried out, and for this reason, the consideration of anticonvulsants has been limited to an examination of existing SRs only. However, all of this evidence has been conducted in a population with epilepsy, rather than a population with a mental health disorder. Where a comparison was made between an exposed population with epilepsy, and an unexposed population with epilepsy, no downgrading for indirectness was applied.

Regarding downgrading for risk of bias, one particular concern for the evidence available for anticonvulsants was that all included meta-analyses analysed the raw data from the included studies; thus, potential confounding was not minimised. However, a decision was made to not downgrade due to risk of bias due to lack of adjustment for confounding where there was a large magnitude of effect; i.e. where the RR lower 95% CI was > 1.25, which is the limit of appreciable harm used by NICE 2015. The rationale for this decision is that while not adjusted for potential confounders, the evidence for anticonvulsants is based on a large number of studies, is highly homogenous, and, being based on patients with epilepsy rather than a psychiatric disorder, is not likely to be subject to the same level of confounding by indication.

As baseline risk was not available in a pregnant unexposed population with a mental health disorder, where available the baseline risks identified for a depressed population were used as a proxy.

A summary of the characteristics of the individual included studies can be found in **Table AppD2-12** in **Appendix D2.1.3.1**. A detailed discussion of the evidence for each intervention and outcome can be found in **Appendix D4.1.3**.

Table D 3-26 presents a summary of the results of the Evidence Review of anticonvulsants and the location of the detailed assessment of the certainty of evidence in the evidence profile tables. Although the certainty of the evidence was very low to low, the results for sodium valproate strongly suggest that maternal exposure during pregnancy is associated with major and cardiac malformations and a reduction in IQ. In addition, the risk was greater following exposure to sodium valproate compared with carbamazepine and lamotrigine. Carbamazepine was also associated with major malformation, and the risk was greater for carbamazepine compared with lamotrigine; there appeared to be no increased risk associated with IQ. The evidence was inadequate for the assessment of maternal exposure to lamotrigine and all outcomes assessed, although as noted above, it was shown to present a lower risk than sodium valproate for major and cardiac malformations, and reduction in IQ, and a lower risk than carbamazepine for major malformation.

Table D 3-26 Summary of results of the Evidence Review for anticonvulsants

Intervention	**Increased/may be increased risk of harm** Outcome Certainty of evidence	**Appears to be no increased risk of harm** Outcome Certainty of evidence	**Decreased/may be decreased risk of harm** Outcome Certainty of evidence	**Uncertain** Outcome ○○○○	**Evidence profile table**
Sodium valproate	Major malformation ●●○○ Major malformation (vs carbamazepine) ●●○○ Major malformation (vs lamotrigine) ●●○○ Cardiac malformation ●●○○ Cardiac malformation (vs carbamazepine) ●●○○ Cardiac malformation (vs lamotrigine) ●●○○ IQ ●●○○ IQ (vs carbamazepine) ●○○○ IQ (vs lamotrigine) ●○○○			Neonatal mortality Preterm birth ASD	**Table D3-27**
Carbamazepine	Major malformation ●○○○ Major malformation (vs lamotrigine) ●○○○	IQ ●○○○		Cardiac malformation Cardiac malformation (vs lamotrigine) Neonatal mortality Preterm birth ASD IQ (vs lamotrigine)	**Table D3-28**
Lamotrigine				Major malformation Cardiac malformation Neonatal mortality Preterm birth ASD IQ	**Table D3-29**

Abbreviations: ASD, autism spectrum disorder; IQ, intelligence quotient.

Note: All comparisons are against non-exposure, unless otherwise stated. Certainty of evidence gradings are as follows: ●●●● – high certainty; ●●●○ – moderate certainty; ●●○○ – low certainty; ●○○○ – very low certainty; ○○○○ – inadequate certainty.

Table D3-27 Evidence Profile table: sodium valproate harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* (No. studies)	Additional risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates		Risk estimate (95% CI)	Anticipated absolute effects	
							With control	With intervention		Risk with control[367]	Risk with intervention[368]
Major malformations: see Section AppD4.1.3.1.1											
3,182 (14 – OBS)[369]	None[370]	None	None	None	None	●●○○ Low	**Unexposed** NA	**Sodium valproate** NA	**RR 3.13 (2.16, 4.54)**	28 per 1000[371]	88 per 1000 (73, 127)
7,078 (25 – OBS)[372]	None[370]	None	None	None	None	●●○○ Low	**Carbamazepine** NA	**Sodium valproate** NA	**RR 2.44 (2.00, 2.94)[373]**	42 per 1000[374]	102 per 1000 (84, 123)
6,185 (7–OBS)[375]	None[370]	None	None	None	None	●●○○ Low	**Lamotrigine** NA	**Sodium valproate** NA	**RR 3.56 (2.77, 4.58)**	Unknown[376]	Not estimable
Evidence Statements: *Maternal use of sodium valproate during pregnancy is associated with an increased risk of major malformation in the newborn, from an absolute risk of 3% to 9% (very low certainty evidence)* *Maternal use of sodium valproate during pregnancy is associated with an increased risk of major malformation in the newborn, when compared with maternal use of carbamazepine during pregnancy, from an absolute risk of 4% to 10% (very low certainty evidence)* *Maternal use of sodium valproate during pregnancy is associated with an increased risk of major malformation in the newborn, when compared with maternal use of lamotrigine during pregnancy (absolute increase in risk not estimable) (very low certainty evidence)*											
Cardiac malformations: see Section AppD4.1.3.2.1											
768 (6 – OBS)[377]	None[378]	None	None	None	None	●●○○ Low	**Unexposed** NA	**Sodium valproate** NA	**RR 4.85 (1.28, 18.47)**	6 per 1000[379]	29 per 1000 (8, 111)

[367] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[368] Calculated by multiplying relative effect by control risk.
[369] Weston 2016 SR (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).
[370] Based on the large magnitude of effect upper 95% CI > RR 1.25), the lack of downgrading for any other reason and the minimal effect of confounding by indication, the evidence will not be downgraded one level due to lack of adjustment for confounding. Also, not downgraded due to consideration of malformations in live births only (not explicitly stated in Weston 2016 but likely to be the case) because inclusion of live births would result in underreporting and likely underestimating the effect, and there is already a strong risk shown here.
[371] Ban 2014a (baseline risk from a population with depression/anxiety).
[372] Weston 2016 (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.
[372] Weston 2016 (includes Campbell 2013, Mawer 2010 and Vajda 2012).
[373] Calculated from the analysis of carbamazepine versus sodium valproate (RR 0.41; 0.34, 0.50).
[374] Calculated from baseline risk with carbamazepine; see **Table D3-28**.
[375] Weston 2016 SR (includes Campbell 2014, Cassina 2013, Hernandez-Diaz 2012, Matrinez Ferri 2009, Mawer 2010, Meador 2006 and Vajda 2012).
[376] Not estimable; see **Table D3-29**
[377] Weston 2016 SR (includes Canger 1999, Fairgrieve 2000, Garza-Morales 1996, Koch 1992, Mawer 2010 and Vajda 2012).
[378] Based on the large magnitude of effect (upper 95% CI > RR 1.25), the lack of downgrading for any other reason and the minimal effect of confounding by indication, the evidence will not be downgraded one level due to lack of adjustment for confounding. Also, not downgraded due to consideration of malformations in live births only (not explicitly stated in Weston 2016 but likely to be the case) because inclusion of live births would result in underreporting and likely underestimating the effect, and there is already a strong risk shown here.
[379] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (baseline risk from a population with depression/anxiety).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[367]**	**Risk with intervention[368]**
6,476 (16 – OBS)[380]	None[378]	None	None	None	None	●●○○ Low	**Carbamazepine** NA	**Sodium valproate** NA	**RR 2.22 (1.47, 3.03)[381]**	Unknown[382]	-
6,151 (6–OBS)[383]	None[378]	None	None	None	None	●●○○ Low	**Lamotrigine** NA	**Sodium valproate** NA	**RR 4.07 (2.33, 7.09)**	Unknown[384]	-
Evidence Statements: *Maternal use of sodium valproate during pregnancy is associated with an increased risk of cardiac malformation in the newborn, from an absolute risk of 0.6% to 3.0% (very low certainty evidence)* *Maternal use of sodium valproate during pregnancy is associated with an increased risk of cardiac malformation in the newborn, when compared with maternal use of carbamazepine during pregnancy (absolute increase in risk not estimable) (very low certainty evidence)* *Maternal use of sodium valproate during pregnancy is associated with an increased risk of cardiac malformation in the newborn, when compared with maternal use of lamotrigine during pregnancy (absolute increase in risk not estimable) (very low certainty evidence)*											
Neonatal mortality: see Section AppD4.1.3.3.1											
3,975 (2 – OBS)[385]	Serious(a)	None	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Sodium valproate** NA	OR 1.93 (0.79, 4.7)	5 per 1000[386]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of sodium valproate during pregnancy and neonatal mortality is uncertain.*											
Preterm birth: see Section AppD4.1.3.4.1											
3,804 (2 – OBS)[387]	Serious(a)	None	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Sodium valproate** NA	RR 1.31 (0.94, 1.83)	60 per 1000[388]	-
Evidence Statement: *Due to the inadequate quality of the evidence, any association between maternal use of sodium valproate during pregnancy and preterm birth is uncertain.*											

[380] Weston 2016 SR (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).
[381] Calculated from the analysis of carbamazepine versus sodium valproate (RR 0.45; 0.31, 0.68).
[382] Not calculable; see **Table D3-28**.
[383] Weston 2016 SR (includes Campbell 2014, Cassina 2013, Hernandez-Diaz 2012, Matrinez Ferri 2009, Meador 2006 and Vajda 2012).
[384] Not calculable, see **Table D3-29.**
[385] NICE 2015 SR (includes Artama 2013 and Diav-Citrin 2001).
[386] Ban 2012 (baseline risk from a population with depression/anxiety).
[387] NICE 215 SR (includes Artama 2013 and Diav-Citrin 2001).
[388] Malm 2015 (baseline risk from a population with depression/anxiety).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[367]**	**Risk with intervention[368]**
Autism spectrum disorder: see Section AppD4.1.3.6.1											
655,495 (1 – OBS)[389]	Serious(a)	NA	Serious(b)	None	None	○○○○ Inadequate	**Unexposed** NA	**Sodium valproate** NA	**RR3.82 (2.15, 6.80)**	9 per 1000[390]	34 per 1000 (19,
Due to the inadequate certainty of the evidence, any association between maternal use of sodium valproate during pregnancy and autism spectrum disorder is uncertain.											
Autism checklist: see Section AppD4.1.3.6.1											
246 (1 – OBS)[391]	Serious(a)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Sodium valproate** NA	RR 0.87 (0.19, 3.98)	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of sodium valproate during pregnancy and autism (as measured by the Modified Checklist for Autism in Toddlers) is uncertain.*											
IQ: see Section AppD4.1.3.7.1											
Full scale IQ - < 1 SD 76 (2 – OBS)[392]	None[393]	None	None	None	None	●●○○ Low	**Unexposed** NA	**Sodium valproate** NA	**RR 10.33 (2.05, 52.01)**	Unknown	-
Full scale IQ 176 (4 – OBS)[394]	Serious(a)	Serious(d)	None	None	None	○○○○ Inadequate	**Unexposed** NA	**Sodium valproate** NA	**MD -8.17 (-12.80, -3.55)**	Unknown	-
Verbal IQ 160 (3 – OBS)[395]	Serious(a)	None	None	None	None	●○○○ Very low	**Unexposed** NA	**Sodium valproate** NA	**-MD -8.81 (-13.32, -4.30)[396]**	Unknown	-
Performance IQ 160 (3 – OBS)[397]	Serious(a)	None	None	None	None	●○○○ Very low	**Unexposed** NA	**Sodium valproate** NA	**MD -7.20 (-12.44, -1.96)[398]**	Unknown	-

[389] NICE 2015 SR (includes Christensen 2013).
[390] Sørensen 2013 and Malm 2016 (baseline risk from a population with depression/anxiety).
[391] NICE 2015 SR (includes Veiby 2013).
[392] Bromley 2014 SR (includes Bromley 2010 and Eriksson 2005).
[393] Based on the large magnitude of effect (lower 95% CI > RR 1.25 or upper 95% CI < 0.5), the lack of downgrading for any other reason and the minimal effect of confounding by indication, the evidence will not be downgraded one level due to lack of adjustment for confounding.
[394] Bromley 2014 SR (includes Bromley 2010, Thomas 2007, Eriksson 2005 and Gaily 2004).
[395] Bromley 2014 SR (includes Bromley 2010, Eriksson 2005 and Gaily 2004).
[396] Corresponds to a SMD -0.64 (-0.98, -0.29).
[397] Bromley 2014 SR (includes Bromley 2010, Eriksson 2005 and Gaily 2004).
[398] Corresponds to a SMD -0.46 (-0.81, -0.12).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[367]**	**Risk with intervention[368]**
Full scale IQ - > 1 SD 178 (3 – OBS)[399]	Serious(a)	None	None	None	None	●○○○ Very low	**Carbamazepine** NA	**Sodium valproate** NA	**RR 2.5** **(1.20, 5.26)[400]**	Unknown	-
Full scale IQ 303 (5 – OBS)[401]	Serious(a)	Serious(d)	None	None	None	○○○○ Inadequate	**Carbamazepine** NA	**Sodium valproate** NA	**MD -8.69** **(-11.87, -5.51)[402]**	Unknown	-
Verbal IQ 226 (3 – OBS)[403]	Serious(a)	None	None	None	None	●○○○ Very low	**Carbamazepine** NA	**Sodium valproate** NA	**MD -8.44** **(-12.66, -4.21)[404]**	Unknown	-
Performance IQ 226 (3 – OBS)[405]	Serious(a)	None	None	None	None	●○○○ Very low	**Carbamazepine** NA	**Sodium valproate** NA	**MD -10.48** **(-14.94, -6.02)[406]**	Unknown	-
Full scale IQ - > 1 SD 157 (2 – OBS)[407]	None[408]	None	None	None	None	●●○○ Low	**Lamotrigine** NA	**Sodium valproate** NA	**RR 4.87** **(1.50, 15.78)**	Unknown	-
Full scale IQ 158 (2 – OBS)[409]	None[410]	None	None	None	None	●●○○ Low	**Lamotrigine** NA	**Sodium valproate** NA	**MD -10.80** **(-14.42, -7.17)[411]**	Unknown	-
Evidence Statements: *Maternal use of sodium valproate during pregnancy is associated with an increased risk of below average IQ (full-scale IQ score at 1 SD level) in the child (low certainty evidence)* *Due to the inadequate certainty of the evidence, any association between maternal use of sodium valproate during pregnancy and full-scale IQ score in the child is uncertain.*											

[399] Bromley 2014 SR (includes Bromley 2010, Eriksson 2005 and Meador 2013).
[400] Calculated from the analysis of carbamazepine versus sodium valproate (RR 0.40; 0.19, 0.83).
[401] Bromley 2014 SR (includes Bromley 2010, Eriksson 2005, Gaily 2014, Meador 2013 and Thomas 2007).
[402] Calculated from the analysis of carbamazepine versus sodium valproate (MD 8.69; 5.51, 11.87).
[403] Bromley 2014 SR (includes Bromley 2010, Eriksson 2005 and Gaily 2004).
[404] Calculated from the analysis of carbamazepine versus sodium valproate (MD 8.44; 4.21, 12.66). Corresponds to a SMD -0.56 (-0.86, -0.26).
[405] Bromley 2014 SR (includes Bromley 2010, Eriksson 2005 and Gaily 2004).
[406] Calculated from the analysis of carbamazepine versus sodium valproate (MD 10.48; 6.02, 14.94). Corresponds to a SMD -0.71 (-1.02, -0.40).
[407] Bromley 2014 SR (includes Bromley 2010 and Meador 2013).
[408] Based on the large magnitude of effect (upper 95% CI > RR 1.25), the lack of downgrading for any other reason and the minimal effect of confounding by indication, the evidence will not be downgraded one level due to lack of adjustment for confounding.
[409] Bromley 2014 SR (includes Bromley 2010 and Meador 2013).
[410] Based on the large magnitude of effect (lower 95% CI < SMD -0.5), the lack of downgrading for any other reason and the minimal effect of confounding by indication, the evidence will not be downgraded one level due to lack of adjustment for confounding.
[411] Corresponds to SMD -0.92 (-1.26, -0.58).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[367]**	**Risk with intervention[368]**
Maternal use of sodium valproate during pregnancy may be associated with a reduction in mean verbal IQ score in the child (very low certainty evidence)											
Maternal use of sodium valproate during pregnancy may be associated with a reduction in mean performance IQ score in the child (very low certainty evidence)											
Maternal use of sodium valproate during pregnancy may be associated with an increased risk of below average IQ (at 1 SD level in the child), compared with maternal use of carbamazepine during pregnancy (very low certainty evidence)											
Due to the inadequate certainty of the evidence, any additional reduction in full-scale IQ score in the child that may be associated with maternal use of sodium valproate during pregnancy, compared with maternal use of carbamazepine during pregnancy, is uncertain.											
Maternal use of sodium valproate during pregnancy may be associated with a reduction in mean verbal IQ score in the child, compared with maternal use of carbamazepine during pregnancy (very low certainty evidence)											
Maternal use of sodium valproate during pregnancy may be associated with a reduction in mean performance IQ score in the child, compared with maternal use of carbamazepine during pregnancy (very low certainty evidence)											
Maternal use of sodium valproate during pregnancy is associated with an increased risk of below average IQ (full-scale IQ score at 1 SD level) in the child, compared with maternal use of lamotrigine during pregnancy (low certainty evidence)											
Maternal use of sodium valproate during pregnancy is associated with a reduction in mean full-scale IQ score in the child, compared with maternal use of lamotrigine during pregnancy (low certainty evidence)											

Footnotes:

a. Downgraded one level due to a moderate risk of bias; analysis of raw data from observational studies.

b. Downgraded one level due to serious risk of indirectness; comparison with a general population.

c. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25 or SMD –0.5/0.5, no measure of precision available, or no events.

d. Downgraded one level due to serious heterogeneity; I^2 between 25% and 59%.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; IQ, intelligence quotient; MD, mean difference; NA, not available; OBS, observational studies; OR, odds ratio; RR, relative risk

Table D3-28 Evidence Profile table: carbamazepine harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* (No. studies)	Additional risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates		Risk estimate (95% CI)	Anticipated absolute effects	
							With control	With intervention		Risk with control[412]	Risk with intervention[413]
Major malformations: see Section AppD4.1.3.1.1											
4,345 (17– OBS)[414]	Serious(a)[415]	None	None	None	None	●○○○ Very low	**Unexposed** NA	**Carbamazepine** NA	**RR 1.50 (1.03, 2.19)**	28 per 1000[416]	42 per 1000 (29, 61)
7,549 (7–OBS)[417]	Serious(a)[415]	None	None	None	None	●○○○ Very low	**Lamotrigine** NA	**Carbamazepine** NA	**RR 1.34 (1.01, 1.76)**	Unknown[418]	40 per 1000 (30, 53)
Evidence Statements: *Maternal use of carbamazepine during pregnancy may be associated with an increased risk of major malformation in the newborn, from an absolute risk of 3% to 4% (very low certainty evidence)* *Maternal use of carbamazepine during pregnancy may be associated with an increased risk of major malformation in the newborn, compared with maternal use of lamotrigine during pregnancy, from an absolute risk of 3.0% to 4.0% (very low certainty evidence)*											
Cardiac malformations: see Section AppD4.1.3.2.1											
1,026 (7 – OBS)[419]	Serious(a)[420]	None	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Carbamazepine** NA	RR 1.84 (0.32, 10.71)	6 per 1000[421]	-
7,509 (6–OBS)[422]	Serious(a)[420]	None	None	Serious(b)	None	○○○○ Inadequate	**Lamotrigine** NA	**Carbamazepine** NA	RR 1.57 (0.85, 2.89)	Unknown[423]	-
Evidence Statements: *Due to the inadequate certainty of the evidence, any association between maternal use of carbamazepine during pregnancy and cardiac malformation in the newborn is uncertain.* *Due to the inadequate certainty of the evidence, any additional risk of cardiac malformation in the newborn that may be associated with maternal use of carbamazepine during pregnancy, compared with maternal use of lamotrigine during pregnancy, is uncertain.*											

[412] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[413] Calculated by multiplying relative effect by control risk.
[414] Weston 2016 SR (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).
[415] Not downgraded due to consideration of malformations in live births only (not explicitly stated in Weston 2016 but likely to be the case) because inclusion of live births would result in underreporting and likely underestimating the effect, and there was already a statistically significant risk shown.
[416] Ban 2014a (baseline risk from a population with depression/anxiety).
[417] Weston 2016 SR (includes Campbell 2014, Cassina 2013, Hernandez-Diaz 2012, Martinez Ferri 2009, Mawer 2010, Meador 2006 and Vajda 2012).
[418] Not calculable; see **Table D3-29**
[419] Weston 2016 SR (includes Al Bunyan 1999, Barqawi 2005, Canger 1999, Fairgrieve 2000, Koch 1992 and Mawer 2010 and Vajda 2012).
[420] Not downgraded due to consideration of malformations in live births only (not explicitly stated in Weston 2016 but likely to be the case) because inclusion of live births would result in underreporting and likely underestimating the effect, and there was already a statistically significant risk shown.
[421] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (baseline risk from a population with depression/anxiety).
[422] Weston 2016 SR (includes Campbell 2014, Cassina 2013, Hernandez-Diaz 2012, Martinez Ferri 2009, Meador 2006, and Vajda 2012).
[423] Not calculable; see **Table D3-29**

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[412]**	**Risk with intervention[413]**
Neonatal mortality: see Section AppD4.1.3.3.1											
3,202 (2 – OBS)[424]	Serious(a)	Very serious(c)	Serious(d)	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Carbamazepine** NA	OR 0.79 (0.12, 5.31)	5 per 1000[425]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of carbamazepine during pregnancy and neonatal mortality is uncertain.*											
Preterm birth: see Section AppD4.1.3.4.1											
3,202 (2 – OBS)[426]	Serious(a)	None	Serious(d)	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Carbamazepine** NA	OR 1.65 (0.64, 4.22)	60 per 1000[427]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of carbamazepine during pregnancy and preterm birth is uncertain.*											
Autism spectrum disorder: see Section AppD4.1.3.5.1											
655,539 (1 – OBS)[428]	Serious(a)	NA	Serious(d)	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Carbamazepine** NA	OR 1.25 (0.47, 3.35)	9 per 1000[429]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of carbamazepine during pregnancy and autism spectrum disorder is uncertain.*											
Autism checklist: see Section AppD4.1.3.6.1											
262 (1 – OBS)[430]	Serious(a)	NA	Serious(d)	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Carbamazepine** NA	OR 0.79 (0.22, 2.8)	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of carbamazepine during pregnancy and autism (as measured by the Modified Checklist for Autism in Toddlers) is uncertain.*											
IQ: see Section AppD4.1.3.7.1											
Full scale IQ 250 (4 – OBS)[431]	Serious(a)	None	None	None[432]	None	●○○○ Very low	**Unexposed** NA	**Carbamazepine** NA	MD 1.84 (-2.13, 5.80)	Unknown	-

[424] NICE 2015 SR (includes Artama 2013 and Diav-Citrin 2001).
[425] Ban 2012 (baseline risk from a population with depression/anxiety).
[426] NICE 215 SR (includes Artama 2013 and Diav-Citrin 2001).
[427] Malm 2015 (baseline risk from a population with depression/anxiety).
[428] NICE 2015 SR (includes Christensen 2013).
[429] Sørensen 2013 and Malm 2016 (baseline risk from a population with depression/anxiety).
[430] NICE 2015 SR (includes Veiby 2013).
[431] Bromley 2014 SR (includes Bromley 2010, Thomas 2007, Eriksson 2005 and Gaily 2004).
[432] Based on analysis conducted for this review; SMD 0.15 (95% CI -0.11, 0.41).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[412]**	**Risk with intervention[413]**
Verbal IQ 232 (3 – OBS)[433]	Serious(a)	None	None	None[434]	None	●○○○ Very low	**Unexposed** NA	**Carbamazepine** NA	MD 0.13 (-3.98, 4.23)	Unknown	-
Performance IQ 232 (3 – OBS)[435]	Serious(a)	None	None	Serious(b)[436]	None	○○○○ Inadequate	**Unexposed** NA	**Carbamazepine** NA	MD 3.65 (-0.60, 7.90)	Unknown	-
Full scale IQ - > 1 SD 159 (2 – OBS)[437]	Serious(a)	None	None	Serious(b)	None	○○○○ Inadequate	**Lamotrigine** NA	**Carbamazepine** NA	RR 2.28 (0.63, 8.22)	Unknown	-
Full scale IQ 162 (2 – OBS)[438]	Serious(a)	None	None	None[439]	None	●○○○ Very low	**Lamotrigine** NA	**Carbamazepine** NA	MD -1.62 (-5.44, 2.21)	Unknown	-

Evidence Statements:

Maternal use of carbamazepine during pregnancy does not appear to be associated with a reduction in mean full-scale IQ score in the child (very low certainty evidence)

Maternal use of carbamazepine during pregnancy does not appear to be associated with a reduction in mean verbal IQ score in the child (very low certainty evidence)

Due to the inadequate certainty of the evidence, any association between maternal use of carbamazepine during pregnancy and mean performance IQ is uncertain.

Due to the inadequate certainty of the evidence, any additional risk of below average IQ (full-scale IQ score at 1 SD level) in the child that may be associated with maternal use of carbamazepine during pregnancy, compared with maternal use of lamotrigine during pregnancy, is uncertain.

Maternal use of carbamazepine during pregnancy does not appear to be associated with a reduction in mean full-scale IQ score in the child, compared with maternal use of lamotrigine during pregnancy (very low certainty evidence)

Footnotes:

a. Downgraded one level due to a moderate risk of bias; analysis of raw data from observational studies.

b. Downgraded one level due to imprecision; 95% CI crosses line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25 or SMD –0.5/0.5, no measure of precision available, or no events.

c. Downgraded two levels due to very serious heterogeneity; $I^2 \geq 60\%$.

d. Downgraded one due to serious risk of indirectness; comparison with a general population

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Those shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; IQ, intelligence quotient; MD, mean difference; NA, not available; OBS, observational studies; OR, odds ratio; RR, relative risk

[433] Bromley 2014 SR (includes Bromley 2001, Eriksson 2005 and Gaily 2004).

[434] Based on analysis conducted for this review; SMD 0.02 (95% CI -0.25, 0.29).

[435] Bromley 2014 SR (includes Bromley 2010, Eriksson 2005 and Gaily 2004).

[436] Based on analysis conducted for this review; SMD 0.25 (95% CI -0.02, 0.52).

[437] Bromley 2014 SR (includes Bromley 2010 and Meador 2013).

[438] Bromley 2014 SR (includes Bromley 2010 and Meador 2013).

[439] Based on analysis conducted for this review; SMD -0.13 (95% CI -0.44, 0.18).

Table D3-29 Evidence Profile table: lamotrigine harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* (No. studies)	Additional risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates		Risk estimate (95% CI)	Anticipated absolute effects	
							With control	With intervention		Risk with control[440]	Risk with intervention[441]
Major malformations: see Section AppD4.1.3.1.1											
3,181 (3– OBS)[442]	Serious(a,b)	None	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Lamotrigine** NA	RR 1.07 (0.64, 1.77)	28 per 1000[443]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lamotrigine during pregnancy and major malformation in the newborn is uncertain.*											
Cardiac malformations: see Section AppD4.1.3.2.1											
542 (2 – OBS)[444]	Serious(a,b)	NA	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Lamotrigine** NA	RR 1.40 (0.15, 13.35)	6 per 1000[445]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lamotrigine during pregnancy and cardiac malformation in the newborn is uncertain.*											
Neonatal mortality: see Section AppD4.1.3.3.1											
1,973 (1 – OBS)[446]	Serious(a)	NA	Serious(d)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Lamotrigine** NA	RR 0.49 (0.03, 8.42)	5 per 1000[447]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lamotrigine during pregnancy and neonatal mortality is uncertain.*											
Preterm birth: see Section AppD4.1.3.4.1											
1,973 (1 – OBS)[448]	Serious(a)	None	Serious(d)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Lamotrigine** NA	RR 0.98 (0.47, 2.05)	60 per 1000[449]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lamotrigine during pregnancy and preterm birth is uncertain.*											

[440] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[441] Calculated by multiplying relative effect by control risk.
[442] Weston 2016 SR (includes Campbell 2013, Mawer 2010 and Vajda 2012).
[443] Ban 2014a (baseline risk from a population with depression/anxiety).
[444] Weston 2016 SR (includes Mawer 2010 (no events) and Vajda 2012).
[445] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (baseline risk from a population with depression/anxiety).
[446] NICE 2015 SR (includes Artama 2013).
[447] Ban 2012 (baseline risk from a population with depression/anxiety).
[448] NICE 215 SR (includes Artama 2013 and Diav-Citrin 2001).
[449] Malm 2015 (baseline risk from a population with depression/anxiety).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[440]**	**Risk with intervention[441]**
Autism spectrum disorder: see Section AppD4.1.3.5.1											
655,394 (1 – OBS)[450]	Serious(a)	NA	Serious(d)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Lamotrigine** NA	RR 1.5 (0.75, 3.01)	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lamotrigine during pregnancy autism spectrum disorder in the child is uncertain.*											
Autism checklist: see Section AppD4.1.3.6.1											
286 (1 – OBS)[451]	Serious(a)	NA	Serious(d)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Lamotrigine** NA	RR 1.83 (0.81, 4.13)	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lamotrigine during pregnancy and autism (as measured by the Modified Checklist for Autism in Toddlers) is uncertain.*											
IQ: see Section AppD4.1.3.7.1											
Full scale IQ 54 (1 – OBS)[452]	Serious(a)	None	None	Serious(c)[453]	None	○○○○ Inadequate	**Unexposed** NA	**Lamotrigine** NA	MD -1.0 (-7.48, 5.48)	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lamotrigine during pregnancy and reduction in full-scale IQ score in the child is uncertain.*											

Footnotes:
a. Downgraded one level due to a moderate risk of bias; analysis of raw data from observational studies.
b. Downgraded one level due to serious risk of bias; selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis.
c. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25 or SMD –0.5/0.5, no measure of precision available, or no events.
d. Downgraded one level due to serious risk of indirectness; comparison with a general population.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; IQ, intelligence quotient; MD, mean difference; NA, not available; OBS, observational studies; OR, odds ratio; RR, relative risk.

[450] NICE 2015 SR (includes Christensen 2013).
[451] NICE 2015 SR (includes Veiby 2013).
[452] Bromley 2014 SR (includes Bromley 2010).
[453] Based on analysis conducted for this review; SMD -0.08 (95% CI -0.62, 0.45).

D3.1.4 Benzodiazepines and z-drugs

The following section presents the Evidence Profile tables for benzodiazepine and z-drugs. No intervention-specific rules were required for downgrading of the certainty of this body of evidence.

As the evidence was based on data from cohort and case-control studies, in many cases the results were presented as odds ratios instead of relative risks. Where the baseline risk was < 7%, it was assumed that the odds ratio approximates the relative risk and the results were interpreted as relative risks. Where baseline risk was not available in a pregnant unexposed population with a mental health disorder, the baseline risks identified for a depressed population were used as a proxy.

A summary of the characteristics of the individual included studies can be found in **Table AppD2-18** in **Appendix D2.1.4.2**. A detailed discussion of the evidence for each group or individual intervention type and outcome can be found in **Appendix D4.1.4**.

Table D 3-30 presents a summary of the results of the Evidence Review of benzodiazepines and z-drugs and the location of the detailed assessment of the certainty of evidence in the evidence profile tables. The majority of the evidence assessed was of inadequate certainty, so the findings for most outcomes were considered uncertain. Exceptions to this were the associations between exposure in late pregnancy to benzodiazepines and respiratory difficult, and zolpidem and preterm birth and the infant being small for gestational age. The evidence suggests maternal exposure to benzodiazepines may not be associated with major malformation, and zolpidem may not be associated with respiratory difficulty.

Table D 3-30 Summary of results of the Evidence Review for benzodiazepines and z-drugs

Intervention	**Increased/may be increased risk of harm** Outcome Certainty of evidence	**Appears to be no increased risk of harm** Outcome Certainty of evidence	**Decreased/may be decreased risk of harm** Outcome Certainty of evidence	**Uncertain** Outcome ○○○○	**Evidence profile table**
Benzodiazepines ± z drugs	Respiratory difficulty[454] ●○○○	Major malformation ●○○○		Cardiac malformation Septal malformation Miscarriage Preterm birth SFGA Convulsions Language competence	**Table D3-31**
Diazepam				Major malformation Cardiac malformation	**Table D3-32**
Temazepam				Major malformation Cardiac malformation	**Table D3-33**
Z-drugs				Major malformation Cardiac malformation	**Table D3-34**
Zolpidem	Preterm birth ●●○○ SFGA ●●○○	Respiratory difficulty ●○○○		Major malformation	**Table D3-35**
Zopiclone				Major malformation Cardiac malformation Miscarriage Preterm birth SFGA	**Table D3-36**

Abbreviations: SFGA, small for gestational age.

Note: All comparisons are against non-exposure, unless otherwise stated. Certainty of evidence gradings are as follows: ●●●● – high certainty; ●●●○ – moderate certainty; ●●○○ – low certainty; ●○○○ – very low certainty; ○○○○ – inadequate certainty.

[454] Late exposure only.

Table D3-31 Evidence Profile table: benzodiazepines ± z-drugs

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* (No. studies)	Additional risk of bias[455]	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Population (N) Unexposed	Population (N) Exposed	Risk estimate (95% CI)	Anticipated absolute effects Risk with control[456]	Anticipated absolute effects Risk with intervention[457]
Major malformations: see Section AppD4.1.4.1.2											
108,288 (1 – OBS)[458]	Serious(a)	NA	None	None	None	●○○○ Very low	**Unexposed** NA	**Benzodiazepines[459] (first trimester)** NA	RD -0.0041 (-0.015, 0.0069)	28 per 1000[460]	28 per 1000 (28, 28)
NR (1 – OBS)[461]	Serious(a)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines and z-drugs[462] –excluding anticonvulsants (any time)** NA	RR 1.22 (0.97, 1.52)	28 per 1000[463]	-
Evidence Statement: *Maternal use of benzodiazepines during the first trimester of pregnancy does not appear to be associated with an increased risk of major malformation in the newborn (very low certainty evidence)*											
Cardiac malformations: see Section AppD4.1.4.2.2											
4,467 (1 – OBS)[464]	Serious(d)	NA	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines[465] (any time)** NA	RR 1.6 (0.9, 2.8)	6 per 1000[466]	-
4,467 (1 – OBS)[467]	Serious(d)	NA	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines[468] (Month 1)** NA	RR 1.6 (0.7, 3.7)	6 per 1000[469]	-

[455] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[456] Based on average risk from unexposed, depressed control groups of population-based cohort studies providing data for that outcome.
[457] Calculated by multiplying relative effect by control risk.
[458] Oberlander 2008a.
[459] Includes lorazepam (44.0%), clonazepam (21.4%), oxazepam (15.0%), alprazolam (6.8%), temazepam (5.1%), diazepam (5.0%) and others.
[460] Ban 2014a (depressed/anxious population).
[461] Wikner 2007.
[462] Of the 2,169 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.
[463] Ban 2014a (depressed/anxious population).
[464] Eros 2002.
[465] Includes nitrazepam, medazepam, tofisopam, alprazolam and clonazepam.
[466] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).
[467] Eros 2002.
[468] Includes nitrazepam, medazepam, tofisopam, alprazolam and clonazepam.
[469] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[455]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[456]**	**Risk with intervention[457]**
4,467 (1 – OBS)[470]	Serious(d)	NA	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines[471] (Months 2-3)** NA	RR 1.0 (0.2, 4.6)	6 per 1000[472]	-
4,467 (1 – OBS)[473]	Serious(d)	NA	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines[474] (Months 4-9)** NA	RR 1.9 (0.8, 4.6)	6 per 1000[475]	-
4,467 (1 – OBS)[476]	Serious(d)	NA	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines[477] (any time)** NA	OR 1.6 (0.7, 3.6)[478]	6 per 1000[479]	-
4,467 (1 – OBS)[480]	Serious(d)	NA	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines[481] (Months 2-3)** NA	OR 5.0 (0.2, 104)[478]	6 per 1000[482]	-
108,288 (1 – OBS)[483]	Serious(d)	NA	None	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepine (any time)** NA	RD –0.0013 (-0.0055, 0.0029)	6 per 1000[484]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of benzodiazepines and an increased risk of cardiac malformation in the newborn is uncertain.*											

[470] Eros 2002.
[471] Includes nitrazepam, medazepam, tofisopam, alprazolam and clonazepam.
[472] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).
[473] Eros 2002.
[474] Includes nitrazepam, medazepam, tofisopam, alprazolam and clonazepam.
[475] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).
[476] Eros 2002.
[477] Includes nitrazepam, medazepam, tofisopam, alprazolam and clonazepam.
[478] McNemar analysis.
[479] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).
[480] Eros 2002.
[481] Includes nitrazepam, medazepam, tofisopam, alprazolam and clonazepam.
[482] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).
[483] Oberlander 2008a.
[484] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[455]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[456]**	**Risk with intervention[457]**
Septal malformations: see Section AppD4.1.4.3.2											
108,288 (1 – OBS)[485]	Very serious(e)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines** NA	RR 1.48 (0.21, 10.65)	3 per 1000[486]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of benzodiazepines and an increased risk of septal malformation in the newborn is uncertain.*											
Miscarriage: see Section AppD4.1.4.4.1											
1,204 (3 – OBS)[487]	Serious(f)	None	Serious(b)	None	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines** NA	**OR 1.83 (1.19, 2.82)**	81 per 1000[488]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of benzodiazepines and an increased risk of miscarriage is uncertain.*											
Preterm birth: see Section AppD4.1.4.5.2											
42,875 (1 – OBS)[489]	Serious(g)	NA	Serious(b)	None	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines or z-drugs[490] (early exposure)** NA	**RR 1.48 (1.26, 1.75)**	60 per 1000[491]	-
42,875 (1 – OBS)[492]	Serious(g)	NA	Serious(b)	None	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines or z-drugs[493] (late exposure)** NA	**RR 2.57 (1.92, 3.43)**	60 per 1000[491]	-
42,875 (1 – OBS)[494]	None	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines or z-drugs – excluding antidepressants (any time)** NA	RR 1.20 (0.97, 1.50)	6 per 1000[491]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of benzodiazepines or z-drugs during pregnancy and an increased risk of preterm birth is uncertain.*											

[485] Based on results presented in NICE 2015 (includes Oberlander 2008a).
[486] The Bérard 2015 (examining antidepressants) study used an insured population and as such the prevalence of septal malformations in this study (1.83%) is not likely to be representative of the general population with depression. To estimate the prevalence, it is assumed that 50% of cardiac malformations are septal, resulting in an estimate of 0.3%.
[487] Based on results presented in NICE 2015 (includes Laegreid 1992, Ornoy 1998 and Pastuszak 1996).
[488] Almeida 2016 and Ban 2012 (depressed/anxious population).
[489] Wikner 2007.
[490] Of the 2,169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs.
[491] Malm 2015 (depressed population).
[492] Wikner 2007.
[493] Of the 415 infants exposed in late pregnancy, 82.2% were exposed to benzodiazepines and 17.8% were exposed to z-drugs.
[494] Wikner 2007.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[455]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[456]**	**Risk with intervention[457]**
Small for gestational age: see Section AppD4.1.4.6.2											
18,260 (1 – OBS)[495]	Serious(g)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines or z-drugs[496] (early exposure)** NA	OR 1.12 (0.87, 1.44)	Unknown	-
18,260 (1 – OBS)[497]	Serious(g)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines or z-drugs[498] (late exposure)** NA	OR 1.39 (0.80, 2.40)	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of benzodiazepines or z-drugs during pregnancy and an increased risk of the newborn being small for gestational age is uncertain.*											
Respiratory difficulty: see Section AppD4.1.4.7.2											
38,638 (1 – OBS)[499]	None	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines or z-drugs[500] (early exposure)** NA	RR 1.19 (0.98, 1.45)	32 per 1000[501]	-
38,638 (1 – OBS)[502]	None	NA	Serious(b)	None	None	●○○○ Very low	**Unexposed** NA	**Benzodiazepines or z-drugs[503] (late exposure)** NA	**RR 2.21 (1.62, 3.02)**	32 per 1000[504]	71 per 1000 (52, 97)
NR (1 – OBS)[505]	None	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzodiazepines or z-drugs[506] - excluding antidepressants (any time)** NA	RR 1.12 (0.88, 1.43)	32 per 1000[507]	-
Evidence Statement: *Maternal use of benzodiazepines during late pregnancy may be associated with an increased risk of respiratory difficulty in the newborn, from an absolute risk of 3.2% to 7% (very low certainty evidence)*											

[495] Wikner 2007.
[496] Of the 2,169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs.
[497] Wikner 2007.
[498] Of the 415 infants exposed in late pregnancy, 82.2% were exposed to benzodiazepines and 17.8% were exposed to z-drugs.
[499] Wikner 2007
[500] Of the 2,169 infant exposures in early pregnancy, 72.3% were to benzodiazepines and 27.7% were to z-drugs.
[501] Malm 2015.
[502] Wikner 2007
[503] Of the 415 infant exposures in late pregnancy, 82.2% were to benzodiazepines and 17.8% were to z-drugs.
[504] Malm 2015.
[505] Wikner 2007
[506] Of the 2,169 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.
[507] Malm 2015.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[455]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[456]**	**Risk with intervention[457]**
Convulsions: see Section AppD4.1.4.8.2											
1,386 (1 – OBS)[508]	Serious(g)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzo or z-drug (early exposure)** NA	RR 1.35 (0.44, 3.15)	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of benzodiazepines or z-drugs during early pregnancy and an increased risk of convulsions in the newborn is uncertain.*											
Language competence: see Section AppD4.1.4.9.2											
51,411 (1 – OBS)[509]	Serious(h)	NA	None	Unknown(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzo or z-drug (short-term use)[510]** NA	OR 1.0 (0.7, 1.3)	Unknown	-
51,174 (1 – OBS)[511]	Serious(h)	NA	None	Unknown(c)	None	○○○○ Inadequate	**Unexposed** NA	**Benzo or z-drug (long-term use)[512]** NA	OR 1.3 (0.8, 2.3)	Unknown	-
Evidence Statement: Due to the inadequate certainty of the evidence, any association between maternal use of benzodiazepines or z-drugs at any time during pregnancy and an increased risk of decreased language competence in the child is uncertain.											

Footnotes:
a. Downgraded one level due to serious risk of bias; selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis.
b. Downgraded one level due to serious indirectness; compared to a general population with no adjustment for potential confounding by indication.
c. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25 or SMD –0.5/0.5, no measure of precision available, or no events.
d. Downgraded one level due to serious risk of bias; selection bias due to exclusion of miscarriages from the analysis.
e. Downgraded two levels due to very serious risk of bias; analysis based on raw data and potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis.
f. Downgraded one level due to serious risk of bias; analysis based on raw data.
g. Downgraded one level due to moderate risk of bias; no adjustment for/consideration of other treatments.
h. Downgraded one level due to moderate risk of bias; self-reported exposure and outcome.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.
Abbreviations: Benzo, benzodiazepine; CI, confidence interval; NA, not available; NR, not reported; OBS, observational studies; OR, odds ratio; RD, risk difference; RE, risk estimate; RR, relative risk; SMD, standardised mean difference.

[508] Wikner 2007.
[509] Odsbu 2015.
[510] Woman reported use on one questionnaire during pregnancy only. Women answered three questionnaires during pregnancy.
[511] Odsbu 2015.
[512] Woman reported use on more than one questionnaire during pregnancy. Women answered three questionnaires during pregnancy.

Table D3-32 Evidence Profile table: diazepam

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[513]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[514]**	**Risk with intervention[515]**
Major malformation: see Section AppD4.1.4.1.2											
Heart anomalies *20,352* (1 – OBS)[516]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Diazepam (first trimester)** NA	RR 0.99 (0.61, 1.61)	28 per 1000[517]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of diazepam during the first trimester of pregnancy and major malformation in the newborn is uncertain.*											
Cardiac malformation: see Section AppD4.1.4.2.2											
Heart anomalies *20,532* (1 – OBS)[518]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Diazepam (first trimester)** NA	OR 1.29 (0.60, 2.80)	6 per 1000[519]	-
Cardiovascular congenital anomalies 42,630 (1 – OBS)[520]	Serious(c)	NA	None	Serious(b)	None	○○○○ Inadequate	**Diazepam (Months 5-6)** NA	**Diazepam (Months 2-3)** NA	OR 1.0 (0.8, 1.4)	6 per 1000[521]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of diazepam during the first trimester of pregnancy and cardiac malformation in the newborn is uncertain.*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis.
b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25 or SMD –0.5/0.5, no measure of precision available, or no events.
c. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of miscarriages and stillborn from the analysis.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.
Abbreviations: CI, confidence interval; NA, not available; NR, not reported; OBS, observational studies; OR, odds ratio; RE, risk estimate; RR, relative risk; SMD, standardised mean difference.

[513] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[514] Based on average risk from unexposed, depressed control groups of population-based cohort studies providing data for that outcome.
[515] Calculated by multiplying relative effect by control risk.
[516] Ban 2014b.
[517] Ban 2014a (depressed/anxious population).
[518] Ban 2014b.
[519] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).
[520] Kjaer 2007.
[521] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).

Table D3-33 Evidence Profile table: temazepam

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[522]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control**[523]	**Risk with intervention**[524]
Major malformation: see Section AppD4.1.4.1.2											
Heart anomalies *19,572* (1 – OBS)[525]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Temazepam (first trimester)** NA	OR 1.04 (0.47, 2.32)	28 per 1000[526]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of temazepam during the first trimester of pregnancy and major malformation in the newborn is uncertain.*											
Cardiac malformation: see Section AppD4.1.4.2.2											
Heart anomalies *19,572* (1 – OBS)[527]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Temazepam (first trimester)** NA	OR 1.31 (0.35, 4.92)	6 per 1000[528]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of temazepam during the first trimester of pregnancy and cardiac malformation in the newborn is uncertain.*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis.
b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25 or SMD –0.5/0.5, no measure of precision available, or no events.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.
Abbreviations: CI, confidence interval; NA, not available; NR, not reported; OBS, observational studies; OR, odds ratio; RE, risk estimate; RR, relative risk; SMD, standardised mean difference.

[522] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[523] Based on average risk from unexposed, depressed control groups of population-based cohort studies providing data for that outcome.
[524] Calculated by multiplying relative effect by control risk.
[525] Ban 2014b.
[526] Ban 2014a (depressed/anxious population).
[527] Ban 2014b.
[528] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).

Table D3-34 Evidence Profile table: z-drugs

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[529]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[530]**	**Risk with intervention[531]**
Major malformation: see Section AppD4.1.4.1.2											
1,127,075 (1 – OBS)[532]	Very serious(a)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Z-drugs (any time)** NA	RR 0.95 (0.69, 1.30)	28 per 1000[533]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of z-drugs at any time during pregnancy and relatively severe malformation[534] in the newborn is uncertain.*											
Cardiac malformation: see Section AppD4.1.4.2.2											
1,127,075 (1 – OBS)[535]	Very serious(a)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Z-drugs (any time)** NA	RR 0.55 (0.27, 1.09)	6 per 1000[536]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of z-drugs at any time during pregnancy and cardiac malformation in the newborn is uncertain.*											

Footnotes:
a. Downgraded two levels due to high risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis and lack of adjustment for use of other treatments.
b. Downgraded one level due to serious indirectness; compared to a general population with no adjustment for potential confounding by indication.
c. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25 or SMD –0.5/0.5, no measure of precision available, or no events.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.
Abbreviations: CI, confidence interval; NA, not available; OBS, observational studies; RE, risk estimate; RR, relative risk; SMD, standardised mean difference.

[529] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[530] Based on average risk from unexposed, depressed control groups of population-based cohort studies providing data for that outcome.
[531] Calculated by multiplying relative effect by control risk.
[532] Wikner 2011.
[533] Ban 2014a (depressed/anxious population).
[534] Excludes preauricular appendix, undescended testicle, unstable hip, patent ductus arteriosus in preterm infants, single umbilical artery, tongue tie and nevus.
[535] Wikner 2011.
[536] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).

Table D3-35 Evidence Profile table: zolpidem

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias[537]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[538]**	**Risk with intervention[539]**
Major malformation: see Section AppD4.1.4.1.2											
14,982 (1 – OBS)[540]	Serious(a)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Zolpidem (any time)** NA	RR 0.70 (0.38, 1.28)	28 per 1000[541]	-
14,447 *(1 – OBS)[542]*	Serious(a)	NA	Serious(b)	Serious(c)	None	○○○○ Inadequate	**Unexposed** NA	**Zolpidem (second or third trimester)** NA	RR 0.74 (0.38, 1.44)	28 per 1000[543]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of zolpidem at any time during pregnancy and major malformation[544] in the neonate is uncertain.*											
Preterm birth: see Section AppD4.1.4.5.2											
14,982 (1 - OBS)[545]	None	NA	None[546]	None	None	●●○○ Low	**Unexposed** NA	**Zolpidem (any time)** NA	**RR 1.49 (1.28, 1.74)**	60 per 1000[547]	89 per 1000 (77, 104)
13,020 (1 – OBS)[548]	None	NA	None[546]	None	None	●●○○ Low	**Unexposed** NA	**Zolpidem (first trimester)** NA	**RR 1.48 (1.10, 1.98)**	60 per 1000[547]	89 per 1000 (66, 119)

[537] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[538] Based on average risk from unexposed, depressed control groups of population-based cohort studies providing data for that outcome.
[539] Calculated by multiplying relative effect by control risk.
[540] Wang 2010.
[541] Ban 2014a (in a depressed/anxious population).
[542] Wang 2010.
[543] Ban 2014a (in a depressed/anxious population).
[544] Limited to hydrocephaly, anencephaly, microcephaly, meningomyelocele, encephalocele and spina bifida.
[545] Wang 2010.
[546] Compared exposure in a non-mental health disorder population with non-exposure in a non-mental health disorder population.
[547] Malm 2015 (depressed population).
[548] Wang 2010.

Certainty assessment							**Summary of findings**				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[537]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[538]**	**Risk with intervention[539]**
14,447 (1 – OBS)[549]	None	NA	None[546]	None	None	●●○○ Low	**Unexposed** NA	**Zolpidem (second or third trimester)** NA	**OR 1.49 (1.26, 1.77)**	Unknown	-
Evidence Statement: *Maternal use of zolpidem at any time during pregnancy is associated with an increased risk of preterm birth, from an absolute risk of 6% to 9% (low certainty evidence)*											
Small for gestational age: see Section AppD4.1.4.6.2											
14,982 (1 - OBS)[550]	None	NA	None[551]	None	None	●●○○ Low	**Unexposed** NA	**Zolpidem (any time)** NA	**OR 1.34 (1.20, 1.49)**	Unknown	-
13,020 (1 – OBS)[552]	None	NA	None[551]	None	None	●●○○ Low	**Unexposed** NA	**Zolpidem (first trimester)** NA	**OR 1.36 (1.09, 1.69)**	Unknown	-
14,447 (1 – OBS)[553]	None	NA	None[551]	None	None	●●○○ Low	**Unexposed** NA	**Zolpidem (second or third trimester)** NA	**OR 1.33 (1.18, 1.50)**	Unknown	-
Evidence Statement: *Maternal use of zolpidem at any time during pregnancy may be associated with an increased risk of the newborn being small for gestational age (low certainty evidence)*											

[549] Wang 2010.
[550] Wang 2010.
[551] Compared exposure in a non-mental health disorder population with non-exposure in a non-mental health disorder population.
[552] Wang 2010.
[553] Wang 2010.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[537]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[538]**	**Risk with intervention[539]**
Respiratory difficulty: see Section AppD4.1.4.7.2											
90 (1 – OBS)[554]	None	NA	None	Unknown(a)	None	●○○○ Very low	**Unexposed – exposed to other psychotropic drugs** NA	**Zolpidem and other psychotropic drugs (any time)** NA	NR P=0.49	32 per 1000[555]	Not estimable
Evidence Statement: *Maternal use of zolpidem at any time during pregnancy does not appear to be associated with an increased risk of respiratory difficulty (very low certainty evidence)*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis.
b. Downgraded one level due to indirectness; compared with a general population.
c. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25 or SMD –0.5/0.5, no measure of precision available, or no events.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.
Abbreviations: CI, confidence interval; NA, not available; NR, not reported; OBS, observational studies; OR, odds ratio; RE, risk estimate; RR, relative risk; SMD, standardised mean difference.

[554] Juric 2009.
[555] Malm 2015.

Table D3-36 Evidence Profile table: zopiclone

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Additional risk of bias**[556]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control**[557]	**Risk with intervention**[558]
Major malformation: see Section AppD4.1.4.1.2											
Heart anomalies *19,599* (1 – OBS)[559]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Zopiclone (first trimester)** NA	OR 0.93 (0.40, 2.15)	28 per 1000[560]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of zopiclone during the first trimester of pregnancy and major malformation in the newborn is uncertain.*											
Cardiac malformation: see Section AppD4.1.4.2.2											
Heart anomalies *19,599* (1 – OBS)[561]	Serious(a)	NA	None	Serious(b)	None	○○○○ Inadequate	**Unexposed** NA	**Zopiclone (first trimester)** NA	OR 2.03 (0.69, 6.02)	6 per 1000[562]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of zopiclone during the first trimester of pregnancy and cardiac malformation in the newborn is uncertain.*											
Miscarriage: see Section AppD4.1.4.4.2											
80 (1 – OBS)[563]	None	NA	Serious(b)	Unknown(c)	None	○○○○ Inadequate	**Unexposed** NA	**Zopiclone (any time)** NA	NR 17.5% vs. 7.5% *NR*	81 per 1000[564]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of zopiclone at any time during pregnancy and miscarriage is uncertain.*											

[556] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns will be noted and may result in further downgrading of the quality of the evidence.
[557] Based on average risk from unexposed, depressed control groups of population-based cohort studies providing data for that outcome.
[558] Calculated by multiplying relative effect by control risk.
[559] Ban 2014b.
[560] Ban 2014a (depressed/anxious population).
[561] Ban 2014b.
[562] Ban 2014a, Huybrechts 2014a, Petersen 2016, Margulis 2013 (depressed/anxious population).
[563] Diav-Citrin 1999.
[564] Almeida 2016 and Ban 2012.

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[556]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)** *P value*	**Anticipated absolute effects**	
							Unexposed	**Exposed**		**Risk with control[557]**	**Risk with intervention[558]**
Preterm birth: see Section AppD4.1.4.5.2											
69 (1 – OBS)[565]	Serious(d)	NA	Serious(b)	Unknown(c)	None	○○○○ Inadequate	**Unexposed** NA	**Zopiclone (any time)** NA	NR 21.9% vs. 5.4% *0.07*	60 per 1000[566]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of zopiclone at any time during pregnancy and preterm birth is uncertain.*											
Small for gestational age: see Section AppD4.1.4.6.2											
68 (1 – OBS)[567]	Serious(d)	NA	Serious(b)	Unknown(c)	None	○○○○ Inadequate	**Unexposed** NA	**Zopiclone (any time)** NA	NR 6.3% vs. 5.6% *NR*	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of zopiclone at any time during pregnancy and being small for gestational age is uncertain.*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and stillborn from the analysis.
b. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25 or SMD –0.5/0.5, no measure of precision available, or no events.
c. Downgraded one level due to moderate risk of bias; potential for selection bias due to exclusion of miscarriages and stillborn from the analysis.
d. Downgraded one level due to moderate risk of bias; substantial number of exposures excluded from analysis.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; NA, not available; NR, not reported; OBS, observational studies; OR, odds ratio; RE, risk estimate; RR, relative risk; SMD, standardised mean difference.

[565] Diav-Citrin 1999.
[566] Malm 2015 (depressed population).
[567] Diav-Citrin 1999.

D3.1.5 Lithium

The following section presents the Evidence Profile tables for lithium use. The quantity of evidence available for the assessment of lithium was limited compared with other pharmacological agents. However, there was sufficient evidence available to limit the final analyses to those that adjusted risk estimates for confounding, or included a comparator population with a psychiatric diagnosis.

It should be noted that the Expert Working Group (EWG) and Harms Expert Subcommittee identified Ebstein's anomaly, a congenital heart defect, as an additional outcome of interest that may be associated with maternal exposure to lithium during pregnancy. As such, additional data relating to this specific outcome was also assessed.

As the evidence was based on data from cohort and case-control studies, in many cases the results were presented as odds ratios instead of relative risks. Where the baseline risk was < 7%, it was assumed that the odds ratio approximates the relative risk and the results were interpreted as relative risks. Where baseline risk was not available in a pregnant unexposed population with a mental health disorder, the baseline risks identified for a depressed population were used as a proxy.

The following observations were made regarding the body of evidence for lithium harms:

- No meta-analyses were feasible for any outcome, so the body of evidence for each outcome comprised single studies.
- Only two of the included studies adjusted for potential confounding in their analyses (for select outcomes only), and only one of those studies adjusted for mental health indication.
- Three studies included an unexposed comparator group with a mental health diagnosis.

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). The NICE 2015 SR noted that there was limited evidence for lithium due to the small number of studies that provided extractable data.

As none of the pooled risk estimates reported in NICE 2015 exclusively used data adjusted for potential confounders, it was necessary to update the literature search and assess the evidence from original comparative studies. A total of eight comparative studies were identified, six from the NICE 2015 and Galbally 2010 SRs and a further two (Diav-Citrin 2014; Källén 2013) from the updated literature search. Where available, studies that adjusted for potential confounders, or used a comparator population with a psychiatric diagnosis, have been designated as primary evidence for the outcomes of interest and are included in the EP table in preference to unadjusted data. Data were available for outcomes relating to lithium exposure during pregnancy and major malformations, cardiac malformations, septal malformations, miscarriage, stillbirth, neonatal mortality and preterm birth.

A summary of the characteristics of the individual included studies can be found in **Table AppD2-21** in **Appendix D2.1.5.2**. A detailed discussion of the evidence can be found in **Appendix D4.1.5**.

Table D 3-37 presents a summary of the results of the Evidence Review of lithium and the location of the detailed assessment of the certainty of evidence in the evidence profile table. The findings suggest that maternal exposure to lithium during pregnancy may be associated with an increased risk of cardiac malformation, miscarriage and neonatal mortality, while the evidence was inadequate and the risk uncertain for major and septal malformations, Ebstein's anomaly, still birth and preterm birth.

Although several studies compared birthweights in babies exposed to lithium during pregnancy versus unexposed controls, only one study was identified that assessed the association between lithium use and being large for gestational age (Troyer 1993). 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.

As noted, comparative data are also shown for the association between lithium exposure and Ebstein's anomaly of the heart in the offspring. In the 1970's, a very strong association was suggested between lithium treatment during pregnancy and Ebstein's anomaly. A retrospective analysis of data from the Danish Register of Lithium Babies suggested a high risk of Ebstein's anomaly: 6 out of 225 (2.7%) exposed children versus an incidence of 1 in 20,000 (0.005%) in the general population (Weinstein et al, 1976). However, this is now understood to be a gross overestimation due to voluntary reporting bias. Several subsequent controlled epidemiologic studies found no association between lithium use and Ebstein's anomaly, and a 1994 review of epidemiological data concluded that the teratogenic risk of first trimester lithium exposure is lower than originally suggested (Cohen et al, 1994).

Four of the comparative studies cited in the two identified SRs did not provide data for the current review but are noteworthy as they specifically relate to Ebstein's anomaly. Correa-Villasenor 1994 reviewed 44 cases of Ebstein's anomaly and 3,572 controls without cardiovascular malformations from the Baltimore-Washington Infant Study (BWIS). None of the case mothers reported lithium use during pregnancy but there were two lithium exposures in the control group. 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 1990 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-Auverge monitoring system.

Table D 3-37 Summary of results of the Evidence Review for lithium

Intervention	**Increased/may be increased risk of harm** Outcome Certainty of evidence	**Appears to be no increased risk of harm** Outcome Certainty of evidence	**Decreased/may be decreased risk of harm** Outcome Certainty of evidence	**Uncertain** Outcome ○○○○	**Evidence profile table**
Lithium	Cardiac malformation ●○○○ Miscarriage ●○○○ Neonatal mortality ●○○○			Major malformation Septal malformation Ebstein's anomaly Stillbirth Preterm birth	**Table D3-38**

Note: All comparisons are against non-exposure, unless otherwise stated. Certainty of evidence gradings are as follows: ●●●● – high certainty; ●●●○ – moderate certainty; ●●○○ – low certainty; ●○○○ – very low certainty; ○○○○ – inadequate certainty.

Table D3-38 Evidence Profile table: lithium harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias**[568]	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control**[569]	**Risk with intervention**[570]
Major malformations: see Section AppD4.1.5.1.2											
(1 – OBS)[571]	Serious (a)	NA	Serious (b)	Serious (d)	None	○○○○ Inadequate	**Unexposed – not adjusted for indication**[572] (N = 1,575,613)	**Lithium (pregnancy)**[573] (N = 234)	ARR 1.09 (0.52, 2.00)	28 per 1000[574]	-
(1 – OBS)[575]	Serious (c)	NA	None	Serious (d)	None	○○○○ Inadequate	**Unexposed – bipolar disorder** (N = 61)	**Lithium (1st trimester)** (N = 123)	RR 1.98 (0.43, 9.06)[576]	28 per 1000[574]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lithium during early pregnancy and major malformation in the newborn is uncertain.*											
Cardiac malformations: see Section AppD4.1.5.2.2											
(1 – OBS)[575]	Serious (e)	NA	None	None	None	●○○○ Very low	**Unexposed – adjusted for bipolar disorder**[577] NR[578]	**Lithium (1st trimester)** NR[578]	**ARR 4.75 (1.11, 20.36)**	6 per 1000[579]	29 per 1000 (7, 122)
(1 – OBS)[575]	Serious (c)	NA	None	Serious (d)	None	○○○○ Inadequate	**Unexposed – bipolar disorder** (N = 61)	**Lithium (1st trimester)** (N = 123)	RR 1.24 (0.25, 6.21)[576]	6 per 1000[579]	-
Evidence Statement: *Maternal use of lithium during the first trimester of pregnancy may be associated with cardiac malformation, from an absolute risk of 0.6% to 2.9% (very low certainty evidence).*											

[568] As the quality of the evidence starts at 'low' for observational studies, the main biases associated with observational study design have already been taken into account. Any additional outcome-specific or other methodological concerns are noted and may result in further downgrading of the quality of the evidence.
[569] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[570] Calculated by multiplying relative effect by control risk.
[571] Källén 2013. Outcome captured as 'relatively severe malformations'.
[572] Adjusted for year of birth, maternal age (5-year class), parity (1-4+), smoking in early pregnancy and BMI.
[573] 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.
[574] Ban 2014a (depressed/anxious population).
[575] Diav-Citrin 2014
[576] Unadjusted risk calculated post hoc from crude data using Review Manager 5.3
[577] Adjusted for pregnancy order, smoking 10 or more cigarettes a day, bipolar disorder.
[578] Cases in analysis: 822

[579] Petersen 2016, Ban 2014a, Huybrechts 2014a and Margulis 2013(depressed/anxious population).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[568]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[569]**	**Risk with intervention[570]**
Septal malformations: see Section AppD4.1.5.3.2											
(1 – OBS)[575]	Serious (c)	NA	None	Serious (d)	None	○○○○ Inadequate	**Unexposed – bipolar disorder** (N = 61)	**Lithium (1st trimester)** (N = 123)	RR 1.49 (0.16, 14.01)[576]	3 per 1000[580]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lithium during the first trimester of pregnancy and septal malformation in the newborn is uncertain.*											
Ebstein's anomaly: see Section AppD4.1.5.4.2											
(1 – OBS)[575]	Serious (c)	NA	None	Serious (d)	None	○○○○ Inadequate	**Unexposed – bipolar disorder** (N = 61)	**Lithium (1st trimester)** (N = 123)	RR 1.50 (0.06, 36.29)[576]	<1 per 1000[581]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lithium during the first trimester of pregnancy and Ebstein's anomaly in the newborn is uncertain.*											
Miscarriage: see Section AppD4.1.5.5.2											
(1 – OBS)[575]	Serious (e)	NA	None	None	None	●○○○ Very low	**Unexposed – adjusted for bipolar disorder[582]** NR[583]	**Lithium (pregnancy)[573]** NR[583]	**AOR 1.94 (1.08, 3.48)**	81 per 1000[584]	NE
(1 – OBS)[575]	Serious (c)	NA	None	Serious (d)	None	○○○○ Inadequate	**Unexposed – bipolar disorder** (N = 72)	**Lithium (1st trimester)** (N = 183)	RR 1.97 (0.86, 4.53)[576]	81 per 1000[584]	-
Evidence Statement: *Maternal use of lithium during early pregnancy may be associated with miscarriage (very low certainty evidence).*											

[580] The Bérard 2015 study used an insured population and as such the prevalence of septal malformations in this study (1.83%) is not likely to be representative of the general population with depression. To estimate the prevalence, it is assumed that 50% of cardiac malformations are septal, resulting in an estimate of 0.3%.
[581] Refers to risk in the general population (0.005%) from Weinstein et al (1976).
[582] Adjusted for maternal age, previous miscarriage, smoking status, bipolar disorder, gestational age at initial contact with the information centre.
[583] Cases in analysis: 911
[584] Based on an unexposed/depressed population (Almeida 2016 and Ban 2012).

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* **(No. studies)**	**Additional risk of bias[568]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[569]**	**Risk with intervention[570]**
Stillbirth: see Section AppD4.1.5.6.2											
(1 – OBS)[575]	Serious (e)	NA	None	Serious (d)	None	○○○○ Inadequate	**Unexposed – bipolar disorder** (N = 72)	**Lithium (pregnancy)[573]** (N = 183)	RR 2.78 (0.15, 53.10) [585]	Unknown	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lithium during early pregnancy and stillbirth is uncertain.*											
Neonatal mortality: see Section AppD4.1.5.6.2											
(1 – OBS)[586]	None	NA	None	Serious (d)	None	●○○○ Very low	**Unexposed – manic depression inpatients** (N = 80)	**Lithium – manic depression inpatients (1st trimester)** (N = 41)	RR 17.36 (0.96, 314.78)[585]	5 per 1000[587]	87 per 1000 (5, 1574)
Evidence Statement: *Maternal use of lithium for severe manic depression[588] during the first trimester of pregnancy may be associated with neonatal mortality (very low certainty evidence).*											
Preterm birth: see Section AppD4.1.5.7.2											
(1 – OBS)[575]	Serious (c)	NA	None	Serious (d)	None	○○○○ Inadequate	**Unexposed – bipolar disorder** (N = 59)	**Lithium (pregnancy)[573]** (N = 131)	RR 1.35 (0.57, 3.23)[585]	60 per 1000[589]	-
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lithium during early pregnancy and preterm birth is uncertain.*											

Footnotes:
a. Downgraded one level due to moderate risk of bias; potential selection bias due to not capturing potential excess malformations coinciding with miscarriage, abortion or stillbirth.
b. Downgraded one level due to indirectness caused by use of control group without a mental health disorder diagnosis, with no adjustment for indication.
c. Downgraded one level due to moderate risk of bias: inadequate adjustment for indication – restricting comparator population to only bipolar disorder.
d. Downgraded one level due to imprecision (95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25).
e. Downgraded one level due to moderate risk of bias: inadequate adjustment for indication –adjusting for only bipolar disorder where 33% of exposure group had other diagnoses.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: AD, antidepressant; AOR, adjusted odds ratio; ARR, adjusted relative risk; CI, confidence interval; NE, not estimable; NR, not reported; OBS, observational studies; OR, odds ratio; RR, relative risk; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[585] Unadjusted risk calculated post hoc from crude data using Review Manager 5.3
[586] Källén 1983
[587] Based on an unexposed/depressed population (Ban 2012).
[588] Women in the study had been treated as an inpatient for manic depression and were therefore likely to have severe disease.
[589] Based on an unexposed/depressed population (Malm 2015).

D3.2 COMPLEMENTARY

The following section presents the Evidence Profile tables for the complementary treatments examined: omega-3 fatty acids, St John's wort and Gingko biloba. These specific complementary agents were identified by the Harms Expert Subcommittee as being used by pregnant women with mental health issues. No intervention-specific rules were required for downgrading of the certainty of this body of evidence.

D3.2.1 Omega-3 fatty acids

A summary of the characteristics of the individual included studies can be found in **Table AppD2-22** in **Appendix D2.2.1.1**. A detailed discussion of the evidence can be found in **Appendix D4.2.1**.

Table D 3-39 presents a summary of the results of the Evidence Review of omega-3 fatty acids and the location of the detailed assessment of the certainty of evidence in the evidence profile table. All comparisons are for exposure versus non-exposure, unless otherwise stated. It should be noted that the assessment of the harms associated with omega-3 fatty acids was limited to SRs of RCTs, due to the large amount of RCT evidence available; all of this evidence has been conducted in a general, rather than a population with a mental health disorder. As this evidence is based on data from RCTs, for all outcomes, results were presented as RRs of MDs, and risks with control could be calculated directly from the study results.

Five SRs were identified, although the assessment of the evidence shown below was limited to the two most recent that reported pregnancy and birth outcomes (Kar 2016 and Saccone 2016b) and one SR reporting on neurodevelopmental outcomes (Gould 2013).

The findings of the Kar 2016 SR suggest that maternal use of omega-3 fatty acids during pregnancy provides some benefit in terms of reducing the rate of preterm birth, and may provide benefit in reducing the risk of the infant being small for gestational age. Interestingly, when Saccone 2016b limited the population to women with a previous preterm birth or small for gestational age infant, these benefits were not seen. Saccone 2016b also showed a reduction in neonatal mortality associated with use of omega-3 fatty acids from prior to 20 weeks' gestation. Finally, Gould 2013 showed no adverse impact of exposure to omega-3 fatty acids during pregnancy and cognitive, motor and language development assessed at various ages; a significant benefit of omega-3 fatty acids on cognitive development was seen as 2-5 years.

In summary, there is no evidence available to suggest that the use of omega-3 fatty acids during pregnancy has an adverse effect on the fetus, infant or child.

Table D 3-39 Summary of results of the Evidence Review for omega-3 fatty acids

Intervention	**Increased/may be increased risk of harm** Outcome Certainty of evidence	**Appears to be no increased risk of harm** Outcome Certainty of evidence	**Decreased/may be decreased risk of harm** Outcome Certainty of evidence	**Uncertain** Outcome ○○○○	**Evidence profile table**
		Cognitive development < 2 years and 5-12 years ●●●○/●●●● Motor development (any time) ●●●● Language development (< 5 years) ●●●○/●●●●	Preterm birth ●●●○ SFGA ●●●○ Neonatal mortality ●●●● Cognitive development (2-5 years) ●●●●		**Table D3-40**

Abbreviations: SFGA, small for gestational age.

Note: All comparisons are against non-exposure, unless otherwise stated. Certainty of evidence gradings are as follows: ●●●● – high certainty; ●●●○ – moderate certainty; ●●○○ – low certainty; ●○○○ – very low certainty; ○○○○ – inadequate certainty.

Table D3-40 Evidence Profile table: omega-3 fatty acids

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[590]**	**Risk with intervention[591]**
Preterm Birth: see Section AppD4.2.1.1.1											
Early preterm birth (< 34 weeks) *4,193* (6 – RCT)[592]	None	None	None	None	None	●●●● High	**Placebo** 3.2%	**Omega-3 fatty acids** 1.3%	**RR 0.42 (0.27, 0.66)**	30 per 1,000[593]	13 per 1,000 (8, 20)
Early preterm birth (< 34 weeks) – high risk *3,670* (3 – RCT)[594]	None	None[595]	None	None	None	●●●● High	**Placebo** NR	**Omega-3 fatty acids** NR	**RR 0.36 (0.18, 0.71)**	30 per 1,000[596]	11 per 1000 (5, 21)
Early preterm birth (< 34 weeks) – any risk *523* (3 – RCT)[597]	None	None[598]	None	Serious(a)	None	●●●○ Moderate	**Placebo** NR	**Omega-3 fatty acids** NR	RR 0.50 (0.24, 1.06)	30 per 1,000[599]	15 per 1000 (7, 32)
Preterm birth (< 37 weeks) 5,980 (9 – RCTs)[600]	None	None	None	None	None	●●●● High	**Placebo** 9.1%	**Omega-3 fatty acids** 7.4%	**RR 0.83 (0.70, 0.98)**	60 per 1,000[601]	50 per 1,000 (42, 59)
Preterm birth (< 37 weeks) – high risk 814 (4 – RCTs)[602]	None	None[603]	None	Serious(a)	None	●●●○ Moderate	**Placebo** NR	**Omega-3 fatty acids** NR	RR 0.83 (0.61, 1.11)	60 per 1,000[604]	50 per 1000 (37, 67)

[590] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[591] Calculated by multiplying relative effect by control risk; it is not considered appropriate to calculate the risk with intervention where the quality of the evidence is inadequate.
[592] Kar 2016 SR (Includes Carlson 2013, Makrides 2010, Mardones 2008, Onwude 1995, Olsen 2000, and Bulstra-Ramakers 1995).
[593] Estimated based on an untreated, depressed population (Malm 2015).
[594] Kar 2016 SR (included studies not reported).
[595] Heterogeneity not reported but largely consistent results across all available studies.
[596] Estimated based on an untreated, depressed population (Malm 2015).
[597] Kar 2016 SR (included studies not reported).
[598] Heterogeneity not reported but largely consistent results across all available studies.
[599] Estimated based on an untreated, depressed population (Malm 2015).
[600] Kar 2016 SR (Includes Carlson 2013, Makrides 2010, Mardones 2008, Onwude 1995, Olsen 2000, Bulstra-Ramakers 1995, Olsen 1992, Ramakrishnan 2010, and Smuts 2003).
[601] Estimated based on an untreated, depressed population (Malm 2015).
[602] Kar 2016 SR (included studies not reported).
[603] Heterogeneity not reported but largely consistent results across all available studies.
[604] Estimated based on an untreated, depressed population (Malm 2015).

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[590]**	**Risk with intervention[591]**
Preterm birth (< 37 weeks) – any risk 5,166 (5 – RCTs)[605]	None	None[606]	None	Serious(a)	None	●●●○ Moderate	**Placebo** NR	**Omega-3 fatty acids** NR	RR 0.83 (0.66, 1.05)	60 per 1,000[607]	50 per 1000 (40, 63)
Preterm birth (< 37 weeks) 5,689 (8 – RCTs)[608]	None	None[609]	None	None	None	●●●● High	**Placebo** NR	**Omega-3 fatty acids (> 400 mg)** NR	**RR 0.83 (0.69, 1.00)**	60 per 1,000[610]	50 per 1000 (41, 60)
Preterm birth (< 37 weeks) 291 (1 – RCT)[611]	None	NA	None	Serious(a)	None	●●●○ Moderate	**Placebo** NR	**Omega-3 fatty acids (< 400 mg)** NR	RR 0.86 (0.44, 1.69)	60 per 1,000[612]	52 per 1000 (26, 101)
Preterm birth (< 37 weeks) 5,156 (7 – RCT)[613]	None	None[614]	None	Serious(a)	None	●●●○ Moderate	**Placebo** NR	**Omega-3 fatty acids (< 24 weeks)** NR	RR 0.84 (0.69, 1.03)	60 per 1,000[615]	50 per 1000 (41, 62)
Preterm birth (< 37 weeks) 824 (2 – RCT)[616]	None	None[617]	None	Serious(a)	None	●●●○ Moderate	**Placebo** NR	**Omega-3 fatty acids (< 24 weeks)** NR	RR 0.75 (0.45, 1.25)	60 per 1,000[618]	45 per 1000 (27, 75)

[605] Kar 2016 SR (included studies not reported).
[606] Heterogeneity not reported but largely consistent results across all available studies.
[607] Estimated based on an untreated, depressed population (Malm 2015).
[608] Kar 2016 SR (included studies not reported).
[609] Heterogeneity not reported but largely consistent results across all available studies.
[610] Estimated based on an untreated, depressed population (Malm 2015).
[611] Kar 2016 SR (included studies not reported).
[612] Estimated based on an untreated, depressed population (Malm 2015).
[613] Kar 2016 SR (included studies not reported).
[614] Heterogeneity not reported but largely consistent results across all available studies.
[615] Estimated based on an untreated, depressed population (Malm 2015).
[616] Kar 2016 SR (included studies not reported).
[617] Heterogeneity not reported but largely consistent results across all available studies.
[618] Estimated based on an untreated, depressed population (Malm 2015).

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[590]**	**Risk with intervention[591]**
Women with no prior preterm birth 3493 (7 RCT)[619]	None	None	None	Serious(a)	None	●●●○ Moderate	**Placebo** 9.1%	**Omega-3 fatty acids** 7.7%	RR 0.90 (0.72, 1.11)	60 per 1,000[620]	54 per 1000 (43, 67)
Evidence Statements: *Maternal use of omega-3 fatty acids at any time during pregnancy is associated with a decreased risk of early preterm birth (< 34 weeks), from an absolute risk of 3% to 1.3% (high certainty evidence).* *Maternal use of omega-3 fatty acids at any time during pregnancy is associated with a decreased risk of preterm birth (< 37 weeks), from an absolute risk of 6% to 5% (high certainty evidence).* *Maternal use of omega-3 fatty acids at any time during pregnancy in women with no prior preterm birth is not associated with a decreased risk of preterm birth (moderate certainty evidence)*											
Small for gestational age: see Section AppD4.2.1.1.2											
5,469 (8 – RCTs)[621]	None	None	None	Serious(a)	None	●●●○ Moderate	**Placebo** NR	**Omega-3 fatty acids** NR	RR 0.82 (0.66, 1.03)	Unknown	Not estimable
History of previous SGA infant 575 (3 – RCTs)[622]	None	None	None	Serious(a)	None	●●●○ Moderate	**Placebo** NR	**Omega-3 fatty acids** NR	RR 1.13 (0.83, 1.54)	Unknown	Not estimable
Evidence Statements: *Maternal use of omega-3 fatty acids at any time during pregnancy may be associated with a decreased risk of the infant being small for gestational age; however, the finding was not statistically significant (moderate certainty evidence).* *Maternal use of omega-3 fatty acids at any time during pregnancy in women with a history of small for gestational age infants is not associated with an increased risk of the infant being small for gestational age (moderate certainty evidence).*											
Neonatal Deaths: see Section AppD4.2.1.1.3											
6,751 (7 – RCTs)[623]	None	None	None	None	None	●●●○ Moderate	**Placebo** NR	**Omega-3 fatty acids** NR	RR 0.51 (0.26, 1.01)	5 per 1000[624]	3 per 1000 (1, 5)

[619] Saccone 2016b SR (included Olsen 1992, Bulstra-Ramakers 1994, Onwude 1995, Malcolm 2003, Tofail 2006, Makrides 2010, Escolano-Margarit 2011).
[620] Estimated based on an untreated, depressed population (Malm 2015).
[621] Kar 2016 SR (Includes Makrides 2010, Mardones 2008, Onwude 1995, Olsen 2000, Bulstra-Ramakers 1995, Olsen 1992, Ramakrishnan 2010, and Smuts 2003).
[622] Saccone 2016b SR (Includes Onwude 1995, Olsen 2000, Bulstra-Ramakers 1995).
[623] Kar 2016 SR (Includes Makrides 2010, Olsen 2000, Bulstra-Ramakers 1995, Olsen 1992, Ramakrishnan 2010).
[624] Estimated based on an untreated, depressed population (Ban 2012).

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[590]**	**Risk with intervention[591]**
2,462 (2 – RCTs)[625]	None	None	None	None	None	●●●● High	**Placebo** 1.2%	**Omega-3 fatty acids (from ≤ 20 w gestation)** 0.3%	**RR 0.27 (0.09, 0.79)**	5 per 1000[626]	1 per 1000 (<1, 4)
Evidence Statement: *Maternal use of omega-3 fatty acids from ≤ 20 weeks gestation is associated with a decreased risk of neonatal mortality; from an absolute risk of 0.5% to 0.1% (high certainty evidence).*											
Cognitive development: see Section AppD4.2.1.1.4											
< 12 months[627] *249* (1 – RCT)[628]	Serious(b)	NA	None	None	None	●●●○ Moderate	**Placebo** NA	**Omega-3 LCPUFA (P & L)** NA	MD 1.00 (-0.96, 2.96)	NA	-
12-24 months[629] *801* (2 – RCT)[630]	None	None	None	None	None	●●●● High	**Placebo** NA	**Omega-3 LCPUFA (P & L)** NA	MD -0.08 (-1.72, 1.57)	NA	-
2-5 years[631] *156* (2 – RCT)[632]	None	None	None	None	None	●●●● High	**Placebo** NA	**Omega-3 LCPUFA (P & L)** NA	**MD 3.92 (0.77, 7.08)**	NA	-
5-12 years[633] *225* (2 – RCT)[634]	None	None	None	None	None	●●●● High	**Placebo** NA	**Omega-3 LCPUFA (P & L)** NA	MD 0.36 (-2.61, 3.32)	NA	-
12-24 months[635] *726* (1 – RCT)[636]	None	NA	None	None	None	●●●● High	**Placebo** NA	**Omega-3 LCPUFA (P only)** NA	MD 0.06 (-1.66, 1.78)	NA	-

[625] Saccone 2016b (includes Bulstra-Ramakers 1994 and Makrides 2010).
[626] Estimated based on an untreated, depressed population (Ban 2012).
[627] Cognitive development measured using the BSID-II.
[628] Gould 2013 SR (includes Tofail 2006).
[629] Cognitive development measured using the BSID-II and III.
[630] Gould 2013 SR (includes Van Goor 2011 and Makrides 2010).
[631] Cognitive development measured using the GMDS and K-ABC.
[632] Gould 2013 SR (includes Dunstan 2008 and Helland 2003).
[633] Cognitive development measured using the K-ABC.
[634] Gould 2013 SR (includes Campoy 2011 and Helland 2008).
[635] Cognitive development measured using BSID III.
[636] Gould 2013 SR (includes Makrides 2010).

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[590]**	**Risk with intervention[591]**
2-5 years[637] *72* (1 – RCT)[638]	Serious(b)	NA	None	Serious(a)	None	●●○○ Low	**Placebo** NA	**Omega-3 LCPUFA (P only)** NA	MD 3.70 (-1.02, 8.42)	NA	-
5-12 years[639] *82* (1 – RCT)[640]	Unknown (b)[641]	NA	None	None	None	●●●○ Moderate	**Placebo** NA	**Omega-3 LCPUFA (P only)** NA	MD 0.00 (-5.52, 5.52)	NA	-
Evidence Statements: *Maternal use of omega-3 fatty acids at any time during pregnancy or lactation is not associated with a reduction in cognitive development at < 12 months, 12-24 months and 5-12 years (moderate to high certainty evidence).* *Maternal use of omega-3 fatty acids at any time during pregnancy or lactation is associated with an improvement in cognitive development at 2-5 years (high certainty evidence).* *Maternal use of omega-3 fatty acids at any time during pregnancy only is not associated with a reduction in cognitive development at 2-5 years (low to high certainty evidence).*											
Motor development: see Section AppD4.2.1.1.5											
< 12 months[642] *249* (1 – RCT)[643]	Serious(b)	NA	None	None	None	●●●○ Moderate	**Placebo** NA	**Omega-3 LCPUFA (P & L)** NA	MD 1.20 (-1.41, 3.81)	NA	-
12-24 months[644] *801* (2 – RCT)[645]	None	Very serious(c)	None	Serious(a)	None	●○○○ Very low	**Placebo** NA	**Omega-3 LCPUFA (P & L)** NA	MD 1.52 (-2.29, 5.32)	NA	-
2-5 years[646] *72* (1 – RCT)[647]	None	NA	None	Serious(a)	None	●●●○ Moderate	**Placebo** NA	**Omega-3 LCPUFA (P & L)** NA	MD 4.60 (-1.14, 10.34)	NA	-

[637] Cognitive development measured using the GMDS.
[638] Gould 2013 SR (includes Dunstan 2008).
[639] Cognitive development measurement used not reported.
[640] Gould 2013 SR (includes Campoy 2011).
[641] Quality for Campoy 2011 not reported in Gould 2013. Assumed to have a moderate risk of bias and downgraded one level for serious risk of bias.
[642] Motor development measured using BSID II.
[643] Gould 2013 (includes Tofail 2006).
[644] Motor development measured using BSID II and III.
[645] Gould 2013 SR (includes Van Goor 2011 and Makrides 2010).
[646] Motor development measured using GMDS.
[647] Gould 2013 SR (includes Dunstan 2008).

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates**		**Risk estimate (95% CI)** ***P value***	**Anticipated absolute effects**	
							With control	**With intervention**		**Risk with control[590]**	**Risk with intervention[591]**
12-24 months[648] *726* (1 – RCT)[649]	None	NA	None	None	None	●●●● High	**Placebo** NA	**Omega-3 LCPUFA (P only)** NA	MD 0.06 (-1.52, 1.64)	NA	-
Evidence Statements: *Maternal use of omega-3 fatty acids at any time during pregnancy or lactation is not associated with a reduction in motor development at < 12 months, 12-24 months and 2-5 years (very low to moderate certainty evidence).* *Maternal use of omega-3 fatty acids at any time during pregnancy only is not associated with a reduction in motor development at 12-24 months (high certainty evidence).*											
Language development: see Section AppD4.2.1.1.6											
12-24 months[650] *726* (1 – RCT)[651]	None	NA	None	None	None	●●●● High	**Placebo** NA	**Omega-3 LCPUFA (P only)** NA	MD -1.47 (-3.58, 0.64)	NA	-
2-5 years[652] *70* (1 – RCT)[653]	None	NA	None	Serious(a)	None	●●●○ Moderate	**Placebo** NA	**Omega-3 LCPUFA (P only)** NA	MD 3.90 (-0.73, 8.53)	NA	-
Evidence Statement: *Maternal use of omega-3 fatty acids at any time during pregnancy only is not associated with a reduction in language development at 12-24 months and 2-5 years (moderate to high certainty evidence).*											
Footnotes: a. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events. b. Downgraded two levels due to high risk of bias; unknown random sequence generation and allocation concealment, and high risk of bias for follow-up and other bias. c. Downgraded two levels due to substantial heterogeneity (I^2 > 60%).											

Abbreviations: BSID, Bayley Scales of Infant Development; CI, confidence interval; GMDS, Griffiths Mental Development Scales; K-ABC, Kaufman Assessment Battery for Children; MD, mean difference; NA, not available; NR, not reported; P, pregnancy; P & L, pregnancy and lactation; PPVT, Peabody Picture Vocabulary Test; RCT, randomised controlled trial; RR, relative risk, w weeks.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

[648] Motor development measured using BSID II.
[649] Gould 2013 SR (includes Makrides 2010).
[650] Language development measured using
[651] Gould 2013 (includes Makrides 2010).
[652] Language development measured using PPVT.
[653] Gould 2013 SR (includes Dunstan 2008).

D3.2.2 St John's wort

A summary of the characteristics of the individual included studies can be found in **Table AppD2-27** in **Appendix D2.2.2.2**. A detailed discussion of the evidence for each group or individual intervention type and outcome can be found in **Appendix D4.2.2**.

Table D 3-41 presents a summary of the results of the Evidence Review of St John's wort and the location of the detailed assessment of the certainty of evidence in the evidence profile table. All comparisons are for exposure versus non-exposure, unless otherwise stated. Three SRs were identified via the searches; however, these each included only one to two cohort studies and two case reports and described them narratively. Two cohort studies were identified; the one by Moretti 2009 (based on data from the Mother-risk program in Canada) was included preferentially because it adjusted for potential confounders. Due to the inadequate certainty of this study, it was determined that the effect of antenatal or post-natal exposure to St John's wort on fetal, infant or child harms is uncertain. Moretti 2009 note 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 D 3-41 Summary of results of the Evidence Review for St John's wort

Intervention	**Increased/may be increased risk of harm** Outcome Certainty of evidence	**Appears to be no increased risk of harm** Outcome Certainty of evidence	**Decreased/may be decreased risk of harm** Outcome Certainty of evidence	**Uncertain** Outcome ○○○○	**Evidence profile table**
St John's wort				Major malformation Major malformation (vs ADs) Preterm birth Preterm birth (vs ADs)	**Table D3-42**

Abbreviations: AD, antidepressant.

Note: All comparisons are against non-exposure, unless otherwise stated. Certainty of evidence gradings are as follows: ●●●● – high certainty; ●●●○ – moderate certainty; ●●○○ – low certainty; ●○○○ – very low certainty; ○○○○ – inadequate certainty.

Table D3-42 Evidence Profile table: St John's wort

Certainty assessment							Summary of findings				
Outcome subgroup (No. studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Population (N)		Risk estimate (95% CI) or % vs. %; P value	Anticipated absolute effects	
							Non-exposure	Exposure		Risk with control[654]	Risk with intervention[655]
Major malformation: see Section AppD4.2.2.2.1											
1 – OBS[656]	Very serious(a)	NA	Serious(b)	Serious(c)[657]	None	○○○○ Inadequate	**Unexposed** 56	**St John's wort (any time)** 38	5.3% vs. 0%; 0.20[658]	28 per 1000[659]	-
1 – OBS[656]	Very serious(a)	NA	None	Serious(c)[660]	None	○○○○ Inadequate	**Antidepressants[661] (any time)** 48	**St John's wort (any time)** 38	5.3% vs. 4.2%; 0.81[658]	42 per 1000[656]	-
Evidence Statements: *Due to the inadequate certainty of the evidence, any association between maternal use of St John's wort at any time during pregnancy and an increased risk of major malformation in the newborn is uncertain.* *Due to the inadequate certainty of the evidence, any additional risk of major malformation in the newborn associated with maternal use of St John's wort at any time during pregnancy, compared with maternal use of conventional pharmacologic treatment for depression during the same period, is uncertain.*											
Preterm birth: see Section AppD4.2.2.2.3											
1 - OBS[656]	Very serious(d)	NA	Serious(b)	Serious(c)[662]	None	○○○○ Inadequate	**Unexposed** 45	**St John's wort (any time)** 43	4.7% vs. 13.3%; 0.18[663]	60 per 1000[664]	-

[654] Based on average risk from unexposed, depressed control groups of population-based cohort studies.
[655] Calculated by multiplying relative effect by control risk; it is not considered appropriate to calculate the risk with intervention where the quality of the evidence is inadequate.
[656] Moretti 2009.
[657] Based on post hoc calculation of risk estimate using Review Manager; RR 7.31 (0.36, 148.09).
[658] Calculated post hoc using Review Manager.
[659] Ban 2014a (depressed/anxious population).
[660] Based on post hoc calculation of risk estimate using Review Manager; RR 1.26 (0.19, 8.56).
[661] Described as conventional pharmacological treatment.
[662] Based on post hoc calculation of risk estimate using Review Manager; RR 0.35 (0.07, 1.63).
[663] Calculated post hoc using Review Manager.
[664] Petersen 2016, Ban 2014a, Huybrechts 2014a and Margulis 2013(depressed/anxious population).

Certainty assessment							Summary of findings				
Outcome subgroup (No. studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI) or % vs. %; P value**	**Anticipated absolute effects**	
							Non-exposure	**Exposure**		**Risk with control[654]**	**Risk with intervention[655]**
1 – OBS[656]	Very serious(d)	NA	None	None	None	○○○○ Inadequate	**Antidepressants[665] (any time)** 39	**St John's wort (any time)** 43	**4.7% vs. 20.5%; 0.05**	205 per 1000	-
Evidence Statements: *Due to the inadequate certainty of the evidence, any association between maternal use of St John's wort at any time during pregnancy and an increased risk of preterm birth newborn is uncertain.* *Due to the inadequate certainty of the evidence, any decreased risk of preterm birth in the newborn associated with maternal use of St John's wort at any time during pregnancy, compared with maternal use of conventional pharmacologic treatment for depression during the same period, is uncertain.*											
Footnotes: a. Downgraded two levels due to high risk of bias; potential for selection bias due to exclusion of planned abortions, miscarriages and still born from the analysis, self-report ascertainment of outcome and incomplete follow-up. b. Downgraded one level due to indirectness; general population comparator group. c. Downgraded one level due to imprecision; 95% CI crosses the line of no effect and includes a measure of appreciable benefit and/or harm – RR 0.75/1.25, no measure of precision available, or no events. d. Downgraded two levels due to high risk of bias; self-report ascertainment of outcome and incomplete follow-up.											

Abbreviations: BSID, Bayley Scales of Infant Development; CI, confidence interval; GMDS, Griffiths Mental Development Scales; K-ABC, Kaufman Assessment Battery for Children; NA, not available; NR, not reported; P, pregnancy; P & L, pregnancy and lactation; PPVT, Peabody Picture Vocabulary Test; RCT, randomised controlled trial; RR, relative risk.

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

[665] Described as conventional pharmacological treatment.

D3.2.3 Gingko biloba

No SRs or individual comparative studies were identified that assessed the effect of perinatal exposure to Gingko biloba on fetal, infant or child harms.

D3.3 PHYSICAL

The following section presents the Evidence Profile tables for the physical treatments examined: ECT and TMS. These specific physical therapies were identified by the Harms Expert Subcommittee as potentially impacting on the fetus. No intervention-specific rules were required for downgrading of the certainty of this body of evidence.

D3.3.1 Electroconvulsive therapy

A summary of the characteristics of the individual included studies can be found in **Table AppD2-30** in **Appendix D2.3.1.2**. A detailed discussion of the evidence for each group or individual intervention type and outcome can be found in **Appendix D4.3.1**.

The EP table reporting the results of the assessment of ECT is presented in **Table D3-43**. The available evidence was based primarily on SRs of case series/reports and one very low certainty prospective cohort study that suggested no harm to the infant following exposure to ECT via breastfeeding (Babu 2013). As such, there is insufficient evidence available to make an Evidence Statement on the fetal/infant/child harms associated with use of ECT during pregnancy or the postnatal period.

Table D3-43 Evidence Profile table: ECT harms

Certainty assessment							Summary of findings				
Outcome subgroup *No. participants* (No. studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Population (N)		Risk estimate (95% CI)	Anticipated absolute effects	
							Non-exposure	Exposed		Risk with control	Risk difference with intervention
ECT – antenatal exposure											
There was no higher certainty evidence regarding the effect of antenatal exposure to ECT on infant harms. One pooled analysis of case reports concluded that ECT should be a "last resort" treatment[666] while three narrative reviews of largely case reports concluded that the risk of adverse harms to the fetus were low.[667] (see Section AppD4.3.1.3.1)											
ECT – postnatal exposure											
There was no higher certainty evidence regarding the effect of postnatal exposure to ECT on infant harms. One small prospective comparative study (without adjustment for potential confounding) suggests that breastfeeding following post-partum ECT does not result in adverse effect to the infant.[668] (see Section AppD4.3.1.4.1)											
Evidence Statement: *There is insufficient evidence available to make an Evidence Statement regarding the effect of antenatal or postnatal exposure to ECT on fetal or infant harms.*											
Footnotes: None											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: CI, confidence interval; ECT, electroconvulsive therapy.

[666] Leikness 2015.

[667] Calaway 2016, Pompili 2014 and Anderson 2009.

[668] Babu 2013.

D3.3.2 Transcranial magnetic stimulation

A summary of the characteristics of the individual included studies can be found in **Table AppD2-31** in **Appendix D2.3.2.2**. A detailed discussion of the evidence for each group or individual intervention type and outcome can be found in **Appendix D4.3.2**.

The EP table reporting the results of the assessment of TMS is presented in **Table D3-44**. No SRs were identified in the SR search and updated search that assessed the impact of antenatal or postnatal exposure to TMS on the fetus, infant or child. The single included study (Eryilmaz 2015) compared the effect of TMS with no TMS in pregnant women with major depressive disorder. This study had a number of methodological deficiencies, the main ones being the use of a non-concurrent control group and a lack of adjustment for potential confounding. As such, there is insufficient evidence available to make an Evidence Statement on the fetal/infant harms associated with use of TMS during pregnancy or the postnatal period. It should be noted that the authors report no significant harms associated with the use of TMS, and showed no significant difference in motor or cognitive development, although there was a non-significant lower prevalence of mothers' perception in language development.

Table D3-44 Evidence Profile table: TMS harms

Certainty assessment							Summary of findings				
Outcome subgroup ***No. participants*** **(No. studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Population (N)**		**Risk estimate (95% CI)**	**Anticipated absolute effects**	
							Non-exposure	**Exposed**		**Risk with control**	**Risk difference with intervention**
TMS – antenatal exposure											
There was no higher certainty evidence regarding the effect of antenatal exposure to TMS on infant harms. One prospective cohort study with a non-concurrent untreated, depressed control group that did not sufficiently adjust for potential confounding showed no difference in infant adverse events or developmental delay at a mean of 32 months using the ADSI.[669] (see Section D4.3.2.1.2)											
Evidence Statement: *There is insufficient evidence available to make an Evidence Statement regarding the effect of antenatal or postnatal exposure to TMS on infant harms.*											
Footnotes: None											

Notes: Relative effects shown in black bold text denote a statistically significantly greater harm in the intervention group. Relative effects shown in grey bold text denote a statistically significantly greater harm in the control group.

Abbreviations: ADSI, Ankara Developmental Screening Inventory; CI, confidence interval; ECT, electroconvulsive therapy.

[669] Eryilmaz 2015.

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