Mental health care in the perinatal period: Australian clinical practice guideline

2023 Update

Technical Report Part D:

Harms associated with treatment and prevention interventions for mental health disorders in the perinatal period

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clinical evidence for the real world

CONSULTATION VERSION

3 November 2022

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Abbreviations

ADHD	attention-deficit/hyperactivity disorder
ADSI	Ankara Developmental Screening Inventory
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
AOR	adjusted odds ratio
ARR	adjusted risk ratio
ASD	autism spectrum disorder
BRIEF-P	Behaviour Rating Inventory of Executive Function – Preschool version
BRS	Behavioral Rating Scale
BSID	Bayley Scales of Infant Development
CI	confidence interval
ECT	electroconvulsive therapy
EPDS	Edinburgh Postnatal Depression Scale
FGA	first generation antipsychotics
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IQ	Intelligence quotient
IUGR	intrauterine growth restriction
LCPUFA	long chain polyunsaturated fatty acids
LFGA	large for gestational age
MD	mean difference
MDI	Mental Development Index
NA	not available
NaSSA	noradrenergic and specific serotonergic antidepressants
NICU	neonatal intensive care unit
NR	not reported
OR	odds ratio
PDI	Provisional Diagnostic Instrument
PICO	population–intervention–comparator–outcome
PNAS	poor neonatal adaptation syndrome
PPH	persistent pulmonary hypertension
RCT	randomised controlled trial
RD	risk difference
RoB	risk of bias
RR	relative risk
SFGA	small for gestational age

SGA	second generation antipsychotic
SMD	standardised mean difference
SR	systematic review
SNRI	serotonin-noradrenalin reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressants
TMS	transcranial magnetic stimulation

D1. Introduction

In October 2017, the Centre of Perinatal Excellence (COPE) published a national clinical practice guideline on *Effective Mental Health Care in the Perinatal Period* (hereafter referred to as the **2017 Australian Guideline**).

The aim of this Evidence Review Update is to assess the body of evidence – including the 'new' evidence – relating to the treatment and prevention of mental health problems in birthing parents during pregnancy and the postnatal period. The following Technical Reports are related to this assessment:

- Part C Technical Report – Effectiveness of treatment and prevention interventions
- Part D Technical Report – Harms associated with treatment and prevention interventions *(this report)*

This Technical Report includes an overview of the methods used to identify and appraise the evidence relating to the **harms** of interventions used for the treatment and prevention of mental health problems in birthing parents during the antenatal or postnatal period, and presents the findings of the assessment of this evidence. Details of the literature search strategies, included/excluded studies, characteristics of included studies, risk of bias assessments and evidence summaries are included in the Appendices.

D2. Methodology

D2.1 Clinical questions

The Research Protocol for this update of the evidence review outlined four questions relating to the different populations that may potentially experience harms as a consequence of interventions for the treatment or prevention of mental health problems in pregnant or postpartum birthing parents. 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 Technical Report Part C.

The research questions and the interventions of interest (see Section D2.2) are similar to those investigated for the 2017 Australian Guideline.

Main research question:

Q6. What are the harms to the fetus or breastfeeding infant that occur as a result of perinatal exposure to pharmacological interventions, complementary interventions and physical interventions used for the treatment or prevention of mental health problems?

Sub-questions:

Q6a. What are the harms that occur to the fetus (defined as malformations) as a result of perinatal exposure to pharmacological, complementary and physical interventions used for the treatment or prevention of mental health problems?

Q6b. What are the harms that occur to the infant (defined as pregnancy and birth outcomes) as a result of perinatal exposure to pharmacological, complementary and physical interventions used for the treatment or prevention of mental health problems?

Q6c. What are the harms that occur to the child (defined as neurodevelopmental outcomes) as a result of perinatal exposure to pharmacological, complementary and physical interventions used for the treatment or prevention of mental health problems?

Q6d. What are the harms that occur to the mother (defined as postpartum haemorrhage) as a result of perinatal exposure to pharmacological, complementary and physical interventions used for the treatment or prevention of mental health problems?

D2.2 Criteria for determining study eligibility

The focus of the harms questions in this Evidence Review Update is the same as that in the 2017 Australian Guideline, which is to identify the highest quality evidence of the harms to the fetus or breastfeeding infant associated with maternal exposure to various pharmacological, complementary and physical mental health interventions.

To determine whether an intervention causes harm, a systematic review (SR) of randomised controlled trials (RCTs) provides the highest level of evidence. 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. Thus, where available, RCT evidence was used, although the majority of evidence is from observational studies. The preference was for observational studies with concurrent control groups.

Table 1 Detailed PICO criteria for Q6: Harms associated with treatment and prevention interventions

Question 6	What are the harms to the fetus or breastfeeding infant that occur as a result of perinatal exposure to pharmacological interventions, complementary interventions and physical interventions used for the treatment or prevention of mental health problems?	
Population	• Pregnant or postpartum/postnatal women (birthing parent) • Infants or children exposed during pregnancy or postnatally	

Intervention	• Pharmacological
	  ○ antidepressants, antipsychotics, mood stabilisers (including anticonvulsants, benzodiazepines and z-drugs), lithium
	• Complementary
	  ○ omega-3 fatty acids, St John's wort, Ginkgo biloba
	• Physical
	  ○ ECT, TMS	

Comparator	• No exposure • Exposure to an active comparator	
Outcomes	**Fetal, infant or child harms** *Malformations* • Major malformations • Cardiac malformations • Septal malformations *Pregnancy and birth outcomes* • Neonatal mortality • Stillbirth • Miscarriage • Preterm birth • SFGA/IUGR • PNAS • Persistent pulmonary hypertension • Respiratory distress • Tremors • Convulsions *Neurodevelopmental outcomes* • Autism spectrum disorder • ADHD • Other disorders measured with validated instruments • Intelligence quotient • Behavioural problems • Depression • Anxiety	**Maternal harms** • Postpartum haemorrhage

Abbreviations: ADHD, attention deficit hyperactivity disorder, ECT, electroconvulsive therapy; IUGR, intrauterine growth restriction; PNAS, poor neonatal adaptation syndrome; SFGA, small for gestational age; TMS, transcranial magnetic stimulation.

The outcomes included to investigate the harms associated with treatment and prevention interventions for mental health problems are categorised as fetal, infant or child harms and maternal harms. The malformations outcome investigates malformations in the fetus, infant or child that occur as a result of antenatal exposure to treatment and prevention interventions, generally in the first trimester. Pregnancy and birth outcomes report on fetal, infant or child harms that can occur as a result of antenatal exposure early in pregnancy (e.g. miscarriage) and later in pregnancy (e.g. poor neonatal adaptation syndrome

[PNAS]). Neurodevelopmental harms to the fetus, infant or child may potentially occur as a result of antenatal or postnatal exposure. As mentioned above, maternal harms focus on postpartum haemorrhage (maternal side effects of treatment are captured as safety outcomes in Technical Report Part C).

D2.3 Literature search

As this is a guideline update, the search strings used for the 2017 Australian Guideline were updated to reflect changes in search terminology since the original search was undertaken. Search strings for identification of studies reporting on the harms of treatment and prevention interventions are shown in Appendix 1.1. The literature search was conducted on 07 March 2022 and captured records included in MEDLINE and Embase since 01 January 2016 (the original searches for the 2017 Australian Guideline were conducted in June 2016 and updated in October 2016).

The search was restricted to English-language, full text articles. As per the Research Protocol, narrative reviews and conference abstracts were excluded. The search was designed to capture systematic reviews and primary studies in separate sets ('SR search set' and 'primary study search set'), which were uploaded separately into an EndNote library. The 'primary study search set' was only screened for eligible interventions if no systematic reviews were identified or the identified systematic reviews were limited in terms of quality or the number of primary studies included.

After deduplicating records in EndNote, unique records were uploaded into systematic review software, DistillerSR, for determination of study eligibility.

The searches did not specifically aim to identify or limit retrieval of articles to studies that addressed socioeconomic, Aboriginal or Torres Strait Islander populations. However, the reviewers were required to document any papers addressing these populations for specific consideration by the EWG. Implications for rural and remote areas, and the Indigenous population, have been considered and documented in the clinical guidance.

D2.4 Study eligibility

Study eligibility was informed by the evidence selection criteria in Table 1. 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. Records were excluded for the following reasons:

- Wrong **publication type** – not a full-text report (excludes protocols, conference abstracts, editorials, letters)
- Wrong **study type** – not a systematic review or clinical study in humans (excludes narrative reviews, non-comparative studies, case reports)
- Wrong **population** – study was not conducted in pregnant or postpartum birthing parents, or children exposed to an intervention antenatally or postnatally
- Wrong **intervention/exposure** – study did not examine at least one of the exposures (pharmacological, complementary or physical interventions) listed in Table 1
- Wrong **comparator** – study did not compare the exposed population to no exposure or exposure to an active comparator
- Wrong **outcome** – study did not examine at least one of the outcomes listed in Table 1
- Not in **English** – full text article not published in English language

Titles and abstracts were screened initially to identify systematic reviews for each intervention type listed in the PICO. Where possible, a '**foundation review**' was selected, based on comprehensiveness, quality and recency of the literature search. This is similar to the approach taken for the 2017 Australian Guideline.

The application of the eligibility criteria above is summarised in Appendix 1.2. Overall, 72 SRs met the eligibility criteria: 65 relating to pharmacological interventions, 3 relating to complementary interventions (all focused on omega-3 fatty acids) and 4 relating to physical interventions.

Appendix 2 provides the citation details and reason for exclusion of studies excluded at full text review.

Appendix 3 provides the citation details for all studies that met the eligibility criteria, by intervention type (pharmacological, complementary, physical).

D2.5 Targeted searches

In cases where a foundation review was not identified, a targeted search was undertaken within the 'primary study search set' to identify primary studies that met the PICO criteria. The search terms and results of the targeted searches are summarised in Appendix 1.3.

Targeted searches were ultimately conducted for all complementary interventions (omega-3 fatty acids, St John's wort, Ginkgo biloba) and physical interventions (ECT and TMS).

Although a recent, comprehensive, high-quality foundation review was identified for pharmacological interventions (refer to Section D3.1 for details), the Harms Expert Subcommittee identified additional antidepressants and antipsychotics relevant to the Australian context that were not included in the foundation review.[1] Targeted searches of the 'primary study search set' were undertaken to identify any primary studies of the following medications:

- Antidepressants: vortioxetine[2], agomelatine, ketamine
- Antipsychotics: cariprazine[2], flupenthixol, zuclopenthixol, amisulpride, droperidol

Targeted searches were also conducted for key PICO interventions or outcomes that were not reported in the foundation review but were deemed to be important for decision-making by the EWG or Harms Expert Subcommittee. These included:

- Neonatal outcomes: poor neonatal adaptation syndrome (PNAS), tremors (a symptom of PNAS).

D2.6 Assessment of the evidence

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 interventions for mental health disorders. This evidence was then described and graded, and recommendations developed.

Risk of bias was assessed using the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews v2)[3] for SRs of randomised and non-randomised studies, ROBINS-I (the Risk of Bias in Non-randomized Studies of Interventions) for non-randomised studies and the Cochrane Risk of Bias 2.0 Tool[4] for randomised trials. Completed assessments are provided in Appendix 5.

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology was used to appraise the quality of the evidence for each intervention and outcome and translate this into recommendations and practice points. The certainty of evidence assessment for GRADE involves

[1] Harms Expert Subcommittee meeting held on 24 June 2022.
[2] This drug was included in the AHRQ research protocol (literature searches), but no studies were identified.
[3] https://amstar.ca
[4] https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

consideration of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. For further details about GRADE see http://www.gradeworkinggroup.org/.

GRADE evidence summary tables are provided in Appendix 6. Where the body of evidence was taken from an existing SR, the summary tables reflect the information reported in the existing SR, including the GRADE rating (overall certainty or strength of evidence for each outcome). This is typically represented as *high* (●●●●), *moderate* (●●●○), *low* (●●○○) or *very low* (●○○○). Chapter 8 of the GRADE handbook advises that the use of three categories is also acceptable (*high*, *moderate* and *low*), with *low* and *very low* reduced to one category.[5]

While not a requirement of GRADE, Evidence Statements for each outcome have been developed for the purpose of the Australian Guideline. This has been done to facilitate the explicit weighting of benefits and harms across multiple outcomes, for the mother versus the infant, in the antenatal versus the postnatal periods.

The wording of the Evidence Statements has been chosen carefully to convey the confidence of the findings, keeping in mind that the findings relate to the presence or absence of *associations*[6] between exposure and the outcomes (most of which are pre-specified as 'harms' not benefits). The specific rules around the wording of the Evidence Statement are as follows:

- If the CI includes 1.00 (relative measures; RR, OR) or 0 (absolute measures; RD, mean difference [MD], standardised mean difference [SMD]):
    - where moderate or high certainty evidence is available, the phrasing "not associated" is used
    - where low or very low certainty evidence is available, the phrasing "does not appear to be associated" is used
    - where inadequate certainty evidence is available, the phrasing "is uncertain" is used.
- If the CI does not include 1.00 (relative measures; RR, OR) or 0 (absolute measures; RD, MD, SMD):
    - where moderate or high certainty evidence is available, the phrasing "is associated" is used
    - where low or very low quality evidence is available, the phrasing "may be associated" is used
    - where low quality evidence is available, but the evidence shows a large magnitude of effect,[7] the phrasing "is associated" is used
    - where inadequate quality evidence is available, the phrasing "appears to be associated, but due to the inadequate quality of the evidence this association is uncertain".

D2.7 Evidence to recommendations process

A structured evidence-to-decision framework was used to assist the EWG to develop new recommendations or amend existing recommendations from the 2017 Australian Guideline.

For recommendations relating to the harms of interventions, the Harms Expert Subcommittee members were provided with a summary of the evidence base and recommendations from the 2017 Australian Guideline (Appendix 4) together with the new evidence identified in the Evidence Review Update (this report). The Harms Expert Subcommittee met on 12 August 2022, and agreed on suggested edits to existing recommendations, and proposed the addition of a new practice point. The Harms Expert Subcommittee suggestions were reviewed by the EWG at their meeting on 29 August 2022 and were accepted without

[5] https://training.cochrane.org/resource/grade-handbook
[6] 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.
[7] 95% exceeds the minimum level of appreciable harm (RR > 1.25 or SMD < -0.5).

alteration. Evidence to decision tables describing the deliberations of the Harms Expert Subcommittee and the EWG are provided in an appendix to the Guideline.

D3. Results

D3.1 Pharmacological

D3.1.1 Selection of the foundation review

The literature searches identified 65 SRs relating to the assessment of harms of pharmacological interventions in the perinatal period. Of the 65 included SRs, 43 related to the use of antidepressants, 6 to antipsychotics, 9 to mood stabilisers, and 1 to lithium. The remaining 6 SRs looked at exposure to various types of pharmacological interventions (see Appendix 3.1).

One of the reviews of various types of pharmacological interventions was a recent, high-quality SR conducted by the Agency for Healthcare Research and Quality (AHRQ), which will be referred to from hereon as AHRQ 2021. This Comparative Effectiveness Review (CER) was considered suitable as a foundation review for harms of pharmacological interventions for the following reasons:

- **Recency:** The AHRQ review was published in 2021. The literature searches were conducted in June 2020, with ongoing surveillance for new publications until March 2021.
- **Relevance:** Although the scope of the AHRQ review was broader than that of the current Evidence Review Update (i.e., AHRQ include preconception), the key questions of the AHRQ review align with those for the current Evidence Review Update. For both, the postnatal period was defined as 12 months after birth. The AHRQ additionally included aspects of care that were not defined in the PICO for the current Evidence Review Update, such as the harms of not treating mental health problems, and of stopping or switching medications in the perinatal period.
- **Comprehensiveness:** The AHRQ PICO criteria broadly align with those for the Australian guideline, and the drugs are grouped similarly. All pharmacological intervention types in the PICO for the current Evidence Review Update were included in the AHRQ review, except for the antipsychotics flupenthixol and zuclopenthixol, which are approved for use in Australia but not in the USA. All outcomes specified in the PICO for the current Evidence Review Update (Table 1) were included in the AHRQ review, except poor neonatal adaptation syndrome (PNAS) and tremors.
- **Quality:** An AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews v2) assessment found this review to be of high quality with overall high confidence in the results of the review, with positive results in all domains (see Appendix 5.1).
- **GRADE:** The AHRQ assessment of the body of evidence was based on the GRADE approach.

Appendix 4, Table App. 5, provides a brief summary of the PICO elements of the AHRQ 2021 Comparative Effectiveness Review.

D3.1.1.1 Foundation review methods

The AHRQ CER used GRADE guidance together with guidance established for the AHRQ Evidence-based Practice Center Program.[8] The five key GRADE domains were incorporated in the assessment: risk of bias (includes study design and aggregate quality), consistency, directness, precision of the evidence, and reporting bias. These domains were reflected in an overall rating regarding the strength of the evidence:

> *High* – High confidence that the evidence reflects the true effect. Further research is very unlikely to change confidence in the estimate of effect.

[8] https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-grading-evidence_methods.pdf

> *Moderate* – Moderate confidence that the evidence reflects the true effect. Further research may change confidence in the estimate of effect and may change the estimate.
>
> *Low* – Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is likely to change the estimate.
>
> *Insufficient* – Evidence is unavailable or does not permit estimation of an effect.

AHRQ methods depart from GRADE guidance on the starting rating for observational studies and the rating consistency domain for single-study bodies of evidence. According to the AHRQ CER 2021 (Appendix A, Detailed Methods), bodies of evidence from observational studies began with a rating of *moderate*, with downgrading based on any of the five domains, and upgrading based on three other domains: dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect). Single study bodies of evidence were downgraded for unknown consistency. The evidence was not downgraded for indirectness because all key outcomes were considered to be 'direct' outcomes. Applicability was assessed following guidance in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness*.[9]

Adjustment for confounding

It was noted in AHRQ 2021 that primary studies looking at harms of exposure to pharmacological agents during pregnancy are most likely to be observational studies (case-control studies, pregnancy registry studies, observational cohort studies, and secondary analyses of administrative databases). Inherent in these study designs is a risk of confounding by indication (the presence of a mental health problem influencing both the exposure to medication and the outcome). Even studies comparing medication use versus no exposure in mothers with the same mental health condition risk confounding by disease severity because women who are receiving pharmacologic treatment may be likely to have more severe underlying disease than women who forgo pharmacologic therapy. AHRQ 2021 noted that studies varied greatly in the extent to which they were able to address underlying severity of mental health disorders. The majority were unable to address confounding due to a lack of the necessary variables in registry datasets. A small number of studies attempted various approaches to address confounding, such as propensity score adjustment or stratification by number of disorders. Controls for confounding reduced the effect size in many instances, and in some cases reversed the direction of effect.

Appendix A of the AHRQ CER 2021 notes the following:

> *To address these limitations, we limited analysis of results of KQs 1 and 3 (benefits and harms of interventions compared with no treatment, usual care, or placebo) to studies that adjusted for confounding through matching, regression, or propensity score adjustments and provided these adjusted results for the comparison of interest (e.g., active intervention vs. no treatment for women with a diagnosis). We did not calculate indirect comparisons from studies that present adjusted results for comparisons outside the remit of this review. For example, several studies presented adjusted results for women with a drug exposure versus women with no drug exposure and no disorders and, separately, adjusted results comparing women with a disorder but no drug exposure versus women with no drug exposure and no disorder. Calculated indirect comparisons for women with a drug exposure versus women with a disorder but no drug exposure would be at risk of violating assumptions about transitivity and would likely have residual confounding.*
>
> *For KQs 2 and 4 (benefits and harms from head-to-head comparisons of interventions), we included studies that did not provide adjusted results that addressed confounding, but we marked down the evidence base for high potential for risk of bias. We excluded studies that*

[9] https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-grading-evidence_methods.pdf

> *did not present mutually exclusive arms: in studies with overlapping cases in exposure arms, the association between the intervention and the outcome cannot be established. We also required clarity on the interventions for both arms. We did not synthesize results from studies comparing an active intervention with "other antidepressants," polytherapy, or co-exposure to other drugs with no further elaboration. In these instances, because we could not discern the nature of the exposure, we could not interpret the clinical significance of differences in outcomes between the arms.*

AHRQ 2021 included studies with comparator arms comprising women with prior exposure to the drug, even if the disorder status was not specified. They restricted the evidence to women with mental health disorders as a means of reducing the potential for confounding in the evidence base. The authors acknowledge that this criterion excluded studies of well-conducted negative controls that might 'bolster' the evidence on the association between the exposure and the outcome. It also resulted in the exclusion of studies reporting on relevant outcomes for exposures to the pharmacological intervention for other clinical conditions. The authors noted that limitations of the evidence and the review criteria mean that the signals of harms that were identified may be partially or wholly attributable to residual confounding.

D3.1.1.2 PICO elements not covered in the foundation review

As mentioned in Section D2.5, targeted searches of the records identified in the literature search were conducted for specific pharmacological agents and key outcomes that were not mentioned in the AHRQ foundation review but were considered important by the EWG or Harms Expert Subcommittee.

The targeted searches did not identify any studies of the specified pharmacological agents (vortioxetine, agomelatine, ketamine, cariprazine, flupenthixol, zuclopenthixol, amisulpride, droperidol) that met the eligibility criteria, including the requirement for concurrent controls and adjusted for multiple confounders.

Likewise, the targeted searches did not identify any studies that met the eligibility criteria and reported the outcomes of PNAS or tremors. A systematic review that specifically examined PNAS after exposure to antidepressants was identified (Kautzky 2022; see Appendix C.1.2). The authors noted the following:

> *Although we aimed at investigating the occurrence of specifically PNAS, it was not possible to apply a unitary definition of this syndrome that would allow analysis across the studies at hand. PNAS has often been operationalized with the Finnegan score using a cut-off of >8; however, this score was designed for neonatal abstinence syndrome after opiate exposure and not for SSRIs and other antidepressants that show a different receptor profile and mode of action… Consequently, no categorical definition of PNAS could reasonably be pooled for this meta-analysis.*

D3.1.2 Harms of antidepressants

D3.1.2.1 Selective serotonin reuptake inhibitors (SSRIs) versus no exposure

The evidence for harms of SSRIs versus no exposure is summarised in Table 2. Further information, including the study design, size and adjusted risk estimate, is available in the SSRI versus no exposure strength of evidence table (Appendix 6.1.1, Table App. 35, taken from AHRQ 2021).

The AHRQ review found low confidence evidence for increased risk of postpartum haemorrhage, persistent pulmonary hypertension, depression and autism spectrum disorder (ASD) with SSRI exposure, compared with no exposure. However*, the possible association between antidepressant use in pregnancy and the development of ASD, and depression in the child should be interpreted with caution.*

The AHRQ (2021) authors found that the study showing a possible association between SSRIs and depression in the child did not control for depression severity and the direction of effect was unclear. Similarly, they found the association between maternal use of SSRIs during pregnancy and ASD to be

uncertain. For the possible association between citalopram and ASD, they noted that residual confounding could potentially explain this effect (see evidence statements in Appendix 6.1.1, Table App.35).

Two other included SRs listed in Appendix 3 expressed similar concerns about the association between antidepressants and ASD. **Leshem (2021)** found a statistically significant association between prenatal exposure to SSRIs/SNRIs and the risk for developing ASD in children, however, they also found an association in women who were exposed to SSRIs/SNRIs before pregnancy, with no exposure in utero. The authors concluded that the association between exposure to SSRIs/SNRIs during pregnancy and ASD may be due to residual confounding, mainly confounding by indication. Similarly, **Halvorsen (2019)** found a statistically significant association between in utero exposure to SSRIs and ASD but identified confounding by indication in most of the relevant included studies. The authors concluded that these associations did not necessarily reflect a causal relationship, as the results included in their meta-analyses were probably affected by residual confounding by indication, which was likely to account for some (or all) of the positive association.

Refer to Appendix 4.1.1, Table App. 7 for the summary of harms developed for the 2017 Australian Guideline.

Table 2 Summary of harms for 2023 Guideline – SSRIs versus no exposure

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○
SSRIs (various)	Postpartum haemorrhage ●○○ Persistent pulmonary hypertension ●○○ Respiratory conditions[10] ●○○ Depression[11] ●○○			Major malformation Cardiac malformation Neonatal mortality Miscarriage Preterm birth SFGA Convulsions ASD ADHD Other neurodevelopment/ behavioural disorders Anxiety
Citalopram	Postpartum haemorrhage ●○○ ASD[12] ●○○			Major malformation Cardiac malformation
Escitalopram	Postpartum haemorrhage ●○○			Major malformation Cardiac malformation
Fluoxetine	Postpartum haemorrhage ●○○			Major malformation Cardiac malformation ASD
Fluvoxamine				Major malformation
Paroxetine	Postpartum haemorrhage ●○○			Major malformation Cardiac malformation ASD
Sertraline	Postpartum haemorrhage ●○○			Major malformation Cardiac malformation ASD

[10] Includes studies that reported respiratory distress, undefined breathing problems, or other respiratory conditions of newborns other than intrauterine hypoxia and birth asphyxia.

[11] Caution: AHRQ (2021) authors note that the study showing this association did not control for depression severity and the direction of effect was unclear

[12] Caution: AHRQ (2021) authors note that residual confounding could potentially explain this effect

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain
Trazodone				Postpartum haemorrhage

Source: Table compiled from results reported in AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; SFGA, small for gestational age; SSRI, selective serotonin reuptake inhibitor.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect.

D3.1.2.2 SSRIs versus active comparator

The evidence for harms of SSRIs compared with active comparators is summarised in Table 3. Further information is available in Table 13 and Appendix B of the AHRQ Comparative Effectiveness Review (2021). Although the AHRQ identified a relatively large body of comparative evidence for SSRIs, all comparative evidence was considered insufficient.

Refer to Appendix 4.1.1, Table App. 7 for the summary of harms developed for the 2017 Australian Guideline.

Table 3 Summary of harms for 2023 Guideline – SSRIs versus active comparator

SSRI	Comparator	Miscarriage	Postpartum Haemorrhage	Neonatal death	Preterm Birth	Small For Gestational Age	Major Malformation	Cardiac Malformation	Respiratory Distress	Persistent Pulmonary Hypertension	Delayed Social, Emotional, and Cognitive Development	Autism Spectrum Disorder	ADHD	Anxiety	Depression
SSRI versus SSRI															
Citalopram	Escitalopram	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Citalopram	Fluoxetine	-	-	-	-	-	-	○○○	-	-	-	○○○	-	-	-
Citalopram	Fluvoxamine	-	-	-	-	-	-	-	-	-	-	○○○	-	-	-
Citalopram	Paroxetine	-	-	-	-	-	-	○○○	-	-	-	○○○	-	-	-
Citalopram	Sertraline	-	-	-	-	-	-	○○○	-	-	-	○○○	-	-	-
Escitalopram	Paroxetine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Escitalopram	Sertraline	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Fluoxetine	Citalopram or escitalopram	○○○	-	○○○	-	-	○○○	○○○	-	-	-	-	-	-	-
Fluoxetine	Escitalopram	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Fluoxetine	Escitalopram or fluvoxamine	○○○	-	○○○	-	-	○○○	-	-	-	-	○○○	-	-	-
Fluoxetine	Sertraline	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Fluvoxamine	Citalopram or escitalopram	○○○	-	○○○	-	-	○○○	-	-	-	-	○○○	-	-	-
Fluvoxamine	Fluoxetine	○○○	-	○○○	-	-	○○○	-	-	-	-	○○○	-	-	-
Fluvoxamine	Paroxetine	○○○	-	○○○	-	-	○○○	-	-	-	-	○○○	-	-	-
Fluvoxamine	Sertraline	○○○	-	○○○	-	-	○○○	-	-	-	-	○○○	-	-	-
Paroxetine	Citalopram or escitalopram	○○○	-	-	-	-	○○○	-	-	-	-	-	-	-	-
Paroxetine	Fluoxetine	○○○	-	○○○	-	-	○○○	○○○	-	-	-	-	-	-	-
Paroxetine	Other SSRI comparators	-	-	-	-	○○○	○○○	○○○	-	-	-	-	-	-	-
Paroxetine	Sertraline	○○○	-	-	-	-	○○○	○○○	-	-	-	○○○	-	-	-
Sertraline	Citalopram or escitalopram	○○○	-	○○○	-	-	○○○	○○○	-	-	-	-	-	-	-
Sertraline	Escitalopram or fluvoxamine	-	-	-	-	-	-	-	-	-	-	○○○	-	-	-
Sertraline	Fluoxetine	○○○	-	○○○	-	-	○○○	-	-	-	-	○○○	-	-	-

SSRI	Comparator	Miscarriage	Postpartum Haemorrhage	Neonatal death	Preterm Birth	Small For Gestational Age	Major Malformation	Cardiac Malformation	Respiratory Distress	Persistent Pulmonary Hypertension	Delayed Social, Emotional, and Cognitive Development	Autism Spectrum Disorder	ADHD	Anxiety	Depression
Sertraline	Non-sertraline SSRIs	-	-	-	-	-	○○○	-	-	-	-	-	-	-	-
SSRI versus SNRI															
SSRIs	SNRIs	○○○	-	-	-	-	-	-	-	-	○○○	○○○	○○○	-	-
SSRIs	Duloxetine	-	○○○	-	○○○	○○○	-	○○○	-	-	-	-	-	-	-
SSRIs	Venlafaxine	○○○	-	-	○○○	○○○	○○○	-	-	-	-	-	-	-	-
Citalopram	Duloxetine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Citalopram	Venlafaxine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Escitalopram	Duloxetine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Escitalopram	Venlafaxine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Fluoxetine	Duloxetine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Fluoxetine	SNRIs	○○○	-	○○○	-	-	○○○	-	-	-	-	-	-	-	-
Fluoxetine	Venlafaxine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Fluvoxamine	Venlafaxine or desvenlafaxine	○○○	-	○○○	-	-	○○○	-	-	-	-	-	-	-	-
Paroxetine	Duloxetine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Paroxetine	SNRIs	-	-	○○○	-	-	○○○	-	-	-	-	-	-	-	-
Paroxetine	Venlafaxine	○○○	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Sertraline	Duloxetine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Sertraline	Venlafaxine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Sertraline	Venlafaxine or desvenlafaxine	-	-	○○○	-	-	○○○	-	-	-	-	-	-	-	-
SSRI versus TCA															
SSRIs	TCAs	○○○	-	-	○○○	○○○	○○○	-	-	-	-	○○○	○○○	-	-
Fluoxetine	TCAs	-	-	-	-	-	○○○	-	-	-	○○○	-	-	-	-
Paroxetine	TCAs	-	-	-	-	-	○○○	-	-	-	-	-	-	-	-
Sertraline	Nortriptyline	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SSRI versus MAOIs															
SSRIs	MAOIs	-	-	-	-	-	-	-	-	-	-	○○○	○○○	-	-
SSRI versus atypical antidepressants															
SSRIs	Mirtazapine	○○○	-	○○○	○○○	-	○○○	-	-	-	-	-	-	-	-
SSRIs	SSRIs + mirtazapine	-	-	-	○○○	-	-	-	-	-	-	-	-	-	-
SSRIs + mirtazapine	Mirtazapine	-	-	-	○○○	-	-	-	-	-	-	-	-	-	-
Citalopram	Bupropion	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Escitalopram	Bupropion	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Fluoxetine	Bupropion	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Paroxetine	Bupropion	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Sertraline	Bupropion	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-

Source: Derived from Table 13 and Appendix B of AHRQ Comparative Effectiveness Review (CER) 2021.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect; - No eligible evidence.

D3.1.2.3 Serotonin–noradrenaline reuptake inhibitors (SNRIs) versus no exposure

The evidence for harms of SNRIs versus no exposure is summarised in Table 4. Further information, including the study design, size and adjusted risk estimate, is available in the SNRI strength of evidence table (Appendix 6.1.1, Table App. 36, taken from AHRQ 2021). The AHRQ review found low confidence evidence for increased risk of postpartum haemorrhage and miscarriage, compared with no exposure.

Refer to Appendix 4.1.1, Table App. 7 for the summary of harms developed for the 2017 Australian Guideline.

Table 4 Summary of harms for 2023 Guideline – SNRIs versus no exposure

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○
SNRIs (various)	Postpartum haemorrhage ●○○ Miscarriage ●○○			Major malformation Cardiac malformation
Duloxetine				Cardiac malformation ASD
Venlafaxine	Postpartum haemorrhage ●○○			Cardiac malformation SFGA ASD

Source: Table compiled from results reported in AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: ASD, autism spectrum disorder; SFGA, small for gestational age; SNRI, serotonin-noradrenalin reuptake inhibitors.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect.

D3.1.2.4 SNRIs versus active comparator

The evidence for harms of SNRIs compared with active comparators is summarised in Table 5. Further information is available in Table 13 and Appendix B of the AHRQ Comparative Effectiveness Review (2021). Although the AHRQ identified a relatively large body of comparative evidence for SNRIs, all comparative evidence was considered insufficient.

Refer to Appendix 4.1.1, Table App. 7 for the summary of harms developed for the 2017 Guideline.

Table 5 Summary of harms for 2023 Guideline – SNRIs versus active comparator

SNRI	Comparator	Miscarriage	Postpartum Haemorrhage	Neonatal death	Preterm Birth	Small For Gestational Age	Major Malformation	Cardiac Malformation	Respiratory Distress	Persistent Pulmonary Hypertension	Delayed Social, Emotional, and Cognitive Development	Autism Spectrum Disorder	ADHD	Anxiety	Depression
SNRI versus SNRI															
Duloxetine	Venlafaxine	-	○○○	-	○○○	○○○	-	○○○	-	-	-	-	-	-	-
SNRI versus SSRI															
SNRIs	SSRIs	○○○	-	-	-	-	-	-	-	-	○○○	○○○	○○○	-	-
SNRIs	Fluoxetine	○○○	-	○○○	-	-	○○○	-	-	-	-	-	-	-	-
SNRIs	Paroxetine	-	-	○○○	-	-	○○○	-	-	-	-	-	-	-	-
Duloxetine	SSRIs	-	○○○	-	○○○	○○○	-	○○○	-	-	-	-	-	-	-
Duloxetine	Citalopram	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Duloxetine	Escitalopram	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Duloxetine	Fluoxetine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-

SNRI	Comparator	Miscarriage	Postpartum Haemorrhage	Neonatal death	Preterm Birth	Small For Gestational Age	Major Malformation	Cardiac Malformation	Respiratory Distress	Persistent Pulmonary Hypertension	Delayed Social, Emotional, and Cognitive Development	Autism Spectrum Disorder	ADHD	Anxiety	Depression
Duloxetine	Paroxetine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Duloxetine	Sertraline	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Venlafaxine	SSRIs	○○○	-	-	○○○	○○○	○○○	-	-	-	-	-	-	-	-
Venlafaxine	Citalopram	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Venlafaxine	Escitalopram	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Venlafaxine	Fluoxetine	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Venlafaxine	Paroxetine	○○○	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Venlafaxine	Sertraline	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Venlafaxine or desvenlafaxine	Sertraline	-	-	○○○	-	-	○○○	-	-	-	-	-	-	-	-
Venlafaxine or desvenlafaxine	Fluvoxamine	○○○	-	○○○	-	-	○○○	-	-	-	-	-	-	-	-
SNRI versus TCA															
SNRIs	TCAs	○○○	-	-	-	-	-	-	-	-	-	-	-	-	-
Venlafaxine	TCAs	-	-	-	-	○○○	-	-	-	-	-	-	-	-	-
SNRI versus MAOI															
SNRIs	MAOIs	-	-	-	-	-	-	-	-	-	-	○○○	○○○	-	-
SNRI versus atypical antidepressants															
Duloxetine	Bupropion	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-
Venlafaxine	Bupropion	-	-	-	-	-	-	○○○	-	-	-	-	-	-	-

Source: Derived from Table 13 and Appendix B of AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect; - No eligible evidence.

D3.1.2.5 Tricyclic antidepressants (TCAs) versus no exposure

The evidence for harms of TCAs versus no exposure is summarised in Table 6. Further information, including the study design, size and adjusted risk estimate, is available in the TCA strength of evidence table (Appendix 6.1.1, Table App. 37, taken from AHRQ 2021). The AHRQ review found insufficient evidence for overall estimation of risk compared to no exposure for all outcomes.

Refer to Appendix 4.1.1, Table App. 7 for the summary of harms developed for the 2017 Guideline.

Table 6 Summary of harms for 2023 Guideline – TCAs versus no exposure

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○
TCAs (various)				Miscarriage Major malformation Cardiac malformation Neonatal death SFGA
Amitriptyline				Postpartum haemorrhage
Amitriptyline or nortriptyline				ASD
Clomipramine				ASD

Source: Table compiled from results reported in AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: ASD, autism spectrum disorder; SFGA, small for gestational age;TCA, tricyclic antidepressant.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect.

D3.1.2.6 TCAs versus active comparator

The evidence for harms of TCAs compared with active comparators is summarised in Table 7. Further information is available in Table 13 and Appendix B of the AHRQ Comparative Effectiveness Review (2021). Although the AHRQ identified comparative evidence for TCAs, it was considered insufficient.

Table 7 Summary of harms for 2023 Guideline – TCAs versus active comparator

TCA	Comparator	Miscarriage	Postpartum Haemorrhage	Neonatal death	Preterm Birth	Small For Gestational Age	Major Malformation	Cardiac Malformation	Respiratory Distress	Persistent Pulmonary Hypertension	Delayed Social, Emotional, and Cognitive Development	Autism Spectrum Disorder	ADHD	Anxiety	Depression
TCA versus SSRI															
TCAs	SSRIs	○○○	-	-	○○○	○○○	○○○	-	-	-	-	○○○	○○○	-	-
TCAs	Fluoxetine	-	-	-	-	-	○○○	-	-	-	○○○	-	-	-	-
TCAs	Paroxetine	-	-	-	-	-	○○○	-	-	-	-	-	-	-	-
Nortriptyline	Sertraline	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TCA versus SNRI															
TCAs	SNRIs	○○○	-	-	-	-	-	-	-	-	-	-	-	-	-
TCAs	Venlafaxine	-	-	-	-	○○○	-	-	-	-	-	-	-	-	-
TCA versus MAOI															
TCAs	MAOIs	-	-	-	-	-	-	-	-	-	-	○○○	○○○	-	-

Source: Derived from Table 13 and Appendix B of AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect; - No eligible evidence.

D3.1.2.7 Atypical antidepressants versus no exposure

The evidence for harms of atypical antidepressants versus no exposure is summarised in Table 8. Further information on atypical antidepressants, including the study design, size and adjusted risk estimate, is available in the strength of evidence table (Appendix 6.1.1, Table App. 38, taken from AHRQ 2021). The AHRQ review found low confidence evidence for increased risk of postpartum haemorrhage, compared with no exposure.

Refer to Appendix 4.1.1, Table App. 7 for the summary of harms developed for the 2017 Guideline.

Table 8 Summary of harms for 2023 Guideline – Atypical antidepressants versus no exposure

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○
NaSSA (mirtazapine)				Postpartum haemorrhage Preterm birth ASD
Bupropion	Postpartum haemorrhage ●○○			Cardiac malformation

Source: Table compiled from results reported in AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: ASD, autism spectrum disorder; NaSSA, noradrenergic and specific serotonergic antidepressants.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect.

D3.1.2.8 Atypical antidepressants versus active comparator

See Table 3 for the comparison of atypical antidepressants versus SSRIs, and Table 5 for atypical antidepressants versus SNRI.

D3.1.3 Harms of antipsychotics

D3.1.3.1 Antipsychotics versus no exposure

The evidence for harms of antipsychotics versus no exposure is summarised in Table 9. Further information, including the study design, size and adjusted risk estimate, is available in the antipsychotics evidence profile table (Appendix 6.1.2, Table App. 39, taken from AHRQ 2021). The AHRQ review found insufficient evidence for overall estimation of risk for all outcomes.

Refer to Appendix 4.1.2, Table App. 9 for the summary of harms developed for the 2017 Guideline.

Table 9 Summary of harms for 2023 Guideline – Antipsychotics versus no exposure

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○
Second generation antipsychotics				Major malformation Cardiac malformation Preterm birth SFGA
First generation antipsychotics				Major malformation Cardiac malformation Preterm birth SFGA
Quetiapine				Major malformation
Risperidone				Major malformation Cardiac malformation

Source: Table compiled from results reported in AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: SFGA, small for gestational age.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect.

D3.1.3.2 Antipsychotics versus active comparator

The evidence for harms of antipsychotics compared with active comparators is summarised in Table 10. Further information is available in Table 13 and Appendix B of the AHRQ Comparative Effectiveness Review (2021). Although the AHRQ identified comparative evidence for antipsychotics, it was considered insufficient.

Refer to Appendix 4.1.2, Table App. 9 for the summary of harms developed for the 2017 Guideline.

Table 10 Summary of harms for 2023 Guideline – Antipsychotics versus active comparator

Antipsychotic	Comparator	Miscarriage	Postpartum Haemorrhage	Neonatal death	Preterm Birth	Small For Gestational Age	Major Malformation	Cardiac Malformation	Respiratory Distress	Persistent Pulmonary Hypertension	Delayed Social, Emotional, and Cognitive Development	Autism Spectrum Disorder	ADHD	Anxiety	Depression
Antipsychotic versus Antipsychotic															
First generation	Second generation	-	-	-	-	○○○	-	-	-	-	○○○	-	-	-	-
Aripiprazole	Risperidone	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clozapine	Aripiprazole	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clozapine	Risperidone	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Haloperidol	Olanzapine	-	-	-	○○○	-	-	-	○○○	-	-	-	-	-	-
Haloperidol	Quetiapine	-	-	-	○○○	-	-	-	○○○	-	-	-	-	-	-
Haloperidol	Risperidone	-	-	-	○○○	-	-	-	○○○	-	-	-	-	-	-
Olanzapine	Aripiprazole	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Olanzapine	Clozapine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Olanzapine	Quetiapine	-	-	-	○○○	-	-	-	○○○	-	-	-	-	-	-
Olanzapine	Risperidone	-	-	-	○○○	-	-	-	○○○	-	-	-	-	-	-
Quetiapine	Aripiprazole	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Quetiapine	Clozapine	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Antipsychotic	Comparator	Miscarriage	Postpartum Haemorrhage	Neonatal death	Preterm Birth	Small For Gestational Age	Major Malformation	Cardiac Malformation	Respiratory Distress	Persistent Pulmonary Hypertension	Delayed Social, Emotional, and Cognitive Development	Autism Spectrum Disorder	ADHD	Anxiety	Depression
Quetiapine	Risperidone	-	-	-	○○○	-	-	-	○○○	-	-	-	-	-	-
Antipsychotic versus Anticonvulsant															
Aripiprazole	Lamotrigine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clozapine	Lamotrigine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Olanzapine	Lamotrigine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Quetiapine	Lamotrigine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Risperidone	Lamotrigine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Antipsychotic versus Lithium															
Aripiprazole	Lithium	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clozapine	Lithium	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Olanzapine	Lithium	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Quetiapine	Lithium	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Risperidone	Lithium	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Source: Derived from Table 13 and Appendix B of AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect; - No eligible evidence.

D3.1.4 Harms of anticonvulsants

D3.1.4.1 Anticonvulsants versus no exposure

The evidence for harms of anticonvulsants versus no exposure is summarised in Table 11. Further information, including the study design, size and adjusted risk estimate, is available in the anticonvulsants evidence profile table (Appendix 6.1.3, Table App. 40, taken from AHRQ 2021). The AHRQ review found insufficient evidence for overall estimation of risk for all outcomes.

Refer to Appendix 4.1.3, Table App. 11 for the summary of harms developed for the 2017 Guideline.

Table 11 Summary of harms for 2023 Guideline – Anticonvulsants versus no exposure

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○
Anticonvulsants				Preterm birth SFGA
Sodium valproate				Preterm birth SFGA
Carbamazepine				Preterm birth SFGA
Lamotrigine				Preterm birth SFGA

Source: Table compiled from results reported in AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: SFGA, small for gestational age.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect.

D3.1.4.2 Anticonvulsants versus active comparator

The evidence for harms of anticonvulsants compared with active comparators is summarised in Table 12. Only one eligible study with a low strength of evidence was identified. This study found that lithium had a greater risk of cardiac and major malformations harms than lamotrigine (see Table 14 of AHRQ CER 2021). Further information is available in Tables 13-14 and Appendix B of the AHRQ Comparative Effectiveness Review (2021). The AHRQ review found low confidence evidence of a lower risk of cardiac and major malformations for lamotrigine when compared with lithium.

Refer to Appendix 4.1.3, Table App. 11 for the summary of harms developed for the 2017 Guideline.

Table 12 Summary of harms for 2023 Guideline – Anticonvulsants versus active comparator

Anticonvulsant	Comparator	Miscarriage	Postpartum Haemorrhage	Neonatal death	Preterm Birth	Small For Gestational Age	Major Malformation	Cardiac Malformation	Respiratory Distress	Persistent Pulmonary Hypertension	Delayed Social, Emotional, and Cognitive Development	Autism Spectrum Disorder	ADHD	Anxiety	Depression
Anticonvulsant versus Antipsychotic															
Lamotrigine	Olanzapine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lamotrigine	Quetiapine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lamotrigine	Aripiprazole	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lamotrigine	Clozapine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lamotrigine	Risperidone	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anticonvulsant versus Lithium															
Lamotrigine	Lithium[13]	-	-	-	-	-	●○○	●○○	-	-	-	-	-	-	-

Source: Derived from Table 13 and Appendix B of AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect; - No eligible evidence.

D3.1.5 Harms of benzodiazepines or z-drugs

D3.1.5.1 Benzodiazepines or z-drugs versus no exposure

The evidence for harms of benzodiazepines or z-drugs versus no exposure is summarised in Table 13. Further information, including the study design, size and adjusted risk estimate, is available in the benzodiazepines or z-drugs evidence profile table (Appendix 6.1.4, Table App. 41, taken from AHRQ 2021). The AHRQ review found low confidence evidence for increased risk of miscarriage, compared with no exposure.

Refer to Appendix 4.1.4, Table App. 13 for the summary of harms developed for the 2017 Guideline.

[13] One study with a low strength of evidence found a greater risk of harms with lithium than lamotrigine for cardiac and major malformations (see Table 14 of AHRQ CER 2021)

Table 13 Summary of harms for 2023 Guideline – Benzodiazepines and z-drugs versus no exposure

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○
Benzodiazepines	Miscarriage ●○○			Neonatal mortality Preterm birth Respiratory distress
Diazepam				Major malformation
Temazepam				Major malformation
Zolpidem				Preterm birth Respiratory distress
Zopiclone				Major malformation

Source: Table compiled from results reported in AHRQ Comparative Effectiveness Review (CER) 2021.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect.

D3.1.5.2 Benzodiazepines or z-drugs versus active comparator

The AHRQ CER (2021) found no eligible studies of the harms of benzodiazepines or z-drugs versus an active comparator (pB-89, AHRQ CER 2021).

D3.1.6 Harms of lithium

D3.1.6.1 Lithium versus no exposure

The evidence for harms of lithium versus no exposure is summarised in Table 14. Further information, including the study design, size and adjusted risk estimate, is available in the lithium evidence profile table (Appendix 6.1.5, Table App. 42 taken from AHRQ 2021). The AHRQ review found insufficient evidence for overall estimation of risk for all outcomes.

Refer to Appendix 4.1.5, Table App. 15 for the summary of harms developed for the 2017 Guideline.

Table 14 Summary of harms for 2023 Guideline – Lithium versus no exposure

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○
Lithium				SFGA Preterm birth IQ

Source: Table compiled from results reported in AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: IQ, intelligence quotient; SFGA, small for gestational age.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect.

D3.1.6.2 Lithium versus active comparator

The evidence for harms of lithium compared with active comparators is summarised in Table 15. Only one eligible study with a low strength of evidence was identified in the foundation review. This study found that lithium had a greater risk of cardiac and major malformations harms than lamotrigine (see Table 14, AHRQ CER 2021). Further information is available in Table 13 and Appendix B of the AHRQ Comparative Effectiveness Review (2021). The AHRQ found low confidence evidence of a greater risk of cardiac and major malformations for lithium when compared with lamotrigine.

Table 15 Summary of harms for 2023 Guideline – Lithium versus active comparator

Lithium	Comparator	Miscarriage	Postpartum Haemorrhage	Neonatal death	Preterm Birth	Small For Gestational Age	Major Malformation	Cardiac Malformation	Respiratory Distress	Persistent Pulmonary Hypertension	Delayed Social, Emotional, and Cognitive Development	Autism Spectrum Disorder	ADHD	Anxiety	Depression
Lithium vs Antipsychotic															
Lithium	Aripiprazole	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithium	Clozapine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithium	Olanzapine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithium	Quetiapine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithium	Risperidone	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lithium vs Anticonvulsant															
Lithium[14]	Lamotrigine	-	-	-	-	-	●○○	●○○	-	-	-	-	-	-	-

Source: Derived from Table 13 and Appendix B of AHRQ Comparative Effectiveness Review (CER) 2021.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder.
Strength of evidence gradings: ●●● – high confidence; ●●○ – moderate confidence; ●○○ – low confidence; ○○○ – insufficient evidence for overall estimation of effect; - No eligible evidence.

D3.2 Complementary

D3.2.1 Included studies

The literature searches identified three reviews relevant to harms of the use of **omega-3 fatty acids** in the perinatal period; two SRs (Middleton 2018, Nevins 2021) and one umbrella review of MAs (Firouzabadi 2022). Using AMSTAR 2, the overall confidence in the results of the reviews was *high* for Middleton 2018, *moderate* for Nevins 2021 and *low* for Firouzabadi 2022 (see Appendix 5.2). Evidence is presented from the Middleton 2018 SR as it was the highest quality and most comprehensive review with the largest number of included RCTs (see Appendix 6.2.1, Table App. 43). The findings of the SR by Nevins (2021) and the umbrella review by Firouzabadi (2022) are discussed narratively.

No SRs or primary studies reporting on harms of **St John's wort** or **Ginkgo biloba** in the perinatal period were identified in the Evidence Review Update.

D3.2.2 Harms of omega-3 fatty acids

The high-quality Cochrane review by Middleton et al. (2018) included 70 RCTs that compared omega-3 interventions (supplements and food) with placebo or no omega-3. The GRADE approach was used to evaluate the quality of the evidence for outcomes relevant to the Evidence Review Update, such as perinatal death, preterm birth, small for gestational age, cognitive development, IQ and behaviour (see Appendix 6.2.1, Table App. 43). Middleton 2018 also included findings for other key outcomes such as postpartum haemorrhage, congenital anomalies, miscarriage, and neurodevelopmental outcomes, but found no significant differences between groups exposed and unexposed to omega-3 during pregnancy. Overall, the Middleton Cochrane review did not find any evidence of harms in the outcomes specified in the PICO for the current Evidence Review Update, and concluded that omega-3 supplementation during

[14] One study with a low strength of evidence found a greater risk of harms with lithium than lamotrigine for cardiac and major malformations (see Table 14 of AHRQ CER 2021)

pregnancy is effective at reducing incidence of preterm birth, but probably increases the incidence of post-term pregnancies.

The moderate-quality SR by Nevins et al. (2021) included 15 RCTs and one prospective cohort study looking at the relationship between supplementation with omega-3 fatty acids during pregnancy and/or lactation and neurodevelopment in children. They concluded that there was limited evidence that omega-3 supplementation during pregnancy may result in favourable cognitive development in the child, and insufficient evidence to evaluate the effects on other developmental outcomes. No harms were reported in this SR.

Firouzabadi et al. (2022) was a low-quality umbrella review of meta-analyses of RCTs. This review included all outcomes reported in published MAs. A total of 28 MAs of 672 RCTs were included. The authors concluded that omega-3 can reduce the risk of low-birth weight and preterm delivery. No harms of omega-3 supplementation were mentioned.

Refer to Appendix 4.2.1, Table App. 17 for the summary of harms, and Table App. 16 for the evidence-based recommendation developed for the 2017 Guideline.

D3.2.3 Harms of St John's wort

The evidence base for St John's wort consists of two cohort studies identified in the search for the 2017 Guideline (Moretti 2009, Kolding 2015). Moretti 2009 used data from a teratogen information service in Canada and was included preferentially because it adjusted for potential confounders. As shown in Appendix 4.2.2, the evidence was judged to be *inadequate* due to very serious risk of bias and serious imprecision. Moretti 2009 reported on 162 pregnant women using St John's wort mainly for depression (72%) compared with depressed women using antidepressants and healthy women not exposed to teratogens. The authors found no statistically significant differences in pregnancy outcomes between St John's wort and the comparator groups.

Refer to Appendix 4.2.2, Table App. 20 for the summary of harms, and Table App. 19 for the consensus recommendation developed for the 2017 Guideline.

D3.2.4 Harms of Ginkgo biloba

The potential harms to the fetus from Ginkgo biloba have not been researched. Refer to Appendix 4.2.3, Table App. 22 for the consensus recommendation developed for the 2017 Guideline.

D3.3 Physical

D3.3.1 Included studies

The searches for the Evidence Review Update identified five studies related to harms of physical interventions in the perinatal period (refer to Appendix 4.3).

For **electroconvulsive therapy**, one overview of SRs was identified (Coshal 2019). The quality of this overview was not assessed as it was a narrative overview of SRs and all included SRs found no relevant RCTs or cohort studies with concurrent controls (Table App. 25).

For **transcranial magnetic stimulation**, three SRs (Cole 2019, Konstantinou 2020, Lee 2020) and one RCT (Kim 2019) were identified (Table App. 27). A foundation review was not chosen for this topic as none of these reviews were sufficiently comprehensive, or of high enough quality. The overall confidence in the results of all three reviews was considered low, according to AMSTAR 2 (see Appendix 5.3).

D3.3.2 Harms of electroconvulsive therapy

The evidence base for ECT consists of only one primary study, which was identified in the literature search for the 2017 guideline (Babu 2013). As noted in Appendix 4.3.1, Babu 2013 was a prospective comparative study (without adjustment for potential confounding) conducted in 78 women with postpartum psychosis. The findings suggested that breastfeeding following postpartum ECT does not result in adverse effects to the infant.

Refer to Appendix 4.3.1, Table App. 24 for the consensus recommendation developed for the 2017 Guideline.

D3.3.3 Harms of transcranial magnetic stimulation

The evidence base for TMS consists of two small primary studies. One observational study was identified in the literature search for the 2017 guideline (Eryilmaz 2015). As mentioned in Appendix 4.3.2, this was a prospective cohort study from Turkey (N=44) with a non-concurrent untreated, depressed control group and insufficient adjustment for potential confounding. Eryilmaz 2015 found no difference in infant adverse events or developmental delay at a mean of 32 months using the ADSI.

The searches for the Evidence Review Update identified one new RCT of rTMS in 26 pregnant women with MDD (14 received rTMS and 12 received sham control; refer to Appendix 4.3.2 for further details). The study (Kim 2019) found no significant differences between groups in infant outcomes, including gestational age at delivery, birth weight and preterm birth (although there were three preterm births in the rTMS group and none in the control group). No cases of major congenital malformations were reported. However, the authors acknowledged that the study was underpowered; based on pilot data they estimated that 33 women would be required per study arm. The authors also acknowledged that the dosing and choice of using right-sided low frequency TMS was a major study limitation, as left-sided, high frequency TMS with taper and maintenance is becoming standard of care.

No recommendations were developed for TMS in the 2017 Guideline.

Appendix 1 Literature search

1.1 Search strings

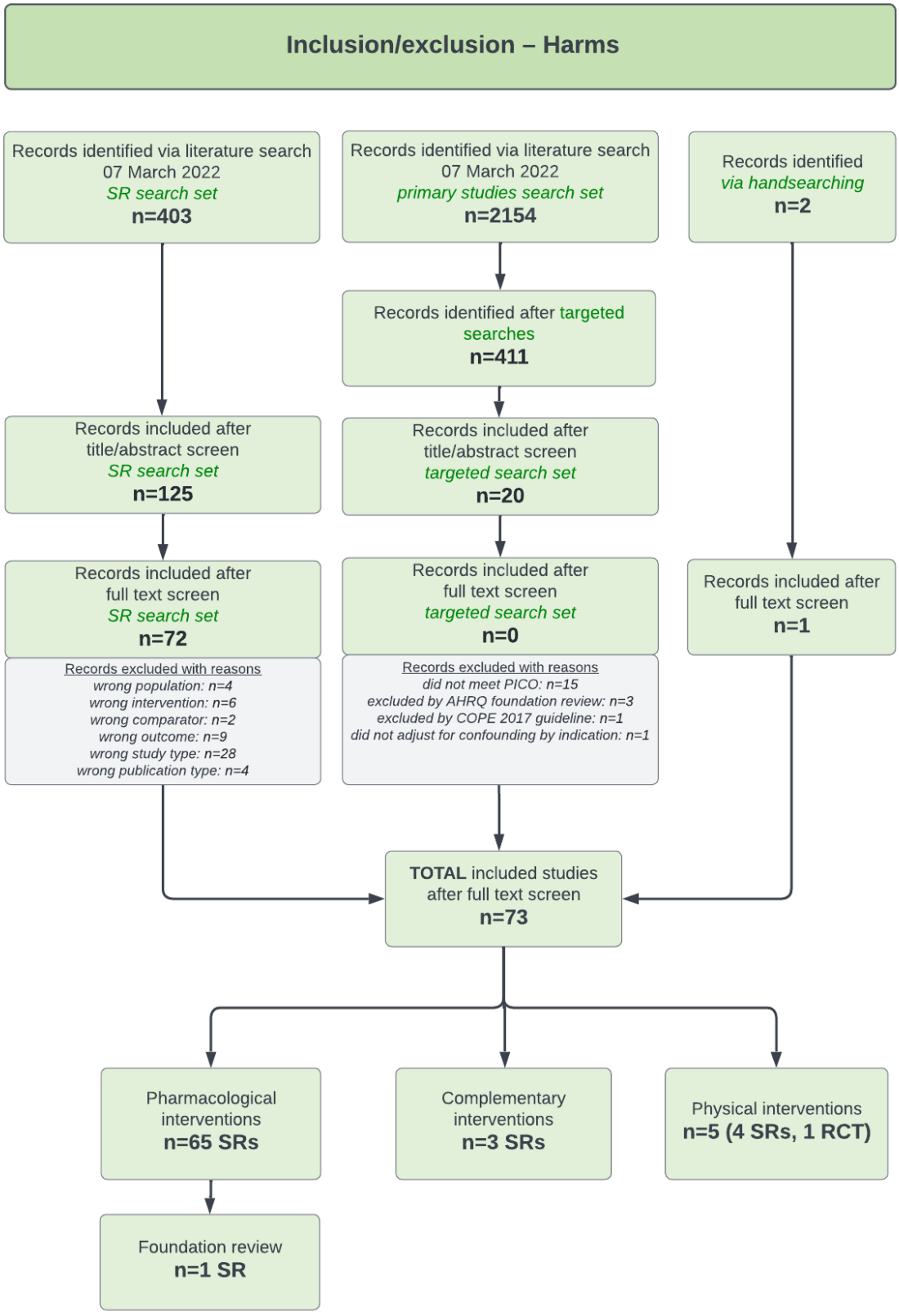
The literature search for the Evidence Review Update covered the period from **01 January 2016** to **07 March 2022**. The search included terms relating to interventions (pharmacological, complementary, ECT and TMS) and terms for relevant outcomes. Terms relating to mental health problems were not used because some interventions may be used in the perinatal period for other indications (e.g. anticonvulsants, omega-3 fatty acids).

Table App. 1 Search strings for Embase and MEDLINE (searched concurrently using EMBASE.com)

Search set		Search string	Records
Perinatal period	#1	pregnancy:ti,ab,kw OR pregnant:ti,ab,kw OR perinatal:ti,ab,kw OR 'peri natal':ti,ab,kw OR peripartum:ti,ab,kw OR 'peri partum':ti,ab,kw OR prenatal:ti,ab,kw OR 'pre natal':ti,ab,kw OR postnatal:ti,ab,kw OR 'post natal':ti,ab,kw OR postpartum:ti,ab,kw OR 'post partum':ti,ab,kw OR antenatal:ti,ab,kw OR 'ante natal':ti,ab,kw OR antepartum:ti,ab,kw OR 'ante partum':ti,ab,kw OR maternal:ti,ab,kw OR neonatal:ti,ab,kw OR 'gestational exposure':ti,ab,kw OR 'prenatal exposure'/exp	1,348,767
Interventions	#2	'antidepressant agent'/exp OR antidepress*:ti,ab OR 'serotonin uptake inhibitor'/exp OR 'serotonin uptake':ti,ab OR 'serotonin reuptake':ti,ab OR ssri:ti,ab OR 'monoamine oxidase inhibitor'/exp OR 'monoamine oxidase':ti,ab OR maoi:ti,ab OR 'tricyclic antidepressant agent'/exp OR tricyclic:ti,ab OR 'noradrenalin uptake inhibitor'/exp OR 'serotonin noradrenalin reuptake inhibitor'/exp OR snri:ti,ab OR ssnri:ti,ab OR 'neuroleptic agent'/exp OR antipsychotic*:ti,ab,kw OR 'anti psychotic':ti,ab,kw OR 'tranquilizer'/exp OR 'lithium'/exp OR lithium:ti,ab,kw OR 'anticonvulsive agent'/exp OR anticonvuls*:ti,ab,kw OR antiepileptic:ti,ab,kw OR 'anti epileptic':ti,ab,kw OR 'anxiolytic agent'/exp OR antianxiety:ti,ab,kw OR 'anti anxiety':ti,ab,kw OR 'hypnotic sedative agent'/exp OR hypnotic:ti,ab,kw OR sedative:ti,ab,kw OR 'benzodiazepine derivative'/exp OR benzodiazepine:ti,ab,kw OR 'zopiclone'/exp OR zopiclone:ti,ab,kw OR zolpidem:ti,ab,kw OR 'zaleplon'/exp OR zaleplon:ti,ab,kw OR 'eszopiclone'/exp OR eszopiclone:ti,ab,kw OR 'z drug':ti,ab,kw	1,405,909
	#3	'hypericum'/exp OR hypericum:ti,ab,kw OR 'st john*s wort':ti,ab,kw OR 'st johns wort':ti,ab,kw OR 'ginkgo biloba extract'/exp OR ginkgo:ti,ab,kw OR 'omega 3 fatty acid'/exp OR 'omega 3':ti,ab,kw	56,639
	#4	'electroconvulsive therapy'/exp OR 'electroconvulsive therapy':ti,ab,kw OR 'electroconvulsive shock therapy':ti,ab,kw OR ect:ti,ab,kw OR 'transcranial magnetic stimulation'/exp OR 'transcranial magnetic':ti,ab,kw OR 'magnetic stimulation':ti,ab,kw OR tms:ti,ab,kw	66,464
	#5	#2 OR #3 OR #4 OR #5	1,504,035
Relevant outcomes	#6	'neonatal outcome*':ti,ab,kw OR 'neonatal complication*':ti,ab,kw OR 'neonatal morbidity':ti,ab,kw OR teratogen*:ti,ab,kw OR malformation*:ti,ab,kw OR 'congenital malformation'/exp OR congenital:ti,ab,kw OR anomaly:ti,ab,kw OR anomalies:ti,ab,kw OR defect*:ti,ab,kw OR mortality:ti,ab,kw OR 'perinatal mortality'/exp OR 'perinatal death*':ti,ab,kw OR 'infant death*':ti,ab,kw OR 'newborn mortality'/exp OR 'live birth*':ti,ab,kw OR 'still birth*':ti,ab,kw OR stillbirth*:ti,ab,kw OR 'non-live':ti,ab,kw OR miscarriage:ti,ab,kw OR 'spontaneous abortion'/exp OR abortion*:ti,ab,kw OR preterm:ti,ab,kw OR 'prematurity'/exp OR 'premature labor'/exp OR 'premature labor':ti,ab,kw OR 'premature labour':ti,ab,kw OR 'small for gestational age':ti,ab,kw OR sga:ti,ab,kw OR 'small for date infant'/exp OR 'small for date':ti,ab,kw OR 'small-for-date':ti,ab,kw OR 'intrauterine growth retardation'/exp OR iugr:ti,ab,kw OR 'intrauterine growth retardation':ti,ab,kw OR 'intrauterine growth restriction':ti,ab,kw OR 'neonatal adaptation syndrome':ti,ab,kw OR pnas:ti,ab,kw OR 'neonatal behaviour syndrome':ti,ab,kw OR 'neonatal behavior syndrome':ti,ab,kw OR 'persistent pulmonary hypertension':ti,ab,kw OR 'neonatal respiratory distress syndrome'/exp OR 'neonatal respiratory distress':ti,ab,kw OR convulsion*:ti,ab,kw OR tremor*:ti,ab,kw OR spasm*:ti,ab,kw OR autism:ti,ab,kw OR 'autism'/exp OR 'attention deficit hyperactivity disorder'/exp OR 'attention deficit hyperactivity disorder':ti,ab,kw OR adhd:ti,ab,kw OR neurodevelopment*:ti,ab,kw OR 'intelligence quotient'/exp OR 'intelligence quotient':ti,ab,kw OR 'intelligence test'/exp OR 'intelligence test*':ti,ab,kw OR 'behavior disorder'/exp OR 'behavior disorder*':ti,ab,kw OR 'behaviour disorder*':ti,ab,kw OR 'behavioral problem*':ti,ab,kw OR 'behavioural problem*':ti,ab,kw OR 'behavioral outcome*':ti,ab,kw OR 'behavioural outcome*':ti,ab,kw OR 'cognitive development':ti,ab,kw OR 'motor development':ti,ab,kw OR 'postpartum hemorrhage'/exp OR 'postpartum hemorrhage':ti,ab,kw OR 'postpartum haemorrhage':ti,ab,kw	4,026,523
Combined	#7	#1 AND #5	57,484
	#8	#6 AND #7	25,588
Study types	#9	'controlled study'/exp OR 'controlled study':ti,ab,kw OR 'comparative study'/exp OR 'comparative study':ti,ab,kw OR 'case control study'/exp OR 'case control':ti,ab,kw OR 'cohort analysis'/exp OR cohort:ti,ab,kw OR 'cross-sectional study'/exp OR 'cross sectional':ti,ab,kw OR 'longitudinal study'/exp OR longitudinal:ti,ab,kw OR 'follow up':ti,ab,kw OR 'observational study'/exp OR observational:ti,ab,kw OR 'prospective study'/exp OR prospective:ti,ab,kw OR 'retrospective study'/exp OR retrospective:ti,ab,kw OR epidemiol*:ti,ab,kw OR regist*:ti,ab,kw	13,578,148

Search set		Search string	Records
Combined	#10	#8 AND #9	12,340
Limits	#11	#10 NOT ([conference abstract]/lim OR [conference review]/lim OR [letter]/lim OR [editorial]/lim)	9,616
	#12	#11 NOT [animals]/lim	7,067
	#13	#12 NOT [english]/lim	6,597
	#14	#13 AND [2016-2022]/py	2,400
Systematic reviews	#15	'systematic review'/exp OR 'systematic review':ab,ti OR 'systematic literature review':ab,ti OR 'systematic literature search':ab,ti OR 'systematic search':ab,ti OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR metaanalysis:ab,ti OR 'pooled analysis':ab,ti OR 'evidence synthesis':ab,ti OR 'technology assessment':ab,ti OR hta:ab,ti OR 'cochrane':ab,ti	591,719
Combined	#16	#8 AND #15	1,159
Limits	#17	#16 NOT ([conference abstract]/lim OR [conference review]/lim OR [letter]/lim OR [editorial]/lim)	969
	#18	#17 NOT [animals]/lim	945
	#19	#18 NOT [english]/lim	904
SR set	#20	#19 AND [2016-2022]/py	**406**
Primary study set	#21	#14 NOT #20	**2,154**

1.2 Study inclusion/exclusion



1.3 Targeted searches

As mentioned in Section D2.5, targeted searches of the records identified in the literature search were conducted for specific pharmacological agents and key outcomes that were not reported in the AHRQ foundation review but were considered important by the EWG or Harms Expert Subcommittee (see Table App. 2 for details).

Additional targeted searches of the 'primary study set' were carried out for complementary and physical interventions in cases where a foundation review was not identified. These were St John's wort and Ginkgo biloba for complementary interventions (Table App. 3), and ECT and TMS for physical interventions (Table App. 4).

1.3.1 Pharmacological interventions

Table App. 2 Search terms and results for pharmacological interventions targeted search of 'primary study set'

Search term/s	Search results (n)	Excluded (n)	Potentially included (n)	Final included (n)
Pharmacological agents				
vortioxetine[15]	3	3	0	0
agomelatine	3	3	0	0
ketamine[16]	34	34	0	0
cariprazine[15]	0	0	0	0
flupenthixol	0	0	0	0
amisulpride	5	5	0	0
zuclopenthixol	0	0	0	0
droperidol	3	3	0	0
Key outcomes				
poor neonatal adaptation syndrome, pnas, poor neonatal adaptation, neonatal adaptation syndrome, neonatal behaviour syndrome, neonatal behavioural syndrome, neonatal behavior syndrome, neonatal behavioral syndrome	40 (excluding duplicates)	36	4	0
tremor	23	22	1	0

The targeted searches did not identify any additional included studies of the specified pharmacological agents: vortioxetine, agomelatine, ketamine, cariprazine, flupenthixol, zuclopenthixol, amisulpride, droperidol.

Key outcomes

The targeted searches identified five potentially included primary studies related to outcomes not covered in AHRQ 2021 (PNAS and tremor). Three of these studies were excluded as they had been identified and excluded in the AHRQ foundation review (Corti 2019, Ogunyemi 2018, and Videman 2017) (see Appendix 2 for reasons for exclusion). The Salisbury 2016 study was identified and excluded in the 2017 Australian Guideline. The final study identified (Rommel 2022) was a large population registry study that looked at PNAS in women with antidepressant exposure compared with no antidepressant exposure during pregnancy (all women had been taking antidepressants prior to pregnancy). Rommel 2022 was excluded due to the risk of unmeasured confounding. The registry contained no data on diagnosis or disease severity, therefore confounding by indication could not be adjusted for (it is conceivable that individuals continuing antidepressants during pregnancy may have more severe symptoms than those who discontinue use).

[15] This drug was included in the AHRQ PICOTS. Although it was not identified in the literature searches, it would have been included in the AHRQ searches.

[16] Studies investigating the use of ketamine in combination with other pharmacological interventions at the delivery stage (i.e., not for the treatment or prevention of mental health problems) were excluded.

The targeted searches did not identify any additional included studies for the outcomes of PNAS or tremors.

1.3.2 Complementary interventions

Table App. 3 Search terms and results for complementary interventions targeted search of 'primary study set'

Search term/s	Search results (n)	Excluded (n)	Potentially included (n)	Final included (n)
Hypericum, john, wort	9	9	0	0
Ginkgo, biloba	0	0	0	0

The targeted searches did not identify any additional included studies for complementary interventions.

1.3.3 Physical interventions

Table App. 4 Search terms and results for physical interventions targeted search of 'primary study set'

Search term/s	Search results (n)	Excluded (n)	Potentially included (n)	Final included (n)
Electroconvulsive, ECT	19	11	8	0
Transcranial, magnetic, stimulation, TMS, tdcs	272	265	7	0

The targeted searches did not identify any additional included studies for physical interventions.

Appendix 2 Excluded studies list

The following studies were excluded during full text screening.

(2020). Lithium during pregnancy: Malformations, fetotoxicity and uncertain long-term effects. Prescrire International, 29(214), 97-99
RefID: 178
Reason for Exclusion: wrong publication type

(2021). SSRI antidepressants and pregnancy: Long-term neuropsychiatric disorders in exposed children? (continued). Prescrire International, 30(222), 16-18
RefID: 99
Reason for Exclusion: wrong study type

Alkhafajy, W. R.,Alyaseen, F. F. (2018). The role of omega 3 supplementation on pregnancy and fetal outcomes. Journal of Pharmaceutical Sciences and Research, 10(7), 1646-1648
RefID: 2774
Reason for Exclusion: wrong study type

Andrade, C. (2019). Gestational exposure to benzodiazepines, 2: The risk of congenital malformations examined through the prism of compatibility intervals. Journal of Clinical Psychiatry, 80(5).
RefID: 231
Reason for Exclusion: wrong publication type

Banu, S.,Ramakrishnan, M. (2019). Teratogenic potential of drugs used – A systematic review to aid in evidence based practice and decision making. Indian Journal of Public Health Research and Development, 10(11), 3580-3583
RefID: 190
Reason for Exclusion: wrong publication type

Beex-Oosterhuis, M. M.,Samb, A.,Heerdink, E. R.,Souverein, P. C.,Van Gool, A. R.,Meyboom, R. H. B.,van Marum, R. J. (2020). Safety of clozapine use during pregnancy: Analysis of international pharmacovigilance data. Pharmacoepidemiology and Drug Safety, 29(6), 725-735
RefID: 2715
Reason for Exclusion: wrong study type

Bernstein, N.,Akram, M.,Yaniv-Bachrach, Z.,Daniyal, M. (2021). Is it safe to consume traditional medicinal plants during pregnancy? Phytotherapy Research, 35(4), 1908-1924
RefID: 66
Reason for Exclusion: wrong intervention purpose

Best, K. P.,Gibson, R. A.,Yelland, L. N.,Leemaqz, S.,Gomersall, J.,Liu, G.,Makrides, M. (2020). Effect of omega-3 LCPUFA supplementation on maternal fatty acid and oxylipin concentrations during pregnancy. Prostaglandins Leukotrienes and Essential Fatty Acids, 162
RefID: 2618
Reason for Exclusion: wrong outcomes

Black, E.,Khor, K. E.,Kennedy, D.,Chutatape, A.,Sharma, S.,Vancaillie, T.,Demirkol, A. (2019). Medication Use and Pain Management in Pregnancy: A Critical Review. Pain Practice.
RefID: 229
Reason for Exclusion: wrong study type

Burrell-Ward, H.,Fromson, J. A.,Cooper, J. J.,de Oliveira, G.,Almeida, M. (2018). Recommendations for the use of ECT in pregnancy: literature review and proposed clinical protocol. Archives of Women's Mental

Health, 1-8
RefID: 277
Reason for Exclusion: wrong study type

Corti, S., Pileri, P., Mazzocco, M. I., Mandò, C., Moscatiello, A. F., Cattaneo, D., Cheli, S., Baldelli, S., Pogliani, L., Clementi, E., & Cetin, I. (2019). Neonatal outcomes in maternal depression in relation to intrauterine drug exposure [Article]. *Frontiers in Pediatrics*, *7*. https://doi.org/10.3389/fped.2019.00309
Reason for Exclusion: excluded by AHRQ 2021, ineligible comparator

Creeley, C. E.,Denton, L. K. (2019). Use of prescribed psychotropics during pregnancy: A systematic review of pregnancy, neonatal, and childhood outcomes. Brain Sciences, 9(9).
RefID: 193
Reason for Exclusion: wrong study type

Dragioti, E.,Solmi, M.,Favaro, A.,Fusar-Poli, P.,Dazzan, P.,Thompson, T.,Stubbs, B.,Firth, J.,Fornaro, M.,Tsartsalis, D.,Carvalho, A. F.,Vieta, E.,McGuire, P.,Young, A. H.,Shin, J. I.,Correll, C. U.,Evangelou, E. (2019). Association of Antidepressant Use with Adverse Health Outcomes: A Systematic Umbrella Review. JAMA Psychiatry, 76(12), 1241-1255
RefID: 186
Reason for Exclusion: wrong population (not focused on perinatal exposure)

Edinoff, A. N.,Odisho, A. S.,Lewis, K.,Kaskas, A.,Hunt, G.,Cornett, E. M.,Kaye, A. D.,Kaye, A.,Morgan, J.,Barrilleaux, P. S.,Lewis, D.,Viswanath, O.,Urits, I. (2021). Brexanolone, a GABAA Modulator, in the Treatment of Postpartum Depression in Adults: A Comprehensive Review. Frontiers in Psychiatry, 12
RefID: 31
Reason for Exclusion: wrong outcome, narrative review

Engeland, A.,Bjørge, T.,Klungsøyr, K.,Skurtveit, S.,Furu, K. (2017). Preterm births and use of medication in early adulthood: a population-based registry study. Pharmacoepidemiology and Drug Safety, 26(7), 742-751
RefID: 2600
Reason for Exclusion: wrong study type

Gentile, S.,Fusco, M. L. (2019). Schizophrenia and motherhood. Psychiatry and Clinical Neurosciences, 73(7), 376-385
RefID: 199
Reason for Exclusion: wrong intervention purpose

Gould, J. F.,Anderson, P. J.,Yelland, L. N.,Gibson, R. A.,Makrides, M. (2021). The influence of prenatal dha supplementation on individual domains of behavioral functioning in school-aged children: Follow-up of a randomized controlled trial. Nutrients, 13(9)
RefID: 2674
Reason for Exclusion: wrong study type

Hauspurg, A.,Lemon, L. S.,Serra, A. E.,Sharma, S.,Venkataramanan, R.,Caritis, S. N. (2018). Impact of Obesity on the Rate of Recurrent Spontaneous Preterm Birth in Women Treated with 17-alpha Hydroxyprogesterone Caproate. American Journal of Perinatology, 35(9), 809-814
RefID: 2642
Reason for Exclusion: wrong intervention

Healy, D.,Le Noury, J.,Mangin, D. (2016). Links between serotonin reuptake inhibition during pregnancy and neurodevelopmental delay/spectrum disorders: A systematic review of epidemiological and physiological evidence. International Journal of Risk and Safety in Medicine, 28(3), 125-141
RefID: 406
Reason for Exclusion: wrong comparator

Heller, H. M.,Ravelli, A. C. J.,Bruning, A. H. L.,de Groot, C. J. M.,Scheele, F.,van Pampus, M. G.,Honig, A. (2017). Increased postpartum haemorrhage, the possible relation with serotonergic and other psychopharmacological drugs: A matched cohort study. BMC Pregnancy and Childbirth, 17(1)
RefID: 328
Reason for Exclusion: wrong study type

Judge, M. P.,Casavant, S. G.,Dias, J. A. M.,McGrath, J. M. (2016). Reduced DHA transfer in diabetic pregnancies: Mechanistic basis and long-term neurodevelopmental implications. Nutrition Reviews, 74(6), 411-420
RefID: 385
Reason for Exclusion: wrong population (focus on diabetic pregnancies)

Khan, S. J.,Fersh, M. E.,Ernst, C.,Klipstein, K.,Albertini, E. S.,Lusskin, S. I. (2016). Bipolar Disorder in Pregnancy and Postpartum: Principles of Management. Current Psychiatry Reports, 18(2), 1-11
RefID: 2571
Reason for Exclusion: wrong study type

Khandelwal, S.,Kondal, D.,Chaudhry, M.,Patil, K.,Swamy, M. K.,Pujeri, G.,Mane, S. B.,Kudachi, Y.,Gupta, R.,Ramakrishnan, U.,Stein, A. D.,Prabhakaran, D.,Tandon, N. (2021). Prenatal maternal docosahexaenoic acid (Dha) supplementation and newborn anthropometry in india: Findings from dhani. Nutrients, 13(3), 1-12
RefID: 2611
Reason for Exclusion: wrong study type

Kim, J. Y.,Son, M. J.,Son, C. Y.,Radua, J.,Eisenhut, M.,Gressier, F.,Koyanagi, A.,Carvalho, A. F.,Stubbs, B.,Solmi, M.,Rais, T. B.,Lee, K. H.,Kronbichler, A.,Dragioti, E.,Shin, J. I.,Fusar-Poli, P. (2019). Environmental risk factors and biomarkers for autism spectrum disorder: an umbrella review of the evidence. The Lancet Psychiatry, 6(7), 590-600
RefID: 197
Reason for Exclusion: wrong population (focus broader than perinatal exposure)

Kuper, S. G.,Abramovici, A. R.,Jauk, V. C.,Harper, L. M.,Biggio, J. R.,Tita, A. T. (2017). The effect of omega-3 supplementation on pregnancy outcomes by smoking status. American Journal of Obstetrics and Gynecology, 217(4), 476.e1-476.e6
RefID: 2648
Reason for Exclusion: wrong outcomes (focus on smoking status)

Lee, S. J.,Woodward, L. J.,Henderson, J. M. T. (2019). Educational achievement at age 9.5 years of children born to mothers maintained on methadone during pregnancy. PLoS ONE, 14(10)
RefID: 2595
Reason for Exclusion: wrong intervention

Letourneau, N.,Aghajafari, F.,Bell, R. C.,Deane, A. J.,Dewey, D.,Field, C.,Giesbrecht, G.,Kaplan, B.,Leung, B.,Ntanda, H. (2022). The Alberta Pregnancy Outcomes and Nutrition (APrON) longitudinal study: Cohort profile and key findings from the first three years. BMJ Open, 12(2)
RefID: 2602
Reason for Exclusion: wrong study type

Makrides, M.,Best, K. (2016). Docosahexaenoic acid and preterm birth. Annals of Nutrition and Metabolism, 69(1), 30-34
RefID: 2656
Reason for Exclusion: wrong study type

Makrides, M.,Best, K.,Yelland, L.,McPhee, A.,Zhou, S.,Quinlivan, J.,Dodd, J.,Atkinson, E.,Safa, H.,Van Dam, J.,Khot, N.,Dekker, G.,Skubisz, M.,Anderson, A.,Kean, B.,Bowman, A.,McCallum, C.,Cashman, K.,Gibson, R.

(2019). A randomized trial of prenatal n−3 fatty acid supplementation and preterm delivery. New England Journal of Medicine, 381(11), 1035-1045
RefID: 2741
Reason for Exclusion: wrong study type

Manuck, T. A.,Stoddard, G. J.,Fry, R. C.,Esplin, M. S.,Varner, M. W. (2016). Nonresponse to 17-alpha hydroxyprogesterone caproate for recurrent spontaneous preterm birth prevention: clinical prediction and generation of a risk scoring system. American Journal of Obstetrics and Gynecology, 215(5), 622.e1-622.e8
RefID: 2655
Reason for Exclusion: wrong intervention

Marco, S.,Dragioti, E.,Arango, C.,Radua, J.,Ostinelli, E.,Kilic, O.,Yilmaz, U. E.,Yalcinay-İnan, M.,Soares, F. C.,Mariano, L.,Mosillo, P.,Cortese, S.,Correll, C. U.,Carvalho, A. F.,Shin, J. I.,Fusar-Poli, P. (2020). Risk and protective factors for mental disorders with onset in childhood/adolescence: an umbrella review of published meta-analyses of observational longitudinal studies. Neuroscience and biobehavioral reviews.
RefID: 129
Reason for Exclusion: wrong population (focus broader than perinatal exposure)

Mesches, G. A.,Wisner, K. L.,Betcher, H. K. (2020). A common clinical conundrum: Antidepressant treatment of depression in pregnant women. Seminars in Perinatology, 44(3)
RefID: 2563
Reason for Exclusion: wrong study type

Middleton, P.,Gomersall, J. C.,Gould, J. F.,Shepherd, E.,Olsen, S. F.,Makrides, M. (2019). Omega-3 Fatty Acid Addition during Pregnancy. Obstetrical and Gynecological Survey, 74(4), 189-191
RefID: 215
Reason for Exclusion: wrong publication type

Munk-Olsen, T.,Liu, X.,Viktorin, A.,Brown, H. K.,Di Florio, A.,D'Onofrio, B. M.,Gomes, T.,Howard, L. M.,Khalifeh, H.,Krohn, H.,Larsson, H.,Lichtenstein, P.,Taylor, C. L.,Van Kamp, I.,Wesseloo, R.,Meltzer-Brody, S.,Vigod, S. N.,Bergink, V. (2018). Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. The Lancet Psychiatry, 5(8), 644-652
RefID: 265
Reason for Exclusion: wrong study type

Ogunyemi, D., Jovanovski, A., Liu, J., Friedman, P., Sugiyama, N., Creps, J., & Madan, I. (2018). The Contribution of Untreated and Treated Anxiety and Depression to Prenatal, Intrapartum, and Neonatal Outcomes [Article]. *AJP Reports*, *8*(3), e146-e157. https://doi.org/10.1055/s-0038-1661379
Reason for Exclusion: excluded by AHRQ 2021, indirect comparison

Ornoy, A.,Liza, W.,Ergaz, Z. (2016). Genetic syndromes, maternal diseases and antenatal factors associated with autism spectrum disorders (ASD). Frontiers in Neuroscience, 10(JUL)
RefID: 2816
Reason for Exclusion: wrong study type

Ostadrahimi, A.,Mohammad-Alizadeh, S.,Mirghafourvand, M.,Farshbaf-Khalili, S.,Jafarilar-Agdam, N.,Farshbaf-Khalili, A. (2017). The effect of fish oil supplementation on maternal and neonatal outcomes: A triple-blind, randomized controlled trial. Journal of Perinatal Medicine, 45(9), 1069-1077
RefID: 2647
Reason for Exclusion: wrong study type

O'Sullivan, D. L.,Byatt, N.,Dossett, E. C. (2022). Long-Acting Injectable Antipsychotic Medications in Pregnancy: A Review. Journal of the Academy of Consultation-Liaison Psychiatry, 63(1), 53-60
RefID: 9
Reason for Exclusion: wrong comparator

Pacchiarotti, I.,León-Caballero, J.,Murru, A.,Verdolini, N.,Furio, M. A.,Pancheri, C.,Valentí, M.,Samalin, L.,Roigé, E. S.,González-Pinto, A.,Montes, J. M.,Benabarre, A.,Crespo, J. M.,de Dios Perrino, C.,Goikolea, J. M.,Gutiérrez-Rojas, L.,Carvalho, A. F.,Vieta, E. (2016). Mood stabilizers and antipsychotics during breastfeeding: Focus on bipolar disorder. European Neuropsychopharmacology, 26(10), 1562-1578
RefID: 374
Reason for Exclusion: wrong outcome

Penfield-Cyr, A.,Monthe-Dreze, C.,Smid, M. C.,Sen, S. (2018). Maternal BMI, Mid-pregnancy Fatty Acid Concentrations, and Perinatal Outcomes. Clinical Therapeutics, 40(10), 1659-1667.e1
RefID: 2640
Reason for Exclusion: wrong outcomes (focus on BMI)

Ramakrishnan, U.,Gonzalez-Casanova, I.,Schnaas, L.,DiGirolamo, A.,Quezada, A. D.,Pallo, B. C.,Hao, W.,Neufeld, L. M.,Rivera, J. A.,Stein, A. D.,Martorell, R. (2016). Prenatal supplementation with DHA improves attention at 5 y of age: A randomized controlled trial. American Journal of Clinical Nutrition, 104(4), 1075-1082
RefID: 2803
Reason for Exclusion: wrong study type

Ramsden, C. E.,Makrides, M.,Yuan, Z. X.,Horowitz, M. S.,Zamora, D.,Yelland, L. N.,Best, K.,Jensen, J.,Taha, A. Y.,Gibson, R. A. (2020). Plasma oxylipins and unesterified precursor fatty acids are altered by DHA supplementation in pregnancy: Can they help predict risk of preterm birth? Prostaglandins Leukotrienes and Essential Fatty Acids, 153.
RefID: 2628
Reason for Exclusion: wrong outcome (narrow focus)

Rommel, A. S., Momen, N. C., Molenaar, N. M., Agerbo, E., Bergink, V., Munk-Olsen, T., & Liu, X. (2022). Antidepressant use during pregnancy and risk of adverse neonatal outcomes: A comprehensive investigation of previously identified associations. Acta Psychiatrica Scandinavica.
Reason for Exclusion: did not adjust for confounding by indication or disease severity

Rönnqvist, I.,Brus, O.,Hammar, (2019). Rehospitalization of Postpartum Depression and Psychosis after Electroconvulsive Therapy: A Population-Based Study with a Matched Control Group. Journal of ECT, 35(4), 264-271
RefID: 2565
Reason for Exclusion: wrong outcome

Rotem-Kohavi, N.,Oberlander, T. F. (2017). Variations in Neurodevelopmental Outcomes in Children with Prenatal SSRI Antidepressant Exposure. Birth Defects Research, 109(12), 909-923
RefID: 325
Reason for Exclusion: wrong study type

Salisbury, A. L., O'Grady, K. E., Battle, C. L., Wisner, K. L., Anderson, G. M., Stroud, L. R., ... & Lester, B. M. (2016). The roles of maternal depression, serotonin reuptake inhibitor treatment, and concomitant benzodiazepine use on infant neurobehavioral functioning over the first postnatal month. American Journal of Psychiatry, 173(2), 147-157.
Reason for Exclusion: excluded in 2017 COPE guideline, wrong outcome

Sass, L.,Bjarnadóttir, E.,Stokholm, J.,Chawes, B.,Vinding, R. K.,Mora-Jensen, A. R. C.,Thorsen, J.,Noergaard, S.,Ebdrup, B. H.,Jepsen, J. R. M.,Fagerlund, B.,Bønnelykke, K.,Lauritzen, L.,Bisgaard, H. (2021). Fish Oil Supplementation in Pregnancy and Neurodevelopment in Childhood-A Randomized Clinical Trial. Child development, 92(4), 1624-1635
RefID: 2676
Reason for Exclusion: wrong study type

Selmer, R.,Haglund, B.,Furu, K.,Andersen, M.,Nørgaard, M.,Zoëga, H.,Kieler, H. (2016). Individual-based versus aggregate meta-analysis in multi-database studies of pregnancy outcomes: the Nordic example of selective serotonin reuptake inhibitors and venlafaxine in pregnancy. Pharmacoepidemiology and Drug Safety, 25(10), 1160-1169
RefID: 375
Reason for Exclusion: wrong study type

Siahanidou, T.,Spiliopoulou, C. (2020). Pharmacological Neuroprotection of the Preterm Brain: Current Evidence and Perspectives. American Journal of Perinatology
RefID: 2630
Reason for Exclusion: wrong study type

Simmonds, L. A.,Sullivan, T. R.,Skubisz, M.,Middleton, P. F.,Best, K. P.,Yelland, L. N.,Quinlivan, J.,Zhou, S. J.,Liu, G.,McPhee, A. J.,Gibson, R. A.,Makrides, M. (2020). Omega-3 fatty acid supplementation in pregnancy—baseline omega-3 status and early preterm birth: exploratory analysis of a randomised controlled trial. BJOG: An International Journal of Obstetrics and Gynaecology, 127(8), 975-981
RefID: 2624
Reason for Exclusion: wrong study type

Smid, M. C.,Stuebe, A. M.,Manuck, T. A.,Sen, S. (2019). Maternal obesity, fish intake, and recurrent spontaneous preterm birth. Journal of Maternal-Fetal and Neonatal Medicine, 32(15), 2486-2492
RefID: 2632
Reason for Exclusion: wrong outcome (focus on obesity)

Smith, B.,Dubovsky, S. L. (2017). Pharmacotherapy of mood disorders and psychosis in pre-and post-natal women. Expert Opinion on Pharmacotherapy, 18(16), 1703-1719
RefID: 2569
Reason for Exclusion: wrong study type

Strain, J. J.,Love, T. M.,Yeates, A. J.,Weller, D.,Mulhern, M. S.,McSorley, E. M.,Thurston, S. W.,Watson, G. E.,Mruzek, D.,Broberg, K.,Rand, M. D.,Henderson, J.,Shamlaye, C. F.,Myers, G. J.,Davidson, P. W.,Van Wijngaarden, E. (2021). Associations of prenatal methylmercury exposure and maternal polyunsaturated fatty acid status with neurodevelopmental outcomes at 7 years of age: Results from the Seychelles Child Development Study Nutrition Cohort 2. American Journal of Clinical Nutrition, 113(2), 304-313
RefID: 2593
Reason for Exclusion: wrong intervention

Thoene, M.,Van Ormer, M.,Yuil-Valdes, A.,Bruett, T.,Natarajan, S. K.,Mukherjee, M.,Thompson, M.,Nordgren, T. M.,Van Lippevelde, W.,Overby, N. C.,Adu-Bonsaffoh, K.,Anderson-Berry, A.,Hanson, C. (2020). Fat-soluble nutrients and Omega-3 fatty acids as modifiable factors influencing preterm birth risk. Placenta, 98, 38-42
RefID: 2620
Reason for Exclusion: wrong study type

Trifu, S. C.,Popescu, A.,Marian, M. A. (2020). Affective disorders: A question of continuing treatment during pregnancy (Review). Experimental and Therapeutic Medicine, 20(4), 3474-3482
RefID: 125
Reason for Exclusion: wrong study type

Uguz, F. (2021). The relationship between maternal antidepressants and neonatal hypoglycemia: A systematic review. Anadolu Psikiyatri Dergisi, 22(5), 224-229
RefID: 104
Reason for Exclusion: wrong outcome, wrong study type

Videman, M., Tokariev, A., Saikkonen, H., Stjerna, S., Heiskala, H., Mantere, O., & Vanhatalo, S. (2017). Newborn Brain Function Is Affected by Fetal Exposure to Maternal Serotonin Reuptake Inhibitors [Article]. *Cerebral Cortex*, *27*(6), 3208-3216. https://doi.org/10.1093/cercor/bhw153
Reason for Exclusion: excluded by AHRQ 2021, ineligible comparator

Womersley, K.,Ripullone, K.,Agius, M. (2017). What are the risks associated with different Selective Serotonin Re-Uptake Inhibitors (SSRIS) to treat depression and anxiety in pregnancy? An evaluation of current evidence. Psychiatria Danubina, 29, S629-S644
RefID: 354
Reason for Exclusion: wrong study type

Appendix 3 Included studies list

3.1 Pharmacological

3.1.1 Foundation review

Viswanathan, M.,Middleton, J. C.,Stuebe, A. M.,Berkman, N. D.,Goulding, A. N.,McLaurin-Jiang, S.,Dotson, A. B.,Coker-Schwimmer, M.,Baker, C.,Voisin, C. E.,Bann, C.,Gaynes, B. N. (2021). Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Meta-Analysis of Pharmacotherapy. Psychiatric Research and Clinical Practice, 3(3), 123-140
RefID: 33

Other related reports and publications associated with the foundation review:

Viswanathan M, Middleton JC, Stuebe A., Berkman N., Goulding AN, McLaurin-Jiang S, Dotson AB, Coker-Schwimmer M, Baker C, Voisin C, Bann C, Gaynes BN. Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Systematic Review of Perinatal Pharmacologic Interventions. Comparative Effectiveness Review No. 236. (Prepared by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 290-2015-00011-I.) AHRQ Publication No. 21-EHC001. Rockville, MD: Agency for Healthcare Research and Quality; April 2021. DOI: https://doi.org/10.23970/AHRQEPCCER236.

Middleton, J., Viswanathan, M., Goulding, A., Hoffman, V., Stuebe, A., Gaynes, B., Bann, C., McLaurin-Jiang, S., Clarke, R., Suvada, K., Voisin, C., Weber, R., Woodell, C. Maternal and fetal effects of mental health treatments in pregnant and breastfeeding women: a systematic review of pharmacological interventions. PROSPERO 2019 CRD42019124057. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019124057

Goulding, A. N., Metz, T. D., Middleton, J. C., Hoffman, M. C., Miller, E. S., Simas, T. A. M., ... & Gaynes, B. N. (2022). Pharmacologic Treatment for Perinatal Mental Health Disorders. *Obstetrics & Gynecology*, *139*(2), 297-303.

3.1.2 Other systematic reviews

Antidepressants

Akioyamen, L. E.,Minhas, H.,Holloway, A. C.,Taylor, V. H.,Akioyamen, N. O.,Sherifali, D. (2016). Effects of depression pharmacotherapy in fertility treatment on conception, birth, and neonatal health: A systematic review. Journal of Psychosomatic Research, 84**,** 69-80
RefID: 389

Al-Fadel, N.,Alrwisan, A. (2021). Antidepressant Use During Pregnancy and the Potential Risks of Motor Outcomes and Intellectual Disabilities in Offspring: A Systematic Review. Drugs - Real World Outcomes, 8(2)**,** 105-123
RefID: 51

Andalib, S.,Emamhadi, M. R.,Yousefzadeh-Chabok, S.,Shakouri, S. K.,Høilund-Carlsen, P. F.,Vafaee, M. S.,Michel, T. M. (2017). Maternal SSRI exposure increases the risk of autistic offspring: A meta-analysis and systematic review. European Psychiatry, 45**,** 161-166
RefID: 320

Araujo, J. S. A.,Delgado, I. F.,Paumgartten, F. J. R. (2020). Antenatal exposure to antidepressant drugs and the risk of neurodevelopmental and psychiatric disorders: a systematic review. Cadernos de saude publica, 36(2)**,** e00026619
RefID: 185

Bérard, A.,Iessa, N.,Chaabane, S.,Muanda, F. T.,Boukhris, T.,Zhao, J. P. (2016). The risk of major cardiac malformations associated with paroxetine use during the first trimester of pregnancy: A systematic review and meta-analysis. British Journal of Clinical Pharmacology, 81(4), 589-604
RefID: 393

Biffi, A.,Cantarutti, A.,Rea, F.,Locatelli, A.,Zanini, R.,Corrao, G. (2020). Use of antidepressants during pregnancy and neonatal outcomes: An umbrella review of meta-analyses of observational studies. Journal of Psychiatric Research, 124, 99-108
RefID: 155

Chang, Q.,Ma, X. Y.,Xu, X. R.,Su, H.,Wu, Q. J.,Zhao, Y. H. (2020). Antidepressant use in depressed women during pregnancy and the risk of preterm birth: A systematic review and meta-analysis of 23 cohort studies. Frontiers in Pharmacology, 11, 1-12
RefID: 154

De Vries, C.,Gadzhanova, S.,Sykes, M. J.,Ward, M.,Roughead, E. (2021). A Systematic Review and Meta-Analysis Considering the Risk for Congenital Heart Defects of Antidepressant Classes and Individual Antidepressants. Drug Safety, 44(3), 291-312
RefID: 73

Eke, A. C.,Saccone, G.,Berghella, V. (2016). Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and risk of preterm birth: a systematic review and meta-analysis. BJOG: An International Journal of Obstetrics and Gynaecology, 123(12), 1900-1907
RefID: 370

Fitton, C. A.,Steiner, M. F. C.,Aucott, L.,Pell, J. P.,Mackay, D. F.,Fleming, M.,McLay, J. S. (2020). In utero exposure to antidepressant medication and neonatal and child outcomes: a systematic review. Acta Psychiatrica Scandinavica, 141(1), 21-33
RefID: 170

Gao, S. Y.,Wu, Q. J.,Sun, C.,Zhang, T. N.,Shen, Z. Q.,Liu, C. X.,Gong, T. T.,Xu, X.,Ji, C.,Huang, D. H.,Chang, Q.,Zhao, Y. H. (2018). Selective serotonin reuptake inhibitor use during early pregnancy and congenital malformations: A systematic review and meta-analysis of cohort studies of more than 9 million births. BMC Medicine, 16(1),
RefID: 249

Gao, S. Y.,Wu, Q. J.,Zhang, T. N.,Shen, Z. Q.,Liu, C. X.,Xu, X.,Ji, C.,Zhao, Y. H. (2017). Fluoxetine and congenital malformations: a systematic review and meta-analysis of cohort studies. British Journal of Clinical Pharmacology, 83(10), 2134-2147
RefID: 352

Grove, K.,Lewis, A. J.,Galbally, M. (2018). Prenatal antidepressant exposure and child motor development: A meta-analysis. Pediatrics, 142(1),
RefID: 270

Halvorsen, A.,Hesel, B.,Østergaard, S. D.,Danielsen, A. A. (2019). In utero exposure to selective serotonin reuptake inhibitors and development of mental disorders: a systematic review and meta-analysis. Acta Psychiatrica Scandinavica, 139(6), 493-507
RefID: 205

Hendrick, V.,Suri, R.,Gitlin, M. J.,Ortiz-Portillo, E. (2017). Bupropion Use During Pregnancy: A Systematic Review. The primary care companion for CNS disorders, 19(5),
RefID: 314

Jiang, H. Y.,Peng, C. T.,Zhang, X.,Ruan, B. (2018). Antidepressant use during pregnancy and the risk of attention-deficit/hyperactivity disorder in the children: a meta-analysis of cohort studies. BJOG: An

International Journal of Obstetrics and Gynaecology, 125(9), 1077-1084
RefID: 266

Jiang, H. Y.,Xu, L. L.,Li, Y. C.,Deng, M.,Peng, C. T.,Ruan, B. (2016). Antidepressant use during pregnancy and risk of postpartum hemorrhage: A systematic review and meta-analysis. Journal of Psychiatric Research, 83, 160-167
RefID: 357

Kaplan, Y. C.,Keskin-Arslan, E.,Acar, S.,Sozmen, K. (2016). Prenatal selective serotonin reuptake inhibitor use and the risk of autism spectrum disorder in children: A systematic review and meta-analysis. Reproductive Toxicology, 66, 31-43
RefID: 358

Kaplan, Y. C.,Keskin-Arslan, E.,Acar, S.,Sozmen, K. (2017). Maternal SSRI discontinuation, use, psychiatric disorder and the risk of autism in children: a meta-analysis of cohort studies. British Journal of Clinical Pharmacology, 83(12), 2798-2806
RefID: 302

Kautzky, A.,Slamanig, R.,Unger, A.,Höflich, A. (2022). Neonatal outcome and adaption after in utero exposure to antidepressants: A systematic review and meta-analysis. Acta Psychiatrica Scandinavica, 145(1), 6-28
RefID: 8

Kobayashi, T.,Matsuyama, T.,Takeuchi, M.,Ito, S. (2016). Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis. Reproductive Toxicology, 65, 170-178
RefID: 373

Leshem, R.,Bar-Oz, B.,Diav-Citrin, O.,Gbaly, S.,Soliman, J.,Renoux, C.,Matok, I. (2021). Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) during pregnancy and the risk for autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) in the offspring: A true effect or a bias? a systematic review & meta-analysis. Current Neuropharmacology, 19(6), 896-903
RefID: 91

Leung, M. T. Y.,Wong, K. H.,Ho, P. W. H.,Ip, P.,Wei, L.,Wong, I. C. K.,Man, K. K. C. (2021). Gestational exposure to antidepressants and risk of seizure in offspring: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 131, 345-359
RefID: 19

Man, K. K. C.,Chan, E. W.,Ip, P.,Coghill, D.,Simonoff, E.,Chan, P. K. L.,Lau, W. C. Y.,Schuemie, M. J.,Sturkenboom, M. C. J. M.,Wong, I. C. K. (2018). Prenatal antidepressant exposure and the risk of attention-deficit hyperactivity disorder in children: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 86, 1-11
RefID: 287

Masarwa, R.,Bar-Oz, B.,Gorelik, E.,Reif, S.,Perlman, A.,Matok, I. (2019). Prenatal exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and risk for persistent pulmonary hypertension of the newborn: a systematic review, meta-analysis, and network meta-analysis. American Journal of Obstetrics and Gynecology, 220(1), 57.e1-57.e13
RefID: 225

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RefID: 331

Mitchell, J.,Goodman, J. (2018). Comparative effects of antidepressant medications and untreated major depression on pregnancy outcomes: a systematic review. Archives of Women's Mental Health, 21(5)**,** 505-516
RefID: 257

Morales, D. R.,Slattery, J.,Evans, S.,Kurz, X. (2018). Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: Systematic review of observational studies and methodological considerations. BMC Medicine, 16(1)**,**
RefID: 299

Ng, Q. X.,Venkatanarayanan, N.,Ho, C. Y. X.,Sim, W. S.,Lim, D. Y.,Yeo, W. S. (2019). Selective Serotonin Reuptake Inhibitors and Persistent Pulmonary Hypertension of the Newborn: An Update Meta-Analysis. Journal of Women's Health, 28(3)**,** 331-338
RefID: 221

Prady, S. L.,Hanlon, I.,Fraser, L. K.,Mikocka-Walus, A. (2018). A systematic review of maternal antidepressant use in pregnancy and short- and long-term offspring's outcomes. Archives of Women's Mental Health, 21(2)**,** 127-140
RefID: 282

Rommel, A. S.,Bergink, V.,Liu, X.,Munk-Olsen, T.,Molenaar, N. M. (2020). Long-term effects of intrauterine exposure to antidepressants on physical, neurodevelopmental, and psychiatric outcomes: A systematic review. Journal of Clinical Psychiatry, 81(3)
RefID: 152

Smit, M.,Dolman, K. M.,Honig, A. (2016). Mirtazapine in pregnancy and lactation - A systematic review. European Neuropsychopharmacology, 26(1)**,** 126-135
RefID: 405

Uguz, F. (2018). Maternal Antidepressant Use during Pregnancy and the Risk of Attention-Deficit/Hyperactivity Disorder in Children: A Systematic Review of the Current Literature. Journal of Clinical Psychopharmacology, 38(3)**,** 254-259
RefID: 275

Uguz, F. (2019). The Use of Antidepressant Medications during Pregnancy and the Risk of Neonatal Seizures: A Systematic Review. Journal of Clinical Psychopharmacology, 39(5)**,** 479-484
RefID: 195

Uguz, F. (2020). Selective serotonin reuptake inhibitors and the risk of congenital anomalies: a systematic review of current meta-analyses. Expert Opinion on Drug Safety, 19(12)**,** 1595-1604
RefID: 111

Uguz, F. (2021). Neonatal and Childhood Outcomes in Offspring of Pregnant Women Using Antidepressant Medications: A Critical Review of Current Meta-Analyses. Journal of Clinical Pharmacology, 61(2), 146-158
RefID: 83

Vega, M. L.,Newport, G. C.,Bozhdaraj, D.,Saltz, S. B.,Nemeroff, C. B.,Newport, D. J. (2020). Implementation of advanced methods for reproductive pharmacovigilance in autism: A meta-analysis of the effects of prenatal antidepressant exposure. American Journal of Psychiatry, 177(6), 506-517
RefID: 151

Vlenterie, R.,van Gelder, M. M. H. J.,Anderson, et al. (2021). Associations Between Maternal Depression, Antidepressant Use During Pregnancy, and Adverse Pregnancy Outcomes: An Individual Participant Data

Meta-analysis. Obstetrics and gynecology, 138(4)**,** 633-646
RefID: 29

Wang, J.,Cosci, F. (2021). Neonatal Withdrawal Syndrome following Late in utero Exposure to Selective Serotonin Reuptake Inhibitors: A Systematic Review and Meta-Analysis of Observational Studies. Psychotherapy and Psychosomatics, 90(5)**,** 299-307
RefID: 44

Xing, D.,Wu, R.,Chen, L.,Wang, T. (2020). Maternal use of antidepressants during pregnancy and risks for adverse perinatal outcomes: a meta-analysis. Journal of Psychosomatic Research, 137**,**
RefID: 126

Zhang, T. N.,Gao, S. Y.,Shen, Z. Q.,Li, D.,Liu, C. X.,Lv, H. C.,Zhang, Y.,Gong, T. T.,Xu, X.,Ji, C.,Wu, Q. J. (2017). Use of selective serotonin-reuptake inhibitors in the first trimester and risk of cardiovascular-related malformations: a meta-analysis of cohort studies. Scientific reports, 7**,** 43085
RefID: 343

Zhao, X.,Liu, Q.,Cao, S.,Pang, J.,Zhang, H.,Feng, T.,Deng, Y.,Yao, J.,Li, H. (2018). A meta-analysis of selective serotonin reuptake inhibitors (SSRIs) use during prenatal depression and risk of low birth weight and small for gestational age. Journal of Affective Disorders, 241**,** 563-570
RefID: 243

Zhou, X. H.,Li, Y. J.,Ou, J. J.,Li, Y. M. (2018). Association between maternal antidepressant use during pregnancy and autism spectrum disorder: An updated meta-analysis. Molecular Autism, 9(1)**,**
RefID: 286

Antipsychotics

Cuomo, A.,Goracci, A.,Fagiolini, A. (2018). Aripiprazole use during pregnancy, peripartum and lactation. A systematic literature search and review to inform clinical practice. Journal of Affective Disorders, 228**,** 229-237
RefID: 289

Gentile, S.,Fusco, M. L. (2017). Neurodevelopmental outcomes in infants exposed in utero to antipsychotics: A systematic review of published data. CNS Spectrums, 22(3)**,** 273-281
RefID: 329

Mehta, T. M.,Van Lieshout, R. J. (2017). A review of the safety of clozapine during pregnancy and lactation. Archives of Women's Mental Health, 20(1)
RefID: 345

Orsolini, L.,Sceusa, F.,Pompili, S.,Mauro, A.,Salvi, V.,Volpe, U. (2021). Severe and persistent mental illness (SPMI) in pregnancy and breastfeeding: focus on second-generation long acting injectable antipsychotics. Expert Opinion on Drug Safety, 20(10)**,** 1207-1224
RefID: 102

Shen, Z. Q.,Gao, S. Y.,Li, S. X.,Zhang, T. N.,Liu, C. X.,Lv, H. C.,Zhang, Y.,Gong, T. T.,Xu, X.,Ji, C.,Wu, Q. J.,Li, D. (2017). Sertraline use in the first trimester and risk of congenital anomalies: a systemic review and meta-analysis of cohort studies. British Journal of Clinical Pharmacology, 83(4)**,** 909-922
RefID: 349

Wang, Z.,Brauer, R.,Man, K. K. C.,Alfageh, B.,Mongkhon, P.,Wong, I. C. K. (2021). Prenatal exposure to antipsychotic agents and the risk of congenital malformations in children: A systematic review and meta-analysis. British Journal of Clinical Pharmacology, 87(11)**,** 4101-4123
RefID: 22

Lithium

Fornaro, M.,et.al. (2020). Lithium exposure during pregnancy and the postpartum period: A systematic review and meta-analysis of safety and efficacy outcomes. American Journal of Psychiatry, 177(1)**,** 76-92
RefID: 173

Mood stabilisers

Giménez, A.,Pacchiarotti, I.,Gil, J.,Murru, A.,Gomes, S. P.,Pinzón, J. E.,Anmella, G.,Gómez-Ramiro, M.,Verdolini, N.,Valentí, M.,Goikolea, J. M.,Vieta, E. (2019). Adverse outcomes during pregnancy and major congenital malformations in infants of patients with bipolar and schizoaffective disorders treated with antiepileptic drugs: A systematic review. Psychiatria Polska, 53(2)**,** 223-244
RefID: 228

Grigoriadis, S.,Graves, L.,Peer, M.,Mamisashvili, L.,Ruthirakuhan, M.,Chan, P.,Hennawy, M.,Parikh, S.,Vigod, S. N.,Dennis, C. L.,Steiner, M.,Brown, C.,Cheung, A.,Dawson, H.,Rector, N.,Guenette, M.,Richter, M. (2020). Pregnancy and Delivery Outcomes Following Benzodiazepine Exposure: A Systematic Review and Meta-analysis. Canadian Journal of Psychiatry, 65(12)**,** 821-834
RefID: 109

Haskey, C.,Galbally, M. (2017). Mood stabilizers in pregnancy and child developmental outcomes: A systematic review. Australian and New Zealand Journal of Psychiatry, 51(11)**,** 1087-1097
RefID: 309

Jackson, A.,Bromley, R.,Morrow, J.,Irwin, B.,Clayton-Smith, J. (2016). In utero exposure to valproate increases the risk of isolated cleft palate. Archives of Disease in Childhood: Fetal and Neonatal Edition, 101(3), F207-F211
RefID: 390

Knight, R.,Wittkowski, A.,Bromley, R. L. (2021). Neurodevelopmental outcomes in children exposed to newer antiseizure medications: A systematic review. Epilepsia.
RefID: 101

Pariente, G.,Leibson, T.,Shulman, T.,Adams-Webber, T.,Barzilay, E.,Nulman, I. (2017). Pregnancy Outcomes Following In Utero Exposure to Lamotrigine: A Systematic Review and Meta-Analysis. CNS Drugs, 31(6), 439-450
RefID: 330

Veroniki, A. A.,Cogo, E.,Rios, P.,Straus, S. E.,Finkelstein, Y.,Kealey, R.,Reynen, E.,Soobiah, C.,Thavorn, K.,Hutton, B.,Hemmelgarn, B. R.,Yazdi, F.,D'Souza, J.,MacDonald, H.,Tricco, A. C. (2017). Comparative safety of anti-epileptic drugs during pregnancy: A systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Medicine, 15(1),
RefID: 333

Veroniki, A. A.,Rios, P.,Cogo, E.,Straus, S. E.,Finkelstein, Y.,Kealey, R.,Reynen, E.,Soobiah, C.,Thavorn, K.,Hutton, B.,Hemmelgarn, B. R.,Yazdi, F.,D'Souza, J.,Macdonald, H.,Tricco, A. C. (2017). Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: A systematic review and network meta-analysis. BMJ Open, 7(7),
RefID: 326

Weston, J.,Bromley, R.,Jackson, C. F.,Adab, N.,Clayton-Smith, J.,Greenhalgh, J.,Hounsome, J.,McKay, A. J.,Tudur Smith, C.,Marson, A. G. (2016). Monotherapy treatment of epilepsy in pregnancy: Congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews, 2016(11),
RefID: 368

Various pharmacological interventions

Grigoriadis, S.,Graves, L.,Peer, M.,Mamisashvili, L.,Dennis, C. L.,Vigod, S. N.,Steiner, M.,Brown, C.,Cheung, A.,Dawson, H.,Rector, N.,Guenette, M.,Richter, M. (2019). Benzodiazepine use during pregnancy alone or in combination with an antidepressant and congenital malformations: Systematic review and meta-analysis. Journal of Clinical Psychiatry, 80(4)
RefID: 230

Poels, E. M. P.,Schrijver, L.,Kamperman, A. M.,Hillegers, M. H. J.,Hoogendijk, W. J. G.,Kushner, S. A.,Roza, S. J. (2018). Long-term neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics: a systematic review and meta-analysis. European Child and Adolescent Psychiatry, 27(9), 1209-1230
RefID: 260

Scrandis, D. A. (2017). Bipolar Disorder in Pregnancy: A Review of Pregnancy Outcomes. Journal of Midwifery and Women's Health, 62(6), 673-683
RefID: 310

Solmi, M.,Dragioti, E.,Arango, C.,Radua, J.,Ostinelli, E.,Kilic, O.,Yilmaz, U. E.,Yalcinay-İnan, M.,Soares, F. C.,Mariano, L.,Mosillo, P.,Cortese, S.,Correll, C. U.,Carvalho, A. F.,Shin, J. I.,Fusar-Poli, P. (2021). Risk and protective factors for mental disorders with onset in childhood/adolescence: An umbrella review of published meta-analyses of observational longitudinal studies. Neuroscience and Biobehavioral Reviews,

120**,** 565-573
RefID: 93

Zwink, N.,Jenetzky, E. (2018). Maternal drug use and the risk of anorectal malformations: Systematic review and meta-analysis. Orphanet Journal of Rare Diseases, 13(1)
RefID: 278

3.2 Complementary

3.2.1 Systematic reviews

Omega-3 fatty acids

Firouzabadi, F. D.,Shab-Bidar, S.,Jayedi, A. (2022). The effects of omega-3 polyunsaturated fatty acids supplementation in pregnancy, lactation, and infancy: An umbrella review of meta-analyses of randomized trials. Pharmacological Research, 177.
RefID: 1

Middleton, P.,Gomersall, J. C.,Gould, J. F.,Shepherd, E.,Olsen, S. F.,Makrides, M. (2018). Omega-3 fatty acid addition during pregnancy. Cochrane Database of Systematic Reviews, 2018(11)
RefID: 248

Nevins, J. E. H.,Donovan, S. M.,Snetselaar, L.,Dewey, K. G.,Novotny, R.,Stang, J.,Taveras, E. M.,Kleinman, R. E.,Bailey, R. L.,Raghavan, R.,Scinto-Madonich, S. R.,Venkatramanan, S.,Butera, G.,Terry, N.,Altman, J.,Adler, M.,Obbagy, J. E.,Stoody, E. E.,De Jesus, J. (2021). Omega-3 Fatty Acid Dietary Supplements Consumed during Pregnancy and Lactation and Child Neurodevelopment: A Systematic Review. Journal of Nutrition, 151(11)**,** 3483-3494
RefID: 26

St John's wort

None identified

Ginkgo biloba

None identified

3.2.2 Primary studies

St John's wort

None identified

Ginkgo biloba

None identified

3.3 Physical

3.3.1 Systematic reviews

ECT

Coshal, S.,Jones, K.,Coverdale, J.,Livingston, R. (2019). An overview of reviews on the safety of electroconvulsive therapy administered during pregnancy. Journal of Psychiatric Practice, 25(1)**,** 2-6
RefID: 241

TMS

Cole, J.,Bright, K.,Gagnon, L.,McGirr, A. (2019). A systematic review of the safety and effectiveness of repetitive transcranial magnetic stimulation in the treatment of peripartum depression. Journal of Psychiatric Research, 115**,** 142-150
RefID: 196

Konstantinou, G. N.,Vigod, S. N.,Mehta, S.,Daskalakis, Z. J.,Blumberger, D. M. (2020). A systematic review of non-invasive neurostimulation for the treatment of depression during pregnancy. Journal of Affective Disorders, 272**,** 259-268
RefID: 144

Lee, H. J., Kim, S. M., Kwon, J. Y. (2021). Repetitive transcranial magnetic stimulation treatment for peripartum depression: systematic review & meta-analyses. BMC Pregnancy and Childbirth, 21, 118 (13 pages)

3.3.2 Primary studies

ECT

None identified

TMS

Kim, D. R.,Wang, E.,McGeehan, B.,Snell, J.,Ewing, G.,Iannelli, C.,O'Reardon, J. P.,Sammel, M. D.,Epperson, C. N. (2019). Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. Brain Stimulation, 12(1), 96-102
RefID: 2584

Appendix 4 Existing and new evidence base

4.1 Pharmacological

New evidence identified in Evidence Review Update

Table App. 5 New evidence – Pharmacological interventions – Foundation Review

Ref ID	Author & year	Study type	Population	Intervention	Comparator	Relevant outcomes
33	AHRQ 2021 *(**High** confidence in results [AMSTAR 2])*	SR of harms and benefits Eligible studies: RCTs, CCTs, case-control studies, cohort studies with comparison arm Literature search: Inception to 05 June 2020, with surveillance to 02 March 2021 Search identified 31,846 records; retrieved 1,812 for full-text review Included studies: • Total 164 (168 articles); 131 studies in analysis (adjusted) • 5 RCTs +70 OBS reported harms vs. no treatment or placebo • 1 RCT + 55 OBS reported comparative harms	Women who were of reproductive age (15-44 years old during preconception [≤12 weeks before pregnancy], pregnant, or postpartum [through 1 year]) with any mental health disorder (new or pre-existing)	Pharmacologic interventions for a mental health disorder: • Antipsychotics (haloperidol, chlorpromazine, aripiprazole, quetiapine, olanzapine, risperidone, clozapine, lurasidone, paliperidone, fluphenazine, perphenazine, iloperidone, asenapine, brexpiprazole, and ziprasidone) • SSRIs and serotonin modulators (citalopram, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, trazodone, vilazodone, and vortioxetine) • SNRIs (venlafaxine, desvenlafaxine, milnacipran, and duloxetine) • TCAs (amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine) • Other antidepressants (bupropion, mirtazapine) • Mood stabilizers (lithium and anticonvulsants [valproate, carbamazepine, oxcarbazepine, topiramate, and lamotrigine]) • Antianxiety agent (benzodiazepines [alprazolam, clobazam, clonazepam, clorazepate, clonidine, chlordiazepoxide, diazepam, lorazepam, temazepam, and triazolam] and buspirone) • Other medications for a mental health disorder (brexanolone, gabapentin, zolpidem, eszopiclone, zaleplon, ramelteon, diphenhydramine, lisdexamfetamine, and hydroxyzine)	• Placebo or no treatment • Other pharmacologic interventions (studies of any psychotherapy, combined pharmacotherapy and psychotherapy are eligible if they report a pharmacologic comparison arm)	• Maternal harms o Harms specific to pregnancy and breastfeeding (infertility, miscarriage, abruption, preterm labour/ preterm birth, preeclampsia, gestational hypertensive disorders, glucose intolerance/ gestational diabetes mellitus, reduced milk production in breastfeeding/ undesired weaning) o Danger to self or infant o Misuse of prescription medication o Serious adverse events related to treatment o Death • Fetal/infant/child harms o Preterm birth/SFGA or LFGA o Congenital anomalies o Perinatal complications (low APGAR, withdrawal, respiratory distress, neonatal intensive care unit time, persistent pulmonary hypertension) o Poor infant attachment/bonding[a] o Delayed social, emotional, and cognitive development[a] o Death

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CCT, controlled clinical trial; LFGA, large for gestational age; OBS, observational; RCT, randomised controlled trial; SFGA, small for gestational age; SNRI, serotonin and norepinephrine reuptake inhibitor; SR, systematic review; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants.
a Outcomes were limited to validated measures

4.1.1 Antidepressants

Summary of evidence in 2017 Guideline

Table App. 6 Evidence base and recommendations in 2017 Guideline – Antidepressants

		Location in 2017 Guideline
Included studies	42 observational studies representing data from 23 cohorts (all adjusted for potential confounders and attempted to minimise confounding by indication) • Almeida 2016/Bérard 2016/Boukhris 2016/Bérard 2015/Nakhai-Pour 2010/Ramos 2008, Petersen 2016/Ban 2014a/Ban 2012, Furu 2015/Kieler 2012, Grzeskowiak 2015/Gidaya 2014/Hviid 2013/Kjaersgaard 2013/Pedersen 2013/Sørensen 2013, Malm 2015/Malnm 2016/Brown 2016, Huybrechts 2014a/Huybrechts 2015, Rai 2013, Brandlistuen 2015, Clements 2015, Cole 2007a/Cole 2007b, Croen 2011, Djulus 2006, El Marroun 2014, Grzeskowiak 2012, Harrington 2014, Hayes 2012, Figueroa 2010, Johnson 2016, Kieviet 2015, Margulis 2013, Nulman 2015, Oberlander 2006/ Oberlander 2008a/Oberlander 2008b, Simon 2002	Appendix to Technical Report Part D, Table AppD4-2, AppD4.1.1.2
Recommendation(s)	**EBR 9:** Consider the use of SSRIs as first-line treatment for moderate to severe depression and/or anxiety in pregnant women.	2017 Guideline, Part C and Appendix C
	EBR 10: Use SSRIs as first-line treatment for moderate to severe depression in postnatal women.	2017 Guideline, Part C and Appendix C

Abbreviations: CBR, consensus-based recommendation; EBR, evidence-based recommendation.
Key to recommendations type and strength: STRONG, CONDITIONAL, CONSENSUS

Table App. 7 Summary of harms in 2017 Guideline – Antidepressants

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain	Location
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○○	Evidence Profile Table
SSRIs[17]	Miscarriage ●●○○ Preterm birth ●●○○ PNAS ●●○○ PNAS (SSRI vs SNRI) ●○○○ PPH ●○○○ Respiratory distress ●○○○ Convulsions ●●○○	Major malformation ●○○○ Cardiac malformation ●○○○ Neonatal mortality ●○○○ IQ ●○○○ Behavioural problems[18] ●○○○		Cardiac malformation (vs non-SSRI) Septal malformation ASD ADHD Other disorders[19] Depression Anxiety Postpartum haemorrhage	Technical Report Part D, Table D3-2
Paroxetine	Miscarriage ●●○○			Major malformation Cardiac malformation Cardiac malformation (vs other ADs) ASD	Technical Report Part D, Table D3-3
Fluoxetine	Septal malformation ●○○○	Miscarriage ●○○○		Major malformation Cardiac malformation ASD	Technical Report Part D, Table D3-4
Sertraline		Miscarriage ●○○○		Major malformation Cardiac malformation ASD	Technical Report Part D, Table D3-5
Citalopram		Miscarriage ●○○○		Major malformation Cardiac malformation ASD	Technical Report Part D, Table D3-6
Escitalopram				Major malformation Cardiac malformation	Technical Report Part D, Table D3-7

[17] Also includes some data on SRIs (SSRIs and SNRIs)
[18] Includes internalising and externalising behaviours.
[19] Includes speech/language, scholastic and motor disorders.

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain	Location
Fluvoxamine		Major malformation ●○○○ Cardiac malformation ●○○○ Miscarriage ●○○○		ASD	Technical Report Part D, Table D3-8
SNRIs/ venlafaxine	Miscarriage ●●○○ Postpartum haemorrhage ●○○○	Major malformation ●○○○		Cardiac malformation ASD ADHD	Technical Report Part D, Table D3-9
NaSSA/ mirtazapine				Major malformation (vs other ADs) Stillbirth (vs other ADs) Miscarriage (vs other ADs) Preterm birth (vs other ADs)	Technical Report Part D, Table D3-10
TCAs	Miscarriage ●○○○	Major malformation ●○○○ Neonatal mortality ●○○○		Cardiac malformation ASD ADHD	Technical Report Part D, Table D3-11
Bupropion				Cardiac malformation Cardiac malformation (vs other ADs) ADHD	Technical Report Part D, 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-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.

4.1.2 Antipsychotics

Summary of evidence in 2017 Guideline

Table App. 8 Evidence base and recommendations in 2017 Guideline – Antipsychotics

		Location in 2017 Guideline
Included studies	11 observational studies (all adjusted for potential confounders) • Cohen 2016, Huybrechts 2016, Petersen 2016a, Sørensen 2015, Vigod 2015, Habermann 2013, Källén 2013, Bodén 2012b, Johnson 2012, Lin 2010, Reis 2008	Appendix to Technical Report Part D, Table AppD2-41
Recommendation(s)	**EBR 11:** Consider the use of antipsychotics for treating psychotic symptoms in pregnant women.	2017 Guideline, Part C and Appendix C
	CBR xxiii: Use caution when prescribing any antipsychotic to pregnant women, particularly for women with a propensity for weight gain and metabolic syndrome.	2017 Guideline, Part C
	CBR xxiv: If women commence or continue antipsychotic treatment during pregnancy, monitor them for excessive weight gain and the development of gestational diabetes and refer them for advice on weight management as required.	2017 Guideline, Part C
	CBR xxv: Do not initiate use of clozapine in pregnant women.	2017 Guideline, Part C

Abbreviations: CBR, consensus-based recommendation; EBR, evidence-based recommendation.
Key to recommendations type and strength: STRONG, CONDITIONAL, CONSENSUS

Table App. 9 Summary of harms in 2017 Guideline – Antipsychotics

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain	Location
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	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	Technical Report Part D, Table D3-14
SGAs		Major malformation ●○○○ Cardiac malformation ●○○○ Preterm birth ●○○○ SFGA ●○○○ LFGA ●○○○		Major malformations (vs FGAs)	Technical Report Part D, Table D3-15
Aripiprazole		Major malformation ●○○○		Cardiac malformation	Technical Report Part D, Table D3-17
Risperidone	Major malformation ●●○○ Cardiac malformation ●●○○				Technical Report Part D, Table D3-23
Ziprasidone				Major malformation Cardiac malformation	Technical Report Part D, Table D3-24
Olanzapine				Major malformation Cardiac malformation Miscarriage	Technical Report Part D, Table D3-20
Quetiapine	Miscarriage ●○○○	Major malformation ●○○○		Cardiac malformation	Technical Report Part D, Table D3-22
FGAs	Preterm birth ●●○○	SFGA ●○○○ LFGA ●○○○		Major malformation Cardiac malformation	Technical Report Part D, Table D3-16
Haloperidol				Major malformation	Technical Report Part D, Table D3-19
Perphenazine				Miscarriage	Technical Report Part D, Table D3-21
Zuclopenthixol				Miscarriage	Technical Report Part D, Table D3-25
Flupenthixol (long-acting)	Miscarriage ●○○○			Major malformation	Technical Report Part D, 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 antipsychotic.

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.

4.1.3 Anticonvulsants

Summary of evidence in 2017 Guideline

Table App. 10 Evidence base and recommendations in 2017 Guideline – Anticonvulsants

		Location in 2017 Guideline
Included studies	An a priori decision was made to limit the assessment of evidence for infant harms related to the use of anticonvulsants to SRs only. 5 SRs (all combined raw data from observational studies; none met the higher quality criteria defined for antidepressants) • Weston 2016 (50 prospective cohort or registry studies), NICE 2015 (21 prospective cohort studies, 10 retrospective cohort studies, 4 retrospective case-control studies), Tanoshima 2015 (44 prospective cohort studies, 15 retrospective cohort studies), Bromley 2014 (22 prospective cohort studies, 6 other), Banach 2010 (11 cohort studies)	Appendix to Technical Report Part D, App D2.1.3.2, Table AppD4-55
Recommendation(s)	**EBR 12:** Do not prescribe sodium valproate to women of childbearing age.	2017 Guideline, Part C and Appendix C
	CBR xxvi: Use great caution in prescribing anticonvulsants as mood stabilisers for pregnant women and seek specialist psychiatric consultation when doing so.	2017 Guideline, Part C
	CBR xxvii: If anticonvulsants are prescribed to a woman who is breastfeeding, arrange close monitoring of the infant and specialist	2017 Guideline, Part C

Abbreviations: CBR, consensus-based recommendation; EBR, evidence-based recommendation; NICE, National Institute for Health and Care Excellence; SR, systematic review.
Key to recommendations type and strength: STRONG, CONDITIONAL, CONSENSUS

Table App. 11 Summary of harms in 2017 Guideline – Anticonvulsants

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain	Location
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	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	Technical Report Part D, Table D3-27
Carbamaze-pine	Major malformation ●○○○ Major malformation (vs lamotrigine) ●○○○	IQ ●○○○		Cardiac malformation Cardiac malformation (vs lamotrigine) Neonatal mortality Preterm birth ASD IQ (vs lamotrigine)	Technical Report Part D, Table D3-28

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain	Location
Lamotrigine				Major malformation Cardiac malformation Neonatal mortality Preterm birth ASD IQ	Technical Report Part D, 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.

4.1.4 Benzodiazepines or z-drugs

Summary of evidence in 2017 Guideline

Table App. 12 Evidence base and recommendations in 2017 Guideline – Benzodiazepines or z-drugs

		Location in 2017 Guideline
Included studies	2 SRs • NICE 2015 (18 observational studies), Enato 2011 (9 observational studies) 9 observational studies • Odsbu 2015, Ban 2014b, Wikner 2011/2007, Wang 2010, Juric 2009, Oberlander 2008a, Kjær 2007, Eros 2002, Diav-Citrin 1999	Appendix to Technical Report Part D, Table AppD4-63, Table AppD4-64
Recommendation(s)	**CBR xxi:** Consider the short-term use of benzodiazepines for treating moderate to severe symptoms of anxiety while awaiting onset of action of an SSRI or TCA in pregnant or postnatal women.	2017 Guideline, Part C

Abbreviations: CBR, consensus-based recommendation; EBR, evidence-based recommendation; NICE, National Institute for Health and Care Excellence; SR, systematic review.
Key to recommendations type and strength: STRONG, CONDITIONAL, CONSENSUS

Table App. 13 Summary of harms in 2017 Guideline – Benzodiazepines and z-drugs

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain	Location
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○○	Evidence Profile Table
Benzodiaze-pines ± z-drugs	Respiratory difficulty[20] ●○○○	Major malformation ●○○○		Cardiac malformation Septal malformation Miscarriage Preterm birth SFGA Convulsions Language competence	Technical Report Part D, Table D3-31
Diazepam				Major malformation Cardiac malformation	Technical Report Part D, Table D3-32
Temazepam				Major malformation Cardiac malformation	Technical Report Part D, Table D3-33
Z-drugs				Major malformation Cardiac malformation	Technical Report Part D, Table D3-34
Zolpidem	Preterm birth ●●○○ SFGA ●●○○	Respiratory difficulty ●○○○		Major malformation	Technical Report Part D, Table D3-35
Zopiclone				Major malformation Cardiac malformation Miscarriage Preterm birth SFGA	Technical Report Part D, Table D3-36

[20] Late exposure only.

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.

4.1.5 Lithium

Summary of evidence in 2017 Guideline

Table App. 14 Evidence base and recommendations in 2017 Guideline – Lithium

		Location in 2017 Guideline
Included studies	1 SR • NICE 2015 (6 observational studies) 8 observational studies • Diav-Citrin 2014, Källén 2013, Reis 2008, Troyer 1993, Jacobson 1992, Czeizel 1990, Källén 1983, Schou 1976	Appendix to Technical Report Part D, TableAppD4-78, Table AppD4-79
Recommendation(s)	**CBR xxviii:** If lithium is prescribed to pregnant women, ensure that maternal blood levels are closely monitored and that there is specialist psychiatric consultation.	2017 Guideline, Part C
	CBR xxix: Where possible, avoid the use of lithium in women who are breastfeeding.	2017 Guideline, Part C

Abbreviations: CBR, consensus-based recommendation; EBR, evidence-based recommendation; NICE, National Institute for Health and Care Excellence; SR, systematic review.
Key to recommendations type and strength: STRONG, CONDITIONAL, CONSENSUS

Table App. 15 Summary of harms in 2017 Guideline – Lithium

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain	Location
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○○	Evidence Profile Table
Lithium	Cardiac malformation ●○○○ Miscarriage ●○○○ Neonatal mortality ●○○○			Major malformation Septal malformation Ebstein's anomaly Stillbirth Preterm birth	Technical Report Part D, 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

4.2 Complementary

4.2.1 Omega-3 fatty acids

Summary of evidence in 2017 Guideline

Table App. 16 Evidence base and recommendations in 2017 Guideline – Omega-3 fatty acids

		Location in 2017 Guideline
Included studies	3 SRs • Kar 2016 (9 RCTs), Saccone 2016b (3 RCTs), Gould 2013 (11 RCTs)	Technical Report Part D, D3.2.1
Recommendation(s)	**EBR 8:** Advise women that omega-3 fatty acid supplementation does not appear to improve depression symptoms but is not harmful to the fetus or infant when taken during pregnancy or while breastfeeding.	2017 Guideline, Part C and Appendix C

Abbreviations: CBR, consensus-based recommendation; EBR, evidence-based recommendation; RCT, randomised controlled trial; SR, systematic review.
Key to recommendations type and strength: STRONG, CONDITIONAL, CONSENSUS

Table App. 17 Summary of harms in 2017 Guideline – Omega-3 fatty acids

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain	Location
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○○	Evidence Profile Table
Omega-3 fatty acids		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) ●●●●		Technical Report Part D, 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.

New evidence identified in Evidence Review Update

Table App. 18 New evidence – Omega-3 fatty acids

Ref ID	Author & year *[Rating][21]*	Study type	Population	Intervention	Comparator	Relevant outcomes
		Systematic reviews				
1	Firouzabadi 2022 ("umbrella review") *[**Low** confidence in results]*	28 SRMAs[22] (672 RCTs)[23] One SRMA was selected per outcome per population (pregnancy, lactation, infancy), based on largest number of RCTs Eligible studies: SRMAs of RCTs Literature search: inception to November 2020	Pregnant or lactating women or infants (<2 years old)	Supplementation with long chain omega-3 fatty acids including EPA and/or DHA	Control group, not defined	Preterm delivery, infant death, stillbirth, IUGR, Bayley Scales of Infant Development (mental development index), intelligence quotient, language development[24], psychomotor development[24]
26	Nevins 2021 (informed *Scientific Report of the 2020 Dietary Guidelines Advisory Committee, US*) *[**Moderate** confidence]*	SR – included 33 articles from 15 RCTs[25] and 1 prospective cohort study Eligible studies: RCTs, non-randomised controlled trials, cohort studies, nested case-control studies Literature search: 1980 to February 2020	Pregnant or lactating women, and women up to 6 mo before pregnancy Children (aged birth to 18 yr) of participating mothers	Exposure to, including intake of, omega-3 fatty acids, including multi-nutrient supplements	Different levels of exposure to omega-3 fatty acid supplements	Child neurodevelopment – cognitive, language/ communication, movement/ physical, social-emotional development, ADD/ADHD, ASD, anxiety, depression
248	Middleton 2018 (Cochrane Review - update) *[**High** confidence]*	SR – included 374 reports of 70 RCTs[26] (including 6 RCTs from the original review) with 19,927 women; 61 RCTs included in MA Eligible studies: RCTs Literature search: previous search to August 2018	Pregnant women, regardless of their risk of pre-eclampsia, preterm birth or IUGR	Supplementation with omega-3 fatty acids, omega enriched food and/or dietary advice	Placebo, no omega-3 fatty acids, alternative omega-3 doses or types (e.g., DHA vs. EPA)	Pregnancy – preterm birth, **prolonged gestation** (>42 wks) Mothers[27] – haemorrhage, miscarriage Babies – stillbirth, neonatal death, perinatal death, low birthweight, SFGA/IUGR, neonatal convulsion, respiratory distress syndrome Longer term infant/child follow-up – mental and emotional health, behaviour, neurological/ neurosensory and developmental outcomes

Abbreviations: ADD, attention deficit disorder; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IUGR, intrauterine growth restriction; MA, meta-analysis; mo, month; RCT, randomised controlled trial; SFGA, small for gestational age; SR, systematic review; SRMA, systematic review and meta-analysis; US, United States; wk, week; yr, year.

[21] Refer to Appendix 5 for AMSTAR 2 assessments.
[22] Does not include Nevins 2021 or Middleton 2018.
[23] It is not clear whether this refers to unique RCTs.
[24] No mention of whether outcome was measured using a validated instrument.
[25] Include 2 RCTs published in 2019 that were not captured in Middleton 2018 Cochrane Review.
[26] Of note, many of the recent RCTs focused on specific populations (e.g., diabetic pregnant women).
[27] Maternal outcomes also included depression during pregnancy based on tool thresholds (Carlson 2013, Su 2008, Vaz 2017) and scores (Kavlani 2014, Su 2008, Freeman 2008, Rees 2008, Keenan 2014), and anxiety during pregnancy (Carlson 2013). The Vaz 2017 RCT was excluded during screening for efficacy of prevention interventions because patients with EPDS ≥9 were enrolled (median EPDS 10 at baseline) and the population is likely to include at risk patients plus some with depression.

4.2.2 St John's wort

Summary of evidence in 2017 Guideline

Table App. 19 Evidence base and recommendations in 2017 Guideline – St John's wort

		Location in 2017 Guideline
Included studies	2 observational studies • Kolding 2015, Moretti 2009	Appendix to Technical Report Part D, Table AppD4-99
Recommendation(s)	**CBR xix:** Advise pregnant women that the evidence on potential harms to the fetus from St John's Wort is limited and uncertain and that use of this treatment during pregnancy is not recommended.	2017 Guideline, Part C

Abbreviations: CBR, consensus-based recommendation; EBR, evidence-based recommendation.
Key to recommendations type and strength: STRONG, CONDITIONAL, CONSENSUS

Table App. 20 Summary of harms in 2017 Guideline –St John's wort

Intervention	Increased/may be increased risk of harm	Appears to be no increased risk of harm	Decreased/may be decreased risk of harm	Uncertain	Location
	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome Certainty of evidence	Outcome ○○○○	Evidence Profile Table
St John's wort				Major malformation Major malformation (vs ADs) Preterm birth Preterm birth (vs ADs)	Technical Report Part D, 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.

New evidence identified in Evidence Review Update

Table App. 21 New evidence – St John's wort

Ref ID	Author & year	Study type	Population	Intervention	Comparator	Relevant outcomes
		Systematic reviews				
-	*None identified*					
		Primary studies				
-	*None identified*					

4.2.3 Ginkgo biloba

Summary of evidence in 2017 Guideline

Table App. 22 Evidence base and recommendations in 2017 Guideline – Ginkgo biloba

		Location in 2017 Guideline
Included studies	No SRs or individual comparative studies were identified that assessed the effect of perinatal exposure to Ginkgo biloba on fetal, infant or child harms.	Technical Report Part D, D3.2.3
Recommendation(s)	**CBR xx:** Advise pregnant women that potential harms to the fetus from Ginkgo biloba have not been researched, and that use of this treatment during pregnancy is not recommended.	2017 Guideline, Part C

Abbreviations: CBR, consensus-based recommendation; EBR, evidence-based recommendation.
Key to recommendations type and strength: STRONG, CONDITIONAL, CONSENSUS

New evidence identified in Evidence Review Update

Table App. 23 New evidence – Ginkgo biloba

Ref ID	Author & year	Study type	Population	Intervention	Comparator	Relevant outcomes
		Systematic reviews				
-	*None identified*					
		Primary studies				
-	*None identified*					

4.3 Physical

4.3.1 Electroconvulsive therapy (ECT)

Summary of evidence in 2017 Guideline

Table App. 24 Evidence base and recommendations in 2017 Guideline – Electroconvulsive therapy (ECT)

		Location in 2017 Guideline
Included studies	1 observational study • Babu 2013	Appendix to Technical Report Part D, Table AppD4-104

		Location in 2017 Guideline
	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 (Leiknes 2015) while three narrative reviews of largely case reports concluded that the risk of adverse harms to the fetus were low (Calaway 2016, Pompili 2014, Anderson 2009). 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 postpartum ECT does not result in adverse effect to the infant (Babu 2013).	Technical Report Part D, Table D3-43
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.	Technical Report Part D, Table D3-43
Recommendation(s)	**CBR xxxii:** Consider ECT when a postnatal woman with severe depression has not responded to one or more trials of antidepressants of adequate dose and duration.	2017 Guideline, Part C
	CBR xxxiii: Consider ECT as first-line treatment for postnatal women with severe depression especially where there is a high risk of suicide or high level of distress; when food or fluid intake is poor; and in the presence of psychotic or melancholic symptoms.	2017 Guideline, Part C

Abbreviations: CBR, consensus-based recommendation; EBR, evidence-based recommendation; ECT, electroconvulsive therapy.
Key to recommendations type and strength: STRONG, CONDITIONAL, CONSENSUS

New evidence identified in Evidence Review Update

Table App. 25 New evidence – Electroconvulsive therapy (ECT)

Ref ID	Author & year	Study type	Population	Intervention	Comparator	Relevant outcomes
		Systematic reviews				
241	Coshal 2019 (narrative "overview")	5 SRs (Calaway 1016, Leiknes 2015, Pompili 2014, Miller 1994; Anderson 2009) – "lack of cohort studies and RCTs" Eligible studies: "Review articles" including primary studies of any design Literature search: Jan 2015 to Mar 2017	"Pregnancy"	ECT	Not defined	"Safety", includes data on vaginal bleeding, premature birth, fetal spasms, developmental delay, fetal deaths miscarriage
		Primary studies				
-	*None identified*					

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

4.3.2 Transcranial magnetic stimulation (TMS)

Summary of evidence in 2017 Guideline

Table App. 26 Evidence base and recommendations in 2017 Guideline – Transcranial magnetic stimulation (TMS)

		Location in 2017 Guideline
Included studies	1 observational study from Turkey without a concurrent control group[28] • Eryilmaz 2015 (N=44)	Appendix to Technical Report Part D, Table AppD4-105
	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 (Eryilmaz 2015).	Technical Report Part D, Table D3-44
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.	
Recommendation(s)	*No recommendations made*	*N/A*

Abbreviations: ADSI, Ankara Developmental Screening Inventory; TMS, transcranial magnetic stimulation.

New evidence identified in Evidence Review Update

Table App. 27 New evidence – Transcranial magnetic stimulation (TMS)

Ref ID	Author & year *[Rating][29]*	Study type	Population	Intervention	Comparator	Relevant outcomes
		Systematic reviews				
N/A	Lee 2021 *[**Low** confidence in results]*	11 studies: 2 RCTs[30], 4 NRS, 5 case studies Eligible studies: RCTs, NRS through to case studies Literature search: To September 2020	Pregnancy and baby blues, postpartum psychosis or MDD from pregnancy to 1 yr after childbirth	TMS or rTMS	Not specified	Safety – preterm birth, birth outcomes (“healthy”)
144	Konstantinou 2020 *[**Low** confidence in results]*	21 studies: 2 RCTs (1 rTMS[31], 1 tDCS), 4 uncontrolled studies, 3 case series, 12 case reports Eligible studies: Any study design Literature search: 1990 to June 2019	Pregnant women (of any gestational age) diagnosed with MDD	Non-invasive neurostimulation treatment (rTMS, tDCS, tACS, TNS, tVNS)	Not specified	Safety – side effects

[28] An RCT was identified in the search for efficacy of TMS (Myczkowski 2012) but no relevant harms outcomes were reported.
[29] Refer to Appendix 5 for AMSTAR 2 assessments.
[30] Kim 2019 and Myczkowski 2012
[31] Kim 2019

Ref ID	Author & year *[Rating][29]*	Study type	Population	Intervention	Comparator	Relevant outcomes
196	Cole 2019 *[**Low** confidence in results]*	12 studies[32]: 1 RCT[33], 3 NRS, 3 case series, 5 case studies Eligible studies: "studies, case reports and articles" Literature search: 2008 to January 2019	Women with depression in the peripartum period	rTMS	Not specified	Safety – side effects/adverse events (including preterm births, cardiac malformation, persistent pulmonary hypertension, cognitive or motor development, language development)
		Primary studies				
2584	Kim 2019	RCT N=26	Pregnant women at 14-34 weeks' gestation with DSM-IV (SCID-I) diagnosis of MDD, HAM-D ≥18 and CGI-S ≥3	TMS, 20 daily sessions (15 minutes each, 5 days per week) administered at 1 Hz as a single train of 900 pulses per session at 100% motor threshold) N=14	Sham control (eSham system used to replicate facial twitching and noise generated by TMS, with very low electrical stimulation 2-7 mA) N=12	Delivery and infant outcomes – preterm birth

Abbreviations: CGI-S, Clinical Global Impression Scale-Severity; DSM, Diagnostic and Statistical Manual; HAM-D, Hamilton Depression Rating Scale; Hz, Hertz; MDD, major depressive disorder; NRS, non-randomised study; RCT, randomised controlled trial; rTMS, repetitive transcranial magnetic stimulation; SCID, Structured Clinical Interview for DSM Disorders; SR, systematic review; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TDS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; TNS, trigeminal nerve stimulation; tVNS, transcutaneous vagus nerve stimulation; yr, year.

Note: The Harms Expert Subcommittee agreed that the Kim 2019 RCT was not powered appropriately to draw any definitive conclusions.

[32] 1 RCT (Myczkowski 2012) and 1 open-label NRS (Garcia 2010) were excluded because TMS treatment was administered to some women outside the peripartum window.
[33] Kim 2019

Appendix 5 Risk of bias

5.1 Pharmacological

Table App. 28 AMSTAR 2 assessment of foundation review (AHRQ 2021) for harms of pharmacological interventions

#	AMSTAR 2 question	Answer
1	Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4	Did the review authors use a comprehensive literature search strategy?	Yes
5	Did the review authors perform study selection in duplicate?	Yes
6	Did the review authors perform data extraction in duplicate?	Yes
7	Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8	Did the review authors describe the included studies in adequate detail?	Yes
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10	Did the review authors report on the sources of funding for the studies included in the review?	Yes
11	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
	Overall confidence in the results of the review	**HIGH**

5.2 Complementary

Table App. 29 AMSTAR 2 assessment of Firouzabadi 2022 for harms of Omega-3 fatty acids

#	AMSTAR 2 question	Answer
1	Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4	Did the review authors use a comprehensive literature search strategy?	Partial Yes
5	Did the review authors perform study selection in duplicate?	No
6	Did the review authors perform data extraction in duplicate?	Yes
7	Did the review authors provide a list of excluded studies and justify the exclusions?	Partial Yes
8	Did the review authors describe the included studies in adequate detail?	Yes
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10	Did the review authors report on the sources of funding for the studies included in the review?	No
11	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes

#	AMSTAR 2 question	Answer
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
	Overall confidence in the results of the review	**LOW**

Table App. 30 AMSTAR 2 assessment of Middleton 2018 for harms of Omega-3 fatty acids

#	AMSTAR 2 question	Answer
1	Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3	Did the review authors explain their selection of the study designs for inclusion in the review?	No
4	Did the review authors use a comprehensive literature search strategy?	Yes
5	Did the review authors perform study selection in duplicate?	Yes
6	Did the review authors perform data extraction in duplicate?	Yes
7	Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8	Did the review authors describe the included studies in adequate detail?	Yes
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10	Did the review authors report on the sources of funding for the studies included in the review?	Yes
11	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
	Overall confidence in the results of the review	**HIGH**

Table App. 31 AMSTAR 2 assessment of Nevins 2021 for harms of Omega-3 fatty acids

#	AMSTAR 2 question	Answer
1	Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4	Did the review authors use a comprehensive literature search strategy?	Partial Yes
5	Did the review authors perform study selection in duplicate?	Yes
6	Did the review authors perform data extraction in duplicate?	Yes
7	Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8	Did the review authors describe the included studies in adequate detail?	Yes
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10	Did the review authors report on the sources of funding for the studies included in the review?	No
11	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No meta-analysis conducted
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No meta-analysis conducted

#	AMSTAR 2 question	Answer
13	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No meta-analysis conducted
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
	Overall confidence in the results of the review	**MODERATE**

5.3 Physical

Table App. 32 AMSTAR 2 assessment of Cole 2019 for harms of rTMS

#	AMSTAR 2 question	Answer
1	Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4	Did the review authors use a comprehensive literature search strategy?	Partial Yes
5	Did the review authors perform study selection in duplicate?	Yes
6	Did the review authors perform data extraction in duplicate?	Yes
7	Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8	Did the review authors describe the included studies in adequate detail?	Yes
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10	Did the review authors report on the sources of funding for the studies included in the review?	No
11	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No meta-analysis conducted
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No meta-analysis conducted
13	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	No
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No meta-analysis conducted
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
	Overall confidence in the results of the review	**LOW**

Table App. 33 AMSTAR 2 assessment of Konstantinou 2020 for harms of rTMS

#	AMSTAR 2 question	Answer
1	Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3	Did the review authors explain their selection of the study designs for inclusion in the review?	No
4	Did the review authors use a comprehensive literature search strategy?	Partial Yes
5	Did the review authors perform study selection in duplicate?	No
6	Did the review authors perform data extraction in duplicate?	Yes
7	Did the review authors provide a list of excluded studies and justify the exclusions?	No
8	Did the review authors describe the included studies in adequate detail?	Yes
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes

#	AMSTAR 2 question	Answer
10	Did the review authors report on the sources of funding for the studies included in the review?	No
11	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No meta-analysis conducted
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No meta-analysis conducted
13	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	No
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No meta-analysis conducted
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
	Overall confidence in the results of the review	**LOW**

Table App. 34 AMSTAR 2 assessment of Lee 2021 for harms of rTMS

#	AMSTAR 2 question	Answer
1	Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3	Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4	Did the review authors use a comprehensive literature search strategy?	Partial Yes
5	Did the review authors perform study selection in duplicate?	Yes
6	Did the review authors perform data extraction in duplicate?	No
7	Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8	Did the review authors describe the included studies in adequate detail?	Yes
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10	Did the review authors report on the sources of funding for the studies included in the review?	No
11	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	No
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
	Overall confidence in the results of the review	**LOW**

Appendix 6 Evidence summaries

6.1 Pharmacological

6.1.1 Antidepressants

Table App. 35 Strength of evidence for harms: SSRIs versus no exposure

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Maternal harms								
Mood or anxiety disorder	**SSRI** current (exposure during delivery)	**Postpartum haemorrhage**	503/12,710 (3.96%) vs. 1,896/69,044 (2.75%)	**ARR, 1.47 (95% CI, 1.33 to 1.62)**	1 cohort, n=81,754	Moderate study limitations, precise, consistency unknown	Low for harms for current exposure with SSRIs	Table 9, p27 row 2
Mood or anxiety disorder	**SSRI** recent (exposure within 1 month before delivery)	**Postpartum haemorrhage**	196/6,096 (3.2%) vs. 1,896/69,044 (2.75%)	**ARR, 1.19 (95% CI, 1.03 to 1.38)**	1 cohort, 75,140	Moderate study limitations, precise, consistency unknown	Low for harms for recent exposure with SSRIs	Table 9, p27 (row 3)
Mood or anxiety disorder	**Citalopram** current	**Postpartum haemorrhage**	36/891 (4%) vs. 1,896/69,044 (2.75%)	**ARR, 1.48 (95% CI, 1.07 to 2.04)**	1 cohort, N=69,935	Moderate study limitations, precise, consistency unknown	Low for harms with citalopram	Table 9, p27 (row 4)
Mood or anxiety disorder	**Escitalopram** current	**Postpartum haemorrhage**	43/1,022 (4.21%) vs. 1,896/69,044 (2.75%)	**ARR, 1. 56 (95% CI, 1.16 to 2.09)**	1 cohort, n=70,006	Moderate study limitations, precise, consistency unknown	Low for harms with escitalopram	Table 9, p28 (row 1)
Women with diagnosis code for mood or anxiety disorder 1-5 months prior to delivery	**Fluoxetine** current (at delivery)	**Postpartum haemorrhage**	Current: 137/3,322 (4.1%) Unexposed: 1,896/69,044 (2.8%)	**ARR, current vs. unexposed: 1.51 (95% CI, 1.27 to 1.79)**	1 cohort, N=72,366	Moderate study limitations, precise, consistency unknown	Low for harms with fluoxetine	Table B-22, pB-48 (row 3)
Mood or anxiety disorder	**Paroxetine** current (at delivery)	**Postpartum haemorrhage**	77/2,055 (3.75%) vs. 1,896/69,044 (2.75%)	**ARR, 1.39 (95% CI, 1.09 to 1.71)**	1 cohort, N= 71,099	Moderate study limitations, precise, consistency unknown	Low for harms with paroxetine	Table 9, p28 (row 2)
Mood or anxiety disorder	**Sertraline** current (at delivery)	**Postpartum haemorrhage**	162/4,526 (3.58%) vs. 1,896/69,044 (2.75%)	**ARR, 1.31 (95% CI, 1.12 to 1.54)**	1 cohort, N= 73,570	Moderate study limitations, precise, consistency unknown	Low for harms with sertraline	Table 9, p28 (row 3)
Mood or anxiety disorder	**Sertraline** recent (<1 month before delivery)	**Postpartum haemorrhage**	78/2,226 (3.50%) vs. 1,896/69,044 (2.75%)	**ARR, 1.27 (95 % CI, 1.01 to 1.59)**	1 cohort, N= 71,270	Moderate study limitations, precise, consistency unknown	Low for harms with sertraline	Table 9, p28 (row 4)

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Mood disorder or anxiety or bupropion- exposed women	Current **trazodone** exposure in pregnancy vs. unexposed women with mood disorder or anxiety	**Postpartum haemorrhage**	NR	ARR, 1.85 (95% CI, 0.90 to 3.80)	1 cohort, n=69,183	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient	Table B-29, pB-61 (row 1)
Mood disorder or anxiety or bupropion- exposed women	Recent **trazodone** exposure in pregnancy vs. unexposed women with mood disorder or anxiety	**Postpartum haemorrhage**	NR	ARR, 2.01 (95% CI, 0.77 to 5.24)	1 cohort, n=69,117	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient	Table B-29, pB-61 (row 2)
Mood disorder or anxiety or bupropion- exposed women	Past **trazodone** exposure in pregnancy vs. unexposed women with mood disorder or anxiety	**Postpartum haemorrhage**	NR	ARR, 0.61 (95% CI, 0.23 to 1.67)	1 cohort, n=69,270	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient	Table B-29, pB-61 (row 3)
Evidence Statement: *Maternal use of SSRIs (as a class, citalopram, escitalopram, fluoxetine, paroxetine, sertraline) at the time of delivery may be associated with an increased risk of postpartum haemorrhage (low certainty evidence);* ***the risk of residual confounding remains because the study was not able to control for confounding factors of inadequate diet, the use of tobacco, and severity of disorder****.* *Maternal use of SSRIs (as a class, sertraline) up to one month before delivery may be associated with an increased risk of postpartum haemorrhage (low certainty evidence);* ***the risk of residual confounding remains because the study was not able to control for confounding factors of inadequate diet, the use of tobacco, and severity of disorder****.* *Due to the inadequate certainty of the evidence, any association between maternal use of trazodone and postpartum haemorrhage, is uncertain.*								
Malformations								
History of depression or anxiety or current or past SSRI- exposed women	Exposed to **SSRIs** in pregnancy vs. unexposed women with history of depression, anxiety or prior exposure	**Major congenital anomalies**	279/2,327 (12.0%) vs. 1,650/14,847 (11.1%); 204/7,683 (2.7%) vs, 380/13,432 (2.8%); 208/4,183 (5.0%) vs. 36/806 (4.5%)	Adjusted prevalence ratio: 1.07 (95% CI, 0.93 to 1.22); AOR, 0.93 (95% CI, 0.78 to 1.11); adjusted effect NR in one study, p=0.9	3 cohorts, n=43,299	High study limitations (all risk-of-bias studies), imprecise (wide CIs), consistent	Insufficient	Table 12, p41 (row 3)
Pregnant women with diagnosis of depression only or depression and or anxiety, or exposed to antidepressants	Maternal exposure to **citalopram** vs. no exposure anxiety and/or depression	**Major congenital anomalies**	NR/1946 vs. 666/23,833 (2.8%) in one study, NR in second	**AOR, 1.36 (95% CI, 1.08 to 1.73)**; OR, 0.97 (95% CI, 0.71 to 1.31)	2 cohort studies; n>25,779	High study limitations (high risk of bias), imprecise (CIs suggestive of both benefits and harms in one study), inconsistent	Insufficient	Table 12, p42 (row 1)
Depression	**Escitalopram** exposure in first trimester vs. unexposed women with depression	**Major congenital anomalies**	7/333 (2.1%) vs. 380/13,432 (2.83%)	AOR, 0.77 (95% CI, 0.36 to 1.66)	1 cohort, n=13,765	Serious study limitations (high risk of bias), imprecision (wide CIs spanning the null), consistency unknown	Insufficient	Table B-21, pB-47 (row 5) & Fig 2, p57

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Pregnant women: Cohort 1: depression and/or anxiety diagnosis and exposure to antidepressants in the year before pregnancy; Cohort 2: depression diagnosis from the year before conception through the first trimester	**Fluoxetine** exposure in the first trimester vs. unexposed	**Major congenital anomalies**	NR/191 vs. 1,650/14,847 (11.1%); 241/3,189 (7.6%) vs. 380/13,432 (2.8%)	AOR, 0.80 (95% CI, 0.49 to 1.31); AOR, 0.85 (95% CI, 0.66 to 1.09)	2 cohorts: N=15,038; N=27,022	High study limitations (both high risk of bias), imprecise (wide CIs); consistent	Insufficient	Table 12, p42 (row 2)
Depression/ anxiety or fluvoxamine- exposed women	**Fluvoxamine** exposure in preconception or pregnancy vs. unexposed women with depression or anxiety	**Major congenital anomalies**	NR	AOR, 0.63, 95% CI, (0.23 to 1.77)	1 cohort, NR	High study limitations (high risk of bias), likely imprecise, consistency unknown	Insufficient	Table B-23, pB-51 (row 1)
Women with depression or anxiety in the year before pregnancy	**Paroxetine** in 1st trimester vs. not exposed in 1st trimester	**Major congenital anomalies**	168/1,132 (14.8%) vs. 1,650/14,847 (11.1%) Paroxetine exposed: 37 cases, 375 controls. No antidepressant: 94 cases, 1134 controls 36/1,200 (3.0%) vs. 380/13,432 (2.8%)	[34]AOR, 1.24 (95% CI, 0.99 to 1.55; 99% CI, 0.79 to 1.66) AOR, 1.27 (95% CI, 0.78 to 2.06) AOR 1.01 (95% CI, 0.71 to 1.44)	2 cohorts, 1 case-control, N≥33,119 (N from two studies; third study may be a subset of one study	High study limitations (two high risk-of-bias studies), imprecise, consistent	Insufficient	Table 12, p42 (row 3)
Women with depression or anxiety in the year before pregnancy	**Sertraline** in 1st trimester vs. not exposed in 1st trimester	**Major congenital anomalies**	NR/365 vs. 1650/14,847 (11.1%) 45/366 (12.31099%) vs.1,651/14,868 (11.1%) from one study with potentially overlapping participants) 25/757 (3.3%) vs. 380/13,432 (2.8%)	[34]AOR, 1.09 (95% CI, 0.80 to 1.50) (ARR, 1.11 (95%CI 0.81 to 1.52) from potentially overlapping citation AOR, 1.17 (95% CI, 0.78 to 1.77)	2 cohorts, N>32,676 (potential overlap of participants in two publications)	High study limitations (two high risk-of- bias studies), consistent	Insufficient	Table 12, p43 (row 1)

[34] results not pooled because two publications potentially draw from the same population

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Depressed or exposed to SSRIs in pregnancy	Exposed to **SSRIs** vs. unexposed to SSRIs during pregnancy with depression or unexposed to SSRIs in early pregnancy	**Cardiac anomalies**	68/7683 (0.9%) vs. 112/13,432 (0.8%); NR in second study; 466 cases/341 controls vs. 149 cases/125 controls	Pooled OR, 1.07 (95% CI, 0.97 to 1.20), I^2: 0% AOR, 1.06 (95% CI, 0.93 to 1.22) AOR, 1.04 (95% CI, 0.76 to 1.41) AOR, 1.14 (95% CI, 0.87 to 1.51)	2 cohorts, 1 case control, N>22,196 (N=NR in one study)	High study limitations (2 high risk-of-bias studies) imprecise (wide CIs), consistent	Insufficient	Table 12, p47 (row 2)
Pregnant women with diagnosis of depression only or depression and or anxiety, or exposed to antidepressants	Maternal exposure to **citalopram** vs. no exposure or unexposed to SSRIs in early pregnancy	**Cardiac congenital anomalies**	NR in two studies; 50 cases/39 controls vs. 149 cases/125 controls	Pooled OR, 1.09 (95% CI, 0.82 to 1.46), I^2: 0% AOR, 1.15 (95% CI, 0.69 to 1.92) AOR, 1.02 (95% CI, 0.61 to 1.70) AOR, 1.11 (95% CI, 0.68 to 1.83)	2 cohort studies, 1 case control, N>363 (N=NR in two studies)	High study limitations (high risk of bias), imprecision (wide CIs), consistent	Insufficient	Table 12, p44 (row 1)
Depression or antidepressant exposed women	**Escitalopram** exposure during early pregnancy vs. unexposed women with depression or unexposed to SSRIs in early pregnancy	**Cardiac anomalies**	3/333 (0.9%) vs. 112/13,432 (0.83%); 43 cases/35 controls vs. 149 cases/125 controls	AOR, 1.09 (95% CI, 0.34 to 3.50) AOR, 1.16 (95% CI, 0.69 to 1.97)	1 cohort, n=13,765, 1 case-control, n=352	Serious study limitations (high risk of bias), imprecision (wide CIs spanning the null), consistency unknown	Insufficient	Table 12, p44 (row 2)
Pregnant women: Cohort 1: depression and/or anxiety diagnosis and antidepressant exposure in 12 months before pregnancy. Cohort 2: depression diagnosis from year before conception through 1st trimester. Cohort 3: timing of depression diagnosis NR	**Fluoxetine** exposure in the first trimester vs. unexposed	**Cardiac anomalies**	NR/191 vs. NR/14,847; 66/3,189 (2.1%) vs. 112/13,432 (0.8%) 84/8,664 (1.0%) vs. 1,497/180,564 (0.8%)	Pooled OR, 0.94, (95% CI, 0.65 to 1.37), I^2: 41.9% AOR, 0.42 (95% CI, 0.10 to 1.73) AOR, 0.79 (95% CI, 0.49 to 1.26) Propensity-score AOR, 1.14 (95% CI, 0.90 to 1.44)	3 cohorts: N=15,038, N=16,621 N=189,228	High study limitations (all high risk-of-bias studies), imprecise (wide CIs), inconsistent	Insufficient	Table 12, p48 (row 1)

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Women with depression or anxiety in the year prior to pregnancy or exposure to antidepressants outside of early pregnancy	**Paroxetine** in first trimester vs. unexposed	**Cardiac anomalies**	NR/1132 vs. NR/14,847 17/1200 (1.4%) vs. 112/13,432 (0.8% 93/11,126 vs. NR/180,564 69 cases/43 controls vs. 149 cases/125 controls	Pooled AOR, 1.26, 95% CI, 0.96 to 1.65, I^2: 58%[35] **AOR, 1.45 (95% CI, 1.12-1.88**; 99% CI, 0.87 to 2.03) AOR, 1.67 (95% CI, 1.00 to 2.80, p=0.051) Propensity score AOR, 0.94 (95% CI, 0.73 to 1.21) AOR, 1.27 (95% CI, 0.8 to 2)	3 cohorts, 1 case-control, N=222,505	High study limitations (3 studies), imprecision (wide CIs), inconsistent	Insufficient	Table 12, p46 (row 1)
Women with depression or anxiety in the year prior to pregnancy	**Sertraline** in 1st trimester vs. unexposed	**Cardiac anomaly**	NR in one study: NR/365 vs. NR/14,847[36] 9/757 (1.0%) vs. NR/13,432; 93/11,126 (0.8%) vs. 1,479/180,564 (0.8%) 156 cases/129 controls vs. 149 cases /125 controls	Pooled AOR, 1.08 (95% CI, 0.91 to 1.28), I^2: 0% AOR, 1.14 (95% CI, 0.60 to 2.15)[37] AOR, 1.39 (95% CI, 0.70 to 2.74) Propensity score AOR, 1.09 (95% CI, 0.88 to 1.34, p=0.051) AOR, 0.97 (95% CI, 0.69 to 1.37)	3 cohorts, 1 case-control, 5 publications, N>250,577 (potential overlap in two publications)	High risk of bias (3 studies), imprecise (wide CIs), consistent	Insufficient	Table 12, p45 (row 1)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and major congenital anomalies, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of citalopram, escitalopram, fluoxetine, paroxetine or sertraline during the 1st trimester of pregnancy and major congenital anomalies, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of fluvoxamine in preconception or during pregnancy and major congenital anomalies, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs in early pregnancy or during pregnancy and cardiac anomalies, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of citalopram in early pregnancy and cardiac congenital anomalies, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of escitalopram, fluoxetine, paroxetine or sertraline in early pregnancy or the 1st trimester and cardiac anomalies, is uncertain.*								

[35] high heterogeneity potentially explained by clinical (differences in the definition of cardiac anomaly) and statistical heterogeneity (differences in direction of effect)
[36] results from publication with overlapping data: 10/366 (2.7%) vs. 344/14,868 (2.3%)
[37] results from one publication potentially overlapping data with study included in meta- analysis is also consistent, with ARR, 1.16 (95% CI, 0.62 to 2.19)

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Pregnancy and birth outcomes								
Depressed or anxious women	**SSRI** exposure in pregnancy vs. unexposed women with depression	**Perinatal mortality**	57/10312 (0.6%) vs. 20/3,647 (0.6%)	ARR, 1.2 (99% CI, 0.6 to 2.3)	1 cohort, n=13,959	High study limitations , imprecise (wide CIs), consistency unknown	Insufficient	Table B-19, pB-34 (row 2)
Depressed women	**SSRI** exposure in pregnancy vs. unexposed women with depression	**Miscarriage**	93/938 (9.9%) vs. 720/8,877 (8.1%); 1,539/10,312 (14.9) vs. 442/3647 (12.1%)	ARR, 1.2, (95% CI, 0.94 to 1.5) and **1.4 (99% CI, 1.2 to 1.7)**	2 cohorts, n=23,774	Moderate study limitations (one high risk-of-bias study) imprecise, consistent	Insufficient	Table 11, p38 (row 3)
Depressed, psychiatric disorders, or discontinued SSRIs during pregnancy exposed to SSRIs	**SSRI** exposure during pregnancy vs. no exposure (exposure prior to pregnancy or depressed or with psychiatric disorder)	**Preterm birth**	741/15,729 (4.7%) vs. 515/9,652; (5.3%); 17/192 (8.8%) vs. 415/5,710 (7.3%); 55/221 (24.9%) vs. 185/1,566 (11.8%); 3/37 (8.11%) vs. 3/19 (15.79%) N=NR for two publications	Overall, 5 of 6 studies do not report increased risks with SSRIs. Prevalence, AOR, ARRs range from 0.84 to 2.68 with CIs spanning the null in 2 of 4 studies[38]	6 cohorts; N>33,666 N= NR in one study)	High study limitations (5 high risk-of-bias studies), mostly consistent, imprecise (wide CIs in some studies)	Insufficient	Table 12, p40 (row 1)
History of mental health disorder or depression or SSRI-exposed women	**SSRI** exposure in pregnancy vs. unexposed women with depression or mental health disorder	**Small for gestational age**	Varies across studies from 2.5% to 17.4% in the treatment arm, and 2.5% to 14.7% in the control arm	Five of 6 studies report nonsignificant results (adjusted prevalence ratios, ARR, AOR, difference in incidence) with CIs spanning the null[39]	5 cohort studies, 1 case-control, n varies by trimester, n=43,185	High study limitations (4 of 6 high risk-of-bias studies), imprecise (wide CIs), mostly consistent	Insufficient	Table 12, p41 (row 1)
Use of antidepressants before or during pregnancy or psychiatric illness	**SSRI** exposure during pregnancy vs. SSRI exposure just before but not during pregnancy or psychiatric illness with no exposure	**Low birth weight**	42/221 (19.0%) vs. 150/1,566 (9.6%); NR in one study; 4/36 (11.11%) vs. 3/19 (15.79%)	Adjusted prevalence ratio: 1.1 (95% CI, 0.9 to 1.3) **AOR, 2.26 (95% CI, 1.31 to 3.91)** NR, p=0.613	3 cohorts, N>1,842, N=NR in one study	High study limitations (high risk of bias), imprecise (wide CIs), inconsistent	Insufficient	Table 12, p41 (row 2)
Depressed	**SSRI** exposure during pregnancy vs. unexposed during pregnancy	**Primary persistent pulmonary hypertension**	94/54,281 (0.2%) vs. 669/567,118 (0.1%)	**AOR, 1.28 (95% CI, 1.01 to 1.70)** AOR, when not restricted to full term or by outcome[40]	1 cohort, n=621,399	Moderate study limitations precise, consistency unknown, adjusting for confounding increased the odds	Low for harms with SSRIs	Table 10, p34 (row 1)

[38] one study reported higher odds in the SSRI group, the other reported lower odds in the SSRI group; difference in incidence: 0.007 (95% CI, -0.018 to 0.034); NR, p = 0.948
[39] one study reported AOR of 1.68 (95% CI, 1.03 to 2.74); ARR varies by trimester of exposure from 0.7 to 1.4, 95% CI spans the null
[40] persistent pulmonary hypertension rather than primary persistent pulmonary hypertension: 1.08 (95% CI, 0.92 to 1.27)

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
History of mental health disorder or depression or SSRI-exposed women	**SSRI** exposure in pregnancy vs. unexposed women with depression or mental health disorder	Respiratory conditions (including **respiratory distress,** *reported in one study only*)	Ranges from 4.3% to 4.9% in the treatment arm and 3.1% to 3.2 in the control arm; *NR in study that reported respiratory distress.*	All three studies reported increased risk. Adjusted prevalence ratios and AOR, range from 1.37 to 1.4 *(these data do not relate to respiratory distress)*	3 cohort studies, n>33,186 *(N=NR in the study that reported respiratory distress)*	High study limitations (2 of 3 are high risk-of-bias studies, precise, wide CIs), consistent	Low for harms with SSRIs	Table 10, p33 (row 3)
Exposed to SSRIs during pregnancy or unexposed with previous exposure or depressed	**SSRI** exposure during pregnancy vs. unexposed depressed or exposed before but not during pregnancy	**Neonatal convulsions**	9/2, 664 (0.3%) vs. 7/5,141 (0.1%); NR in one study	Adjusted prevalence ratio: 2.28 (95% CI, 0.87 to 5.97) Difference in incidence: 0.00077 (95% CI, -0.001 to 0.0036) p value 0.3	2 cohort studies, n>7,805 (N NR in one study)	High study limitations (1 of 2 studies are high risk of bias) imprecise, consistent	Insufficient	Table 12, p40 (row 2)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and neonatal mortality, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and miscarriage, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and preterm birth, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and small for gestational age newborn, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and low birth weight newborn, is uncertain.* *Maternal use of SSRIs during pregnancy may be associated with an increased risk of primary persistent pulmonary hypertension of the newborn (without cardiac malformation or lung hypoplasia in full-term deliveries) compared with women with untreated depression during pregnancy (low certainty evidence);* ***the absolute risk increase is small (33 more cases per 100,000 persons)****.* *Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and neonatal convulsions, is uncertain.*								
Neurodevelopmental outcomes								
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to **SSRIs** during pregnancy vs. unexposed with a psychiatric diagnosis	**Autism spectrum disorder**	88/15,729 (0.6%) vs. 79/9,651 (0.8%)[63]	AHR: 0.88 (95% CI, 0.65 to 1.2) p=0.428	1 cohort, n=25,380	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient	Table B-19, pB-40 (row 4)
Pregnant with or without a known psychiatric condition	**Citalopram** exposure vs. no maternal exposure to any antidepressant but with a known psychiatric condition	**Autism spectrum disorder**	46/1064 (4.3%) vs. 291/12325 (2.4%)	**AOR, 1.75 (95% CI, 1.25 to 2.45)**	1 cohort , n=13,389	Moderate study limitations, precise, consistency unknown	Low for harms with citalopram	Table 10, p34 (row 3)
Pregnant women: Any lifetime depression or anxiety diagnosis	**Fluoxetine** during pregnancy vs. unexposed women	**Autism spectrum disorder**	8/327 (2.1%) vs. 282/14,805 (1.9%); 16/453 (3.5%) vs. 353/12,325 (2.9%)	By 7- or 8-year follow-up ARR, 1.08 (0 95% CI, 0.53 to 2.21); 4-year or more follow-up: AOR, 1.42 (95% CI, 0.84 to 2.39)	2 cohorts: N=15,132; N=12,778 (potential overlap of participants in the publications)	Moderate study limitations, imprecise (wide CIs); consistent	Insufficient	Table 12, p50 (row 2)

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Women with current or past mental health disorder	**Paroxetine** vs. unexposed to antidepressants during pregnancy	**Autism spectrum disorder**	5/264 (1.9%) vs. 353/12,325 (2.9%) 3/108 (2.8%) vs. 282/14,805 (1.9%)	ARR, 0.61 (95% CI, 0.25 to 1.49) ARR, 1.21 (95% CI, 0.38 to 3.8)[41]	2 cohorts, N>35,218 (potential overlap of participants in the publications)	Moderate study limitations, imprecise (wide CIs), consistency unknown (potential overlap of participants)	Insufficient	Table 12, p51 (row 1)
Women with current or past mental health disorder	**Sertraline** vs. unexposed to antidepressants during pregnancy	**Autism spectrum disorder**	31/912 (3.4%) vs. 353/12,325 (2.9%) 16/672 (2.4%) vs. 282/14,805 (1.9%)	AOR, 1.45 (95% CI, 0.98 to 2.16) ARR, 1.17, (95% CI, 0.99 to 2.32)[42]	2 cohorts, N>15,47728,714 (potential overlap of participants in the publications)	Moderate study limitations, imprecise (wide CIs), some consistency	Insufficient	Table 12, p52 (row 1)
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to **SSRIs** during pregnancy vs. unexposed with a psychiatric diagnosis	**ADHD**	160/15,729 (1.0%) vs. 137/9,651 (1.4%)	AHR: 0.98 (95% CI, 0.77 to 1.24) p=0.847	1 cohort, n=25,380	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient	Table B-19, pB-40 (row 5)
Depressed or anxious or exposed to SSRIs in pregnancy	Exposed to **SSRIs** vs. unexposed during pregnancy with depression or anxiety	**Infant and child behaviour and development**	Varies by measure[43]	Results vary by specific outcome, but the majority of outcomes are not statistically significant; exceptions include 1 subscale measure for CBCL and NEPSY-II, and 3 of 13 NNNS subscale measures; studies with significant findings did not adjust for multiple comparisons	4 cohorts, N=4,410	High study limitations (3 of 4 are high risk of bias, imprecise, consistency unknown (single measures of outcomes not repeated in multiple studies)	Insufficient	Table 12, p50 (row 1)
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	**SSRIs** exposure during pregnancy vs. unexposed with a psychiatric diagnosis	**Depression**	60/15,729 (0.4%) vs. 30/9,651 (0.3%)	**AHR, 1.78 (95% CI, 1.12 to 2.82) p=0.015**	1 cohort, n=25,380	Moderate study limitations, precise, consistency unknown	Low for harms with SSRIs	Table 10, p34 (row 2)

[41] results adjusting for the number of mental health disorders show attenuating risks of autism spectrum disorder ≥1 mental health disorder: ARR, 1.36 (95% CI, 0.51 to 3.64) ≥2 mental health disorders: ARR, 1.02 (95% CI, 0.38 to 2.78) ≥3 mental health disorders: ARR, 0.74 (95% CI, 0.27 to 2.04

[42] results adjusting for the number of mental health disorders show attenuating risks of autism spectrum disorder ≥1 mental health disorder: ARR, 1.32 (95% CI, 0.86 to 2.24) ≥2 mental health disorders: ARR, 0.99 (95% CI, 0.63 to 1.55) ≥3 mental health disorders: ARR, 0.71 (95% CI, 0.43 to 1.17)

[43] measures include CBCL [including subscales], Behaviour Rating Inventory of Executive Function— Preschool version (BRIEF-P), Snijders-Oomen Niet-verbale intelligentie Test- Revisie (SON-R 2 1/2-7), NEPSY-II, NICU network neurobehavioral (NNNS [including subscales])— Attention scores, Mental Development Index (MDI), Provisional Diagnostic Instrument (PDI), Behavioral Rating Scale (BRS)

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Exposed to SSRIs during pregnancy or unexposed with a psychiatric diagnosis	Exposed to **SSRIs** during pregnancy vs. unexposed with a psychiatric diagnosis	**Anxiety**	65/ 15,729 (0.4%) vs. 39/9,651 (0.4%)	AHR: 1.3 (95% CI, 0.84 to 2.01) p=0.234	1 cohort, n=25,380	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient	Table B-19, pB-41 (row 1)

Evidence Statement:

Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs (fluoxetine, paroxetine, sertraline) during pregnancy and autism spectrum disorder, is uncertain.

Maternal use of citalopram during pregnancy may be associated with an increased risk of autism spectrum disorder in the child compared with unexposed women with a known mental health disorder (low certainty evidence); ***residual confounding could potentially explain this effect****.*

Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and ADHD in the child, is uncertain.

Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and infant and child behaviour and development (various measures) [44]*, is uncertain.*

Maternal use of SSRIs during pregnancy in women with a psychiatric diagnosis may be associated with an increased risk of depression in the child compared with no treatment (low certainty evidence); ***the study did not control for depression severity and the direction of effect is unclear.***

Due to the inadequate certainty of the evidence, any association between maternal use of SSRIs during pregnancy and anxiety in the child, is uncertain.

Source: AHRQ Comparative Effectiveness Review (CER) 2021, *with minor modifications for clarity of presentation and the addition of Evidence Statements.*

Abbreviations: AHR, adjusted hazard ratio; AOR, adjusted odds ratio; ARR, adjusted risk ratio; BRIEF-P, Behaviour Rating Inventory of Executive Function – Preschool version; CBCL, childhood behavior checklist; CI, confidence interval; N/n, number; NEPSY-II, Developmental NEuroPSYchological Assessment-II; NNNS, NICU Network Neurobehavioral Scale subscale measures; NR, not reported; OR, odds ratio; SON-R, Snijders-Oomen Niet-verbale intelligentie Test-Revisie; SSRI, selective serotonin reuptake inhibitor; vs., versus.

[44] measures include CBCL [including subscales], Behaviour Rating Inventory of Executive Function— Preschool version (BRIEF-P), Snijders-Oomen Niet-verbale intelligentie Test- Revisie (SON-R 2 1/2-7), NEPSY-II, NICU network neurobehavioral (NNNS [including subscales])— Attention scores, Mental Development Index (MDI), Provisional Diagnostic Instrument (PDI), Behavioral Rating Scale (BRS)

Table App. 36 Strength of evidence for harms: SNRIs versus no exposure

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Maternal harms								
Pregnant women with mood or anxiety disorders	**SNRI** exposure at time of delivery	**Postpartum haemorrhage**	35/702 (5.0%) vs. 1,896/69,044 (2.75%)	**ARR, 1.90 (1.37 to 2.63)**	1 cohort, N=69,746	Moderate study limitations, precise, consistency unknown	Low for harms with SNRIs	Table 9, p28 (row 5)
Pregnant women with mood or anxiety disorders	**Venlafaxine** exposure at time of delivery	**Postpartum haemorrhage**	46/763 (6.0%) vs. 1,896/69,044 (2.75%)	**ARR, 2.24 (1.69 to 2.97)**	1 cohort, N=69,807	Moderate study limitations, precise, consistency unknown	Low for harms with venlafaxine	Table 9, p28 (row 6)
Evidence Statement: *Maternal use of SNRIs (as a class, venlafaxine) at the time of delivery may be associated with an increased risk of postpartum haemorrhage (low certainty evidence);* ***the risk of residual confounding remains because the study was not able to control for confounding factors of inadequate diet, the use of tobacco, and severity of disorder****.*								
Malformations								
Pregnant women: depression and/or anxiety diagnosis and exposure to antidepressants in the 12 months before pregnancy	**SNRI** exposure in the first trimester vs. unexposed	**Major congenital anomaly**	91/738 (12.3%) vs. 1,650/14,847 (11.1%)	Through 11 years post-delivery: AOR, 1.10 (0.87 to 1.38)	1 cohort: N=15,585	High study limitations (high risk of bias) imprecise (wide CIs); consistency unknown	Insufficient	Table B-27, pB-64 (row 5)
Women with depression or anxiety before pregnancy or exposure to antidepressants outside of early pregnancy or duloxetine in the first trimester vs. discontinuation of duloxetine before the first trimester	**Venlafaxine**; **SNRI**; exposure in the first trimester vs. unexposed; **Duloxetine**, exposure in the first trimester	**Cardiac anomalies**	SNRI: 69/1,497 (4.6%) vs. 1,497/180,564 (0.8%); 59 cases/27 controls vs. 149 cases/125 controls Venlafaxine: NR/738 vs. NR/14,847; 47 cases/21 controls vs. 149 cases/125 controls Duloxetine: 59/2,532 (2.33%) vs. 43/2,456 (1.75%)	SNRI Propensity score AOR, 1.20 (0.91 to 1.57) AOR, 1.14 (95% CI, 0.44 to 3.01) Venlafaxine AOR, 0.80 (0.47 to 1.38) **AOR, 1.91 (95% CI, 1.05 to 3.45) SNRIs** Duloxetine ARR, 1.41 (95% CI, 0.92 to 2.17)	3 cohorts, 1 case control: N=202,994	High study limitations (high risk of bias), imprecise (wide CIs), inconsistent	Insufficient	Table 12, p48 (row 2)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of SNRIs (as a class) during the 1st trimester of pregnancy and major congenital anomalies, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of venlafaxine or duloxetine during the 1st trimester of pregnancy and cardiac anomalies, is uncertain.*								

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Pregnancy and birth outcomes								
Pregnant women: SNRI exposure or depression diagnosis in past 4 years	**SNRI** exposure in 1st trimester vs. unexposed to any antidepressant	**Miscarriage**	20/90 (22%) vs. 720/7,034 (10%); results corrected for induced abortions: 20/137 (15%) vs. 720/8,877 (8.1%)	**ARR, 2.1 (95% CI, 1.4 to 3.0); corrected for induced abortions ARR, 1.7 (95% CI, 1.2 to 2.6)**	1 cohort, n=7,134, corrected for induced abortion, n=9,014	Moderate study limitations, precise, consistency unknown	Low for harms with SNRIs	Table 9, p29 (row 5)
Pregnant women with a psychiatric disorder diagnosis, used AD ≥30 days in prior year	**Venlafaxine** during 2nd trimester vs. unexposed	**Small for gestational age**	NA, case- control	**ARR, 2.55 (1.04 to 6.27)**	1 case-control: N=755	Moderate study limitations, imprecise (few events, wide CIs); consistency unknown	Insufficient	Table B-27, pB-64 (row 4)
Evidence Statement: *Maternal use of SNRIs (as a class) during the 1st trimester of pregnancy may be associated with an increased risk of miscarriage (low certainty evidence).* *Due to the inadequate certainty of the evidence, any association between maternal use of venlafaxine during the 2nd trimester of pregnancy and small for gestational age neonate, is uncertain.*								
Neurodevelopmental outcomes								
Pregnant women: Any lifetime psychiatric disorders	**Duloxetine** during pregnancy vs. unexposed women	**Autism spectrum disorder**	NR/52 (NR%) vs. control ≥1 psychiatric disorder: NR/24,285 (NR%); control ≥2 psychiatric disorders NR/5,839 (NR%); control ≥3 psychiatric disorders NR/5,839 (NR%)	Results not presented for any comparison	Duloxetine and control ≥1 psychiatric disorder: N=24,337; duloxetine and control ≥2 psychiatric disorders: N=5,891; duloxetine and control ≥3 psychiatric disorders: N=1946	Moderate study limitations, no result estimates	Insufficient	Table B-27, pB-66 (row 1)
Pregnant women: Any lifetime depression or anxiety diagnosis	**Venlafaxine** during pregnancy vs. unexposed women	**Autism spectrum disorder**	4/195 (2.1%) vs. 282/14,805 (1.9%); 11/213 (5.1%) vs. 353/12,325 (2.9%)	By 7- or 8-year follow-up ARR, 0.74 (0.32 to 1.72); 4-year or more follow-up: AOR, 1.81 (0.89 to 3.71)[45]	2 cohorts: N=27,538	Moderate study limitations, imprecise (wide CIs); inconsistent	Insufficient	Table 12, p53 (row 1)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of venlafaxine or duloxetine during pregnancy and autism spectrum disorder in the child, is uncertain.*								

Source: AHRQ Comparative Effectiveness Review (CER) 2021, *with minor modifications for clarity of presentation and the addition of Evidence Statements.*
Abbreviations: AOR, adjusted odds ratio; ARR, adjusted risk ratio; CI, confidence interval; NA, not available; N/n, number; NR, not reported; OR, odds ratio; SNRI, serotonin-norepinephrine reuptake inhibitor; vs., versus.

[45] ≥1 mental health disorder: ARR, 1.36 (95% CI, 0.61 to 3.04) ≥2 mental health disorders: ARR, 1.01 (95% CI, 0.44 to 2.29) ≥3 mental health disorders: ARR, 0.74 (95% CI, 0.32 to 1.72)

Table App. 37 Strength of evidence for harms: TCAs versus no exposure

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Maternal harms								
Mood or anxiety disorder during pregnancy or exposed to amitriptyline	Current **amitriptyline** exposure (at delivery), or unexposed	**Postpartum haemorrhage**	NR	ARR, 1.68 (95% CI, 0.89 to 3.16)	1 cohort, N=69,220	Moderate study limitations, precise, consistency unknown	Insufficient	Table B-28, pB-68 (row 2)
Mood or anxiety disorder during pregnancy or exposed to amitriptyline	Recent **amitriptyline** exposure (<1 month before delivery) or unexposed	**Postpartum haemorrhage**	NR	ARR, 1.13 (95% CI, 0.29 to 4.42)	1 cohort, N=69,113	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient	Table B-28, pB-68 (row 3)
Mood or anxiety disorder during pregnancy or exposed to amitriptyline	Past **amitriptyline** exposure (>1 to 5 months before delivery) or unexposed	**Postpartum haemorrhage**	NR	ARR, 1.08 (95% CI, 0.48 to 2.42)	1 cohort, n=69,250	Moderate study limitations, precision (wide CIs), consistency unknown	Insufficient	Table B-28, pB-68 (row 4)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of amitriptyline (at delivery, within one month of delivery, or one to five months before delivery) and postpartum haemorrhage, is uncertain.*								
Malformations								
History of depression, depression or anxiety or mental health disorder or TCA-exposed women	**TCA** exposure during the first trimester vs. unexposed with history of depression, anxiety, or mental health disorder	**Major congenital anomalies**	51/382 (13.4%) vs. 1,650/14,847 (11.1%); 74/2,428 (3.0%) vs. 380/13,432 (2.8%); NR in other study	Results not pooled because two publications potentially draw from the same population AOR, 1.16 (95% CI, 0.86 to 1.56) AOR, 1.02 (95% CI, 0.79 to 1.32) AOR, 0.78 (95% CI, 0.30 to 2.02)	1 case-control, 2 cohorts, n≥31,089 N from two studies; (potential overlap of participants in the publications)	High study limitations (two high risk-of-bias studies), imprecise (wide CIs), consistent	Insufficient	Table 12, p43 (row 2)
History of depression or anxiety or TCA- exposed women	**TCA** in first trimester vs. unexposed women with history of depression	**Cardiac anomalies**	20/2,428 (0.82%) vs. 112/13,432 (0.83%); NR in other studies	Pooled AOR, 0.86 (95% CI, 0.65 to 1.13), I^2: 0%	3 cohorts, n>15,860 (N=NR in two studies)	High study limitations (all risk-of-bias studies), imprecise (wide CIs), consistent	Insufficient	Table 12, p49 (row 1)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of TCA during the first trimester of pregnancy and major congenital anomalies, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of TCA during the first trimester of pregnancy and cardiac anomalies, is uncertain.*								

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Pregnancy and birth outcomes								
Depressed or anxious or TCA-exposed women	**TCA** exposure in pregnancy vs. unexposed women with depression	**Perinatal mortality**	18/3,019 (0.6%) vs. 20/3647 (0.6%)	ARR, 1.2 (99% CI, 0.5 to 2.7)	1 cohort, n=6,666	High study limitations, imprecise (wide CIs), consistency unknown	Insufficient	Table B-28, pB-68 (row 6)
Depressed or TCA-exposed women	**TCA** exposure in pregnancy vs. unexposed women with depression	**Miscarriage**	20/112 (17.9%) vs. 720/7,034 (10.2%) NR in second	ARR, 1.5, (95% CI, 0.96 to 2.2) and **1.3 (99% CI, 1.1 to 1.5)**	2 cohorts, n=7,146 in one cohort, NR in second	Moderate study limitations (one high risk-of-bias study), imprecise, consistent	Insufficient	Table 11, p38 (row 2)
History of psychiatric disorder or TCA-exposed women	**TCA** exposure in pregnancy vs. unexposed women with psychiatric disorder	**Small for gestational age**	Not applicable for case-control	ARR, varies by trimester from 0.69 to 2.12, 95% CI, spans the null	1 case- control, n varies by trimester, >1,535	Moderate study limitations, imprecise (wide CIs), consistency unknown	Insufficient	Table B-28, pB-68 (row 7)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of TCA during pregnancy and perinatal mortality, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of TCA during pregnancy and miscarriage, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of TCA during pregnancy and SFGA neonates, is uncertain.*								
Neurodevelopmental outcomes								
Psychiatric disorder or amitriptyline or nortriptyline-exposed women	**Amitriptyline or nortriptyline** vs. unexposed women with history of psychiatric disorder	**Autism spectrum disorder**	NR	ARR, 0.47 (95% CI, 0.07 to 3.31) ≥1 psychiatric disorder: ARR, 0.47 (95% CI, 0.07 to 3.31) ≥2 psychiatric disorders: ARR, 0.35 (0.05 to 2.49) ≥3 psychiatric disorders: ARR, 0.25 (0.04 to 1.84)	1 cohort, n=24,418	Moderate study limitations, imprecise, consistency unknown	Insufficient	Table B-28, pB-70 (row 1)
Mental health disorder or clomipramine- exposed women	**Clomipramine** vs. unexposed women with history of psychiatric disorder	**Autism spectrum disorder**	16/235 (6.8%) vs. 353/12,325 (2.9%); NR in second study	**AOR, 1.76 (95% CI, 1.01 to 3.05); ARR, 3.36, 95% CI, 1.39 to 8.13**[46]	2 cohorts, n=36,936 (potential overlap of participants in the publications)	Moderate study limitations, imprecise, consistent	Insufficient	Table 12, p54 (row 1)

[46] results not statistically significant when corrected for multiple testing ≥1 mental health disorder: ARR, 3.36 (95% CI, 1.39 to 8.13) ≥2 mental health disorders: ARR, 2.53 (95% CI, 1.02 to 6.22) ≥3 mental health disorders: ARR, 1.88 (95% CI, 0.7 to 4.73)

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of amitriptyline or nortriptyline during pregnancy and autism spectrum disorder in the child, is uncertain.* *Maternal use of clomipramine during pregnancy appears to be associated with an increased risk of autism spectrum disorder in the child, but due to the inadequate quality of the evidence, this association is uncertain.*								

Source: AHRQ Comparative Effectiveness Review (CER) 2021, *with minor modifications for clarity of presentation and the addition of Evidence Statements.*
Abbreviations: AOR, adjusted odds ratio; ARR, adjusted risk ratio; CI, confidence interval; N/n, number; NR, not reported; TCA, tricyclic antidepressant; vs., versus.

Table App. 38 Strength of evidence for harms: Atypical antidepressants versus no exposure

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Maternal harms								
Mood disorder or anxiety or bupropion-exposed women	Past **bupropion** exposure in pregnancy vs. bupropion unexposed women with mood disorder or anxiety	**Postpartum haemorrhage**	61/1712 (3.6%) vs. 1,896/69,044 (2.75%)	**ARR, 1.32 (95% CI, 1.02 to 1.69)**	1 cohort, n=70,206	Moderate study limitations, precise, consistency unknown	Low for harms of bupropion	Table 9, p28 (row 7)
Women with mood disorder or anxiety	**Mirtazapine** exposure during pregnancy (current)	**Postpartum haemorrhage**	NR/129 (NR%) vs. 1,896/69,044 (2.7%)	ARR, 0.87 (95% CI, 0.29 to 2.66)	1 cohort, n=69,173	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient	Table B-31, pB-75 (row 1)
Women with mood disorder or anxiety	**Mirtazapine** exposure during pregnancy (recent, 1-30 days prior to delivery)	**Postpartum haemorrhage**	0/57 (0%) vs. 1,896/69,044 (2.7%)	ARR, NA	1 cohort, n=69,101	Moderate study limitations, likely imprecision (few treatment cases and no events), consistency unknown	Insufficient	Table B-31, pB-75 (row 2)
Women with mood disorder or anxiety	**Mirtazapine** exposure during pregnancy (past exposure 1-5 months prior to delivery)	**Postpartum haemorrhage**	NR/135 (NR%) vs. 1,896/69,044 (2.7%)	ARR, 1.07 (95% CI, 0.4 to 2.82)	1 cohort, n=69,179	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient	Table B-31, pB-76 (row 1)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of mirtazapine during pregnancy and postpartum haemorrhage, is uncertain.* *Maternal use of bupropion one to five months before delivery may be associated with an increased risk of postpartum haemorrhage (low certainty evidence).*								
Malformations								
Depressed or bupropion- exposed women	**Bupropion** exposure in pregnancy vs. unexposed women with depression or unexposed in early pregnancy	**Cardiac anomalies**	NR; 57 cases/45 controls vs.149 cases/125 controls122	AOR, 0.92 (95% CI, 0.69 to 1.22); AOR, 1.06 (0.66 to 1.71)	1 cohort,1 case-control, n NR in cohort N in case-control=376	Serious study limitations (high risk of bias) imprecise (wide CIs spanning the null), consistency unknown	Insufficient	Table 12, p49 (row 2)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of bupropion during pregnancy and cardiac anomalies, is uncertain.*								

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Pregnancy and birth outcomes								
Women with psychiatric diagnosis	**Mirtazapine** exposure during pregnancy vs. unmedicated psychiatric diagnosis	**Preterm birth**	1/15 vs. 3/19	NR, p = 0.767	1 cohort, n=3,439	High study limitations (high risk of bias), imprecision (wide CIs), consistency unknown	Insufficient	Table B-31, pB-76 (row 3)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of mirtazapine during pregnancy and preterm birth, is uncertain.*								
Neurodevelopmental outcomes								
Women exposed to antidepressants	**Mirtazapine** exposure during pregnancy vs. unexposed women with prior antidepressant prescription	**Autism spectrum disorder**	NR/625 (NR) vs. NR/24,285 (NR) ≥1 psychiatric disorder: ARR, 1.55 (95% CI, 0.39 to 6.29) ≥2 psychiatric disorders: ARR, 1.24 (95% CI, 0.30 to 5.06) ≥3 psychiatric disorders: ARR, 0.99 (95% CI, 0.24 to 4.09)	ARR, 1.55 (95% CI, 0.39 to 6.29)	1 cohort, n=24,347	Moderate study limitations, imprecision (wide CIs), consistency unknown	Insufficient	Table B-31, pB-77 (row 1)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of mirtazapine during pregnancy and autism spectrum disorder in the child, is uncertain.*								

Source: AHRQ Comparative Effectiveness Review (CER) 2021, *with minor modifications for clarity of presentation and the addition of Evidence Statements.*
Abbreviations: AOR, adjusted odds ratio; ARR, adjusted risk ratio; CI, confidence interval; N/n, number; NR, not reported; vs. = versus.

6.1.2 Antipsychotics

Table App. 39 Strength of evidence for harms: Antipsychotics versus no exposure

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Malformations								
Women with a psychiatric condition or women with schizophrenia, bipolar disorder, or psychosis	**Second- generation antipsychotic** exposure in first trimester vs. unexposed to second-generation antipsychotic	**Major congenital anomalies**	209/3,995 (5.2%) vs, 471/11,606 (4.1%) 3/214 (1.4%) vs. 1/89 (1.1%)	AOR, 1.16 (95% CI, 0.99 to 1.35) AOR, 0.69 (95% CI, 0.06 to 8.09)	2 cohorts, n=15,904	Moderate study limitations (one high risk- of-bias study precise, inconsistent	Insufficient	Table 12, p43 (row 3) & Table B-33, pB-86 (row 3)
Women with schizophrenia, bipolar disorder, or psychosis	**First- generation antipsychotic** exposure in first trimester vs. unexposed to first-generation antipsychotic	**Major congenital anomalies**	16/381 (4.2%) vs. 417/10,418 (4.0%)	AOR, 0.93 (95% CI, 0.57 to 1.51)	1 cohort, n=10,799	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient	Table B-33, pB-86 (row 4)

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Women with a psychiatric condition	**Quetiapine** exposure in first trimester vs. unexposed to second-generation antipsychotic	**Major congenital anomalies**	2/155 (1.3%) vs. 3/210 (1.4%)	AOR, 0.9 (95% CI, 0.15 to 5.46)	1 cohort, n=357	High study limitations (high risk of bias) imprecise (wide CIs), consistency unknown	Insufficient	Table B-33, pB-86 (row 2)
Women exposed to risperidone during or before pregnancy	**Risperidone** continued in first trimester vs. risperidone discontinued before pregnancy	**Major congenital anomalies**	44/895 (4.9%) vs. 72/1737 discontinued before pregnancy (4.1%) N reduces in both arms as more restrictive definitions of control group are used (no prescriptions 4, 6, and 8 weeks before pregnancy)	AOR, 1.00 (95% CI, 0.70 to 1.43) AOR increases when more restrictive definitions of control group are used (no prescriptions 4, 6, and 8 weeks before pregnancy) from 1.13 to 1.64; CIs wide in all cases and span the null	1 cohort, n=2,632	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient	Table B-33, pB-85 (row 5)
Women with schizophrenia, bipolar disorder, or psychosis	**Second- generation antipsychotic** exposure in first trimester vs. unexposed to second-generation antipsychotic	**Cardiac anomalies**	79/3,995 (2.0%) vs. 169/11,606 (1.5%)	AOR, 1.21 (95% CI, 0.93 to 1.57)	1 cohort, n=15,601	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient	Table B-33, pB-86 (row 5)
Women with schizophrenia, bipolar disorder, or psychosis	**First- generation antipsychotic** exposure in first trimester vs. unexposed to first-generation antipsychotic	**Cardiac anomalies**	≤10/381 (≤2.6%) vs. 152/10,418 (2.6%)	AOR, 0.91 (95% CI, 0.43 to 1.91)	1 cohort, n=10,799	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient	Table B-33, pB-87 (row 1)
Women exposed to risperidone during or before pregnancy	**Risperidone** continued in first trimester vs. risperidone discontinued before pregnancy	**Cardiac anomalies**	18/895 (2.0%) vs. 26/1,737 (discontinued before pregnancy) (1.5%) N reduces in both arms as more restrictive definitions of control group are used (no prescriptions 4, 6, and 8 weeks before pregnancy)	AOR, 0.85. (95% CI, 0.49 to 1.46) AOR increases with more restrictive definitions of control group are used (no prescriptions 4, 6, and 8 weeks before pregnancy) from 1.31 to 2.46; CIs wide in all cases and span the null	1 cohort, n=2,632	Moderate study limitations imprecise (wide CIs), inconsistency unknown	Insufficient	Table B-33, pB-86 (row 1)

Evidence Statement:

Due to the inadequate certainty of the evidence, any association between maternal use of antipsychotics (as a class, 1st or 2nd generation) during the 1st trimester of pregnancy and major congenital abnormalities, is uncertain.

Due to the inadequate certainty of the evidence, any association between maternal use of quetiapine or risperidone during the 1st trimester of pregnancy and major congenital abnormalities, is uncertain.

Due to the inadequate certainty of the evidence, any association between maternal use of antipsychotics (as a class, 1st or 2nd generation) during the 1st trimester of pregnancy and cardiac anomalies, is uncertain.

Due to the inadequate certainty of the evidence, any association between maternal use of risperidone during the 1st trimester of pregnancy and cardiac anomalies, is uncertain.

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2021 location
Pregnancy and birth outcomes								
Women with schizophrenia	**Second- generation antipsychotic** vs. no antipsychotic	**Preterm birth**	6/48 (12.5%) vs. 37/454 (8.1%)	AOR, 1.61 (95% CI, 0.63 to 4.12)	1 cohort, n=696	High study limitations (high risk of bias) imprecise (wide CIs), consistency unknown	Insufficient	Table B-33, pB-84 (row 5)
Women with schizophrenia	**First- generation antipsychotic** vs. no antipsychotic	**Preterm birth**	35/194 (18.0%) vs. 37/454 (8.1%)	**AOR, 2.46 (95% CI, 1.5 to 4.11)**	1 cohort, n=648	High study limitations (high risk of bias) precise, consistency unknown	Insufficient	Table B-33, pB-84 (row 4)
Women with schizophrenia	**Second- generation antipsychotic** vs. no antipsychotic	**Small for gestational age**	10/48(20.8%) vs. 92/454 (20.3%)	AOR, 1.15 (95% CI, 0.55 to 2.41)	1 cohort, n=696	High study limitations (high risk of bias) imprecise (wide CIs), consistency unknown	Insufficient	Table B-33, pB-85 (row 2)
Women with schizophrenia	**First- generation antipsychotic** vs. no antipsychotic	**Small for gestational age**	49/194 (25.3%) vs. 92/454 (20.3%)	AOR, 1.39 (95% CI, 0.93 to 2.08)	1 cohort, n=696	High study limitations (high risk of bias) imprecise (wide CIs), consistency unknown	Insufficient	Table B-33, pB-85 (row 1)

Evidence Statement:
Due to the inadequate certainty of the evidence, any association between maternal use of 2nd generation antipsychotics during pregnancy and preterm birth, is uncertain.
Maternal use of 1st generation antipsychotics during pregnancy appears to be associated with an increased risk of preterm birth, but due to the inadequate quality of the evidence, this association is uncertain.
Due to the inadequate certainty of the evidence, any association between maternal use of antipsychotics (as a class, 1st or 2nd generation) during pregnancy and SFGA neonate, is uncertain.

Source: AHRQ Comparative Effectiveness Review (CER) 2021, *with minor modifications for clarity of presentation and the addition of Evidence Statements.*
Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; N/n, number; OR, odds ratio; vs., versus.

6.1.3 Anticonvulsants

Table App. 40 Strength of evidence for harms: Anticonvulsants versus no exposure

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2011 location
Pregnancy and birth outcomes								
Pregnant women with bipolar disorder	**Mood stabilizer monotherapy**[47] vs. no exposure to mood stabilizers	**Preterm birth**	NR	ARR, 0.95 (95% CI, 0.87 to 1.04) (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient	Table B-32, pB-78 (row 4)
Pregnant women with bipolar disorder	**Mood stabilizer monotherapy**[47] vs. no exposure to mood stabilizers	**Small for gestational age**	NR	**ARR, 0.80 (95% CI, 0.65 to 0.97)** (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient	Table B-32, pB-78 (row 3)
Pregnant women with bipolar disorder	**Carbamazepine** vs. no exposure to mood stabilizers	**Preterm birth**	NR	ARR, 1.05 (95% CI, 0.74 to 1.48) (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient	Table B-32, pB-80 (row 6)
Pregnant women with bipolar disorder	**Carbamazepine** vs. no exposure to mood stabilizers	**Small for gestational age**	NR	ARR, 1.45 (95% CI, 0.76 to 2.77) (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient	Table B-32, pB-80 (row 5)
Pregnant women with bipolar disorder	**Lamotrigine** vs. no exposure to mood stabilizers	**Preterm birth**	NR	ARR, 0.97 (95% CI, 0.84 to 1.13) (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size),consistency unknown	Insufficient	Table B-32, pB-79 (row 2)
Pregnant women with bipolar disorder	**Lamotrigine** vs. no exposure to mood stabilizers	**Small for gestational age**	NR	ARR, 0.78 (95% CI, 0.58 to 1.07) (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient	Table B-32, pB-79 (row 1)
Pregnant women with bipolar disorder	**Valproate** vs. no exposure to mood stabilizers	**Preterm birth**	NR	ARR, 1.06 (95% CI, 0.92 to 1.23) (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient	Table B-32, pB-79 (row 6)
Pregnant women with bipolar disorder	**Valproate** vs. no exposure to mood stabilizers	**Small for gestational age**	NR	ARR, 0.70 (95% CI, 0.49 to 1.00) (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient	Table B-32, pB-79 (row 5)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of carbamazepine, lamotrigine or valproate during pregnancy and preterm birth, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of carbamazepine, lamotrigine or valproate during pregnancy and SFGA neonate, is uncertain.*								

Source: AHRQ Comparative Effectiveness Review (CER) 2021, *with minor modifications for clarity of presentation and the addition of Evidence Statements.*
Abbreviations: ARR, adjusted risk ratio; CI, confidence interval; N/n, number; NR, not reported; vs., versus.

[47] Includes exposure to anticonvulsants (lamotrigine, valproate, topiramate, carbamazepine or oxcarbazepine) or lithium.

6.1.4 Benzodiazepines or z-drugs

Table App. 41 Strength of evidence for harms: Benzodiazepines or z-drugs versus no exposure

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2011 location
Malformations								
Pregnant women with depression or anxiety	**Diazepam** use in first trimester vs. untreated depression or anxiety during pregnancy	**Major congenital anomalies**	31/1,159 (2.7%) vs. 518/19,193 (2.7%)	AOR, 0.99 (95% CI, 0.61 to 1.61)	1 cohort, N=20,352	High study limitations (high risk of bias) imprecision (wide CIs spanning the null), consistency unknown	Insufficient	Table B-17, pB-27 (row 6)
Pregnant women with depression or anxiety	**Temazepam** use in first trimester vs. untreated depression or anxiety during pregnancy	**Major congenital anomalies**	11/379 (2.9%) vs. 518/19,193 (2.7%)	AOR, 1.04 (95% CI, 0.47 to 2.32)	1 cohort, N=19,572	High study limitations (high risk of bias[71]) imprecision (wide CIs spanning the null), consistency unknown	Insufficient	Table B-17, pB-28 (row 1)
Women with depression or anxiety	**Zopiclone** exposure during pregnancy vs. unexposed women with untreated depression or anxiety	**Major congenital anomalies**	10/406 (2.5%) vs. 518/19193 (2.7%)	AOR: 0.93 (95% CI, 0.4 to 2.15)	1 cohort; n=19,599	Imprecise, consistent, high risk of bias	Insufficient	Table B-18, pB-30 (row 9)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of diazepam or temazepam during 1st trimester of pregnancy and major congenital anomalies, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of zopiclone during pregnancy and major congenital anomalies, is uncertain.*								
Pregnancy and birth outcomes								
Pregnant women with depression or anxiety	**Benzodiazepine** exposure in first trimester vs. untreated depression or anxiety during pregnancy	**Perinatal death**	16/2,384 (0.7%) vs. 20/3,647 (0.5%)	RRR, 1.4 (95% CI, 0.6 to 1.9)	1 cohort, N=6,031	High study limitations (high risk of bias), imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient	Table B-17, pB-27 (row 2)
Pregnant women with depression or anxiety	Continuation of **benzodiazepine** through first trimester vs. discontinuation of benzodiazepine during first trimester	**Perinatal death**	6/611 (1%) vs. 19/2,717 (0.7%)	RRR, 1.7 (95% CI, 0.5 to 6.0)	1 cohort, N=3,328	High study limitations (high risk of bias) imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient	Table B-17, pB-27 (row 4)
Pregnant women with depression or anxiety	**Benzodiazepine** exposure in first trimester or within the first 19 weeks vs. untreated or a history of mood disorders or anxiety during pregnancy	**Spontaneous abortion**	386/2,384 (16%) vs. 442/3,647 (12%) 198 cases/570 controls vs. 3,221 cases/15,382 controls	**ARR, 1.6 (95% CI, 1.3 to 1.9)** **AOR: 2.85 (95% CI, 1.72 to 4.72)**	1 cohort, 1 case-control study, N=21,983	Moderate study limitations (high risk of bias) precise, consistent	Low for harms with benzodiazepine	Table 9, p29 (row 6)
Pregnant women with depression or anxiety	Continuation of **benzodiazepine** through first trimester vs. discontinuation of benzodiazepine during first trimester	**Spontaneous abortion**	105/611 (17%) vs. 415/2,717 (15%)	RRR, 1.5 (95% CI, 1.0 to 2.1)	1 cohort, N=3,328	High study limitations (high risk of bias) precise, consistency unknown	Insufficient	Table B-17, pB-27 (row 5)

Population	Intervention	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ CER 2011 location
Pregnant women with a psychiatric disorder	**Benzodiazepine** exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	**Prematurity**	17/144 (11.8%) vs. 87/650 (13.4%)	AOR, 1.31 (95% CI, 0.55 to 2.32)	1 cohort, N=794	Moderate study limitations, serious imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient	Table B-17, pB-29 (row 1)
Women with psychiatric illness	**Zolpidem** exposure during pregnancy vs. unexposed to zolpidem during pregnancy	**Preterm delivery**	12/45 (26.7%) vs. 6/45 (13.3%)	NR, NS based on multivariate conditional logistic regression, p<.18	1 cohort, n=90	Imprecise, consistent, high risk of bias	Insufficient	Table B-18, pB-30 (row 2)
Pregnant women with a psychiatric disorder	**Benzodiazepine** exposure during pregnancy vs. unexposed to benzodiazepine use during pregnancy	**Breathing difficulty in neonate**	20/96 (20.8%) vs. 78/387 (20.2%)	AOR, 1.84 (95% CI, 0.87 to 3.93)	1 cohort, N=483	Moderate study limitations, serious imprecision (wide CIs spanning the null, few events), consistency unknown	Insufficient	Table B-17, pB-28 (row 4)
Women with psychiatric illness	**Zolpidem** exposure during pregnancy vs. unexposed to zolpidem during pregnancy	**Respiratory difficulty**	10/45 (22.2%) vs. 14/45 (31.1%)	NR, NS based on multivariate conditional logistic regression, p<.49	1 cohort, n=90	Imprecise, consistent, high risk of bias	Insufficient	Table B-18, pB-30 (row 6)

Evidence Statement:

Due to the inadequate certainty of the evidence, any association between maternal use of benzodiazepine during 1st trimester of pregnancy and perinatal death, is uncertain.

Maternal use of benzodiazepine during 1st trimester of pregnancy or within the first 19 weeks may be associated with an increased risk of miscarriage (low certainty evidence).

Due to the inadequate certainty of the evidence, any association between maternal continuation of benzodiazepine through 1st trimester of pregnancy and miscarriage, is uncertain.

Due to the inadequate certainty of the evidence, any association between maternal use of benzodiazepine during pregnancy and neonatal prematurity, is uncertain.

Due to the inadequate certainty of the evidence, any association between maternal use of zolpidem during pregnancy and preterm delivery, is uncertain.

Source: AHRQ Comparative Effectiveness Review (CER) 2021, *with minor modifications for clarity of presentation and the addition of Evidence Statements.*

Abbreviations: AOR, adjusted odds ratio; ARR, adjusted risk ratio; CI, confidence interval; N/n, number; NR, not reported; NS, not sufficient; RRR, relative risk ratio; vs., versus.

6.1.5 Lithium

Table App. 42 Strength of evidence for harms: Lithium versus no exposure

Population	Intervention and Comparator	Outcome	Incidence or Mean Effect by arm	Results	Study Design and Sample Size	Factors that affect the Strength of Evidence	Overall Evidence Strength	AHRQ location
Pregnancy & birth outcomes								
Pregnant women with bipolar disorder	**Lithium** vs. no exposure to mood stabilizers	**Preterm birth**	NR	ARR, 0.83 (95% CI, 0.67 to 1.02) (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient	Table B-32 pB-81 (row 8)
Pregnant women with bipolar disorder	**Lithium** vs. no exposure to mood stabilizers	**Small for gestational age**	NR	ARR, 0.95 (95% CI, 0.64 to 1.41) (personal communication with author)	1 cohort, N NR	Moderate study limitations, likely imprecise (wide CIs, likely small sample size), consistency unknown	Insufficient	Table B-32 pB-81 (row 7)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lithium during pregnancy and preterm birth, is uncertain.* *Due to the inadequate certainty of the evidence, any association between maternal use of lithium during pregnancy and SFGA neonate, is uncertain.*								
Neurodevelopmental outcomes								
Mood disorders	**Lithium** exposure in pregnancy vs. unexposed women with mood disorders	Child 's fullscale **IQ** at 4-5 years from the Wechsler Preschool and Primary Scale of Intelligence	Medians 107.5 vs. 98	Regression coefficient for no lithium vs. lithium: -6.3, p=0.15	1 cohort, n=27	High study limitations (high risk of bias), seriously imprecise (wide CIs, small sample size), consistency unknown	Insufficient	Table B-32 pB-82 (row 1)
Evidence Statement: *Due to the inadequate certainty of the evidence, any association between maternal use of lithium during pregnancy and IQ of the child at 4-5 years, is uncertain.*								

Source: AHRQ Comparative Effectiveness Review (CER) 2021, *with minor modifications for clarity of presentation and the addition of Evidence Statements.*
Abbreviations: ARR, adjusted risk ratio; CI, confidence interval; IQ, intelligence quotient; N/n, number; NR, not reported; vs., versus.

6.2 Complementary

6.2.1 Omega-3 fatty acids

The Cochrane review by Middleton et al. (2016) used the GRADE approach to evaluate the quality of the evidence for the outcomes shown in Table App. 43 below. This Cochrane review also included findings for other key outcomes such as postpartum haemorrhage, congenital anomalies, miscarriage and various neurodevelopmental outcomes, but found no significant differences between groups exposed and unexposed to Omega-3 during pregnancy. Overall, this review did not find any evidence of harms in the outcomes specified in the PICO for the current Evidence Review Update, and concluded the following:

> *Omega-3 LCPUFA supplementation during pregnancy is an effective strategy for reducing the incidence of preterm birth, although it probably increases the incidence of post-term pregnancies. (Middleton 2018 p.2)*

6.2.2 St John's wort

No new evidence was identified in the literature search for the current Evidence Review Update. Refer to Appendix 4.2.2 for a summary of harms of St John's wort from the 2017 Australian Guideline.

6.2.3 Ginkgo biloba

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

6.3 Physical

6.3.1 Electroconvulsive therapy

No new primary studies with concurrent controls were identified in the literature search for the current Evidence Review Update. 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.

6.3.2 Transcranial magnetic stimulation

One new primary study was identified in the literature search for the current Evidence Review Update but was not sufficiently powered for evaluation of the benefits or harms of TMS. There is insufficient evidence available to make an Evidence Statement regarding the effect of antenatal or postnatal exposure to TMS on infant harms.

Table App. 43 Summary of Findings: Omega-3 fatty acids (Middleton 2018)

Population	Intervention and Comparator	Outcome	Assumed risk: risk with no omega-3	Corresponding risk: risk with omega-3 (95% CI)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
Pregnancy & birth outcomes							
Pregnant women and their babies	Omega-3 vs. no omega-3	**Perinatal death**	20/1000	15 per 1000 (11 to 21)	RR 0.75 (0.54 to 1.03)	7416 (10 RCTs)	⊕⊕⊕⊖ MODERATE[48]
Pregnant women and their babies	Omega-3 vs. no omega-3	**Preterm birth <37 weeks**	134/1000	119 per 1000 (109 to 130)	**RR 0.89 (0.81 to 0.97)**	10,304 (26 RCTs)	⊕⊕⊕⊕ HIGH[49]
Pregnant women and their babies	Omega-3 vs. no omega-3	**Early preterm birth <34 weeks**	46/1000	27 per 1000 (20 to 35)	**RR 0.58 (0.44 to 0.77)**	5204 (9 RCTs)	⊕⊕⊕⊕ HIGH[50]
Pregnant women and their babies	Omega-3 vs. no omega-3	**SFGA/IUGR**	129/1000	130 per 1000 (116 to 146)	RR 1.01 (0.90 to 1.13)	6907 (8 RCTs)	⊕⊕⊕⊖ MODERATE[51]
Evidence Statement: *Maternal use of omega-3 fatty acids at any time during pregnancy is not associated with an increased risk of perinatal death (moderate certainty evidence); it may reduce risk of perinatal death. Maternal use of omega-3 fatty acids at any time during pregnancy is associated with a decreased risk of preterm birth <37 weeks and early preterm birth <34 weeks (high certainty evidence). Maternal use of omega-3 fatty acids at any time during pregnancy is not associated with an increased risk of SFGA/IUGR (moderate certainty evidence).*							
Neurodevelopmental outcomes							
Children of women randomised to omega-3 or no omega-3 during pregnancy	Omega-3 vs. no omega-3	**Cognition:** BSID II score at < 24 months	The mean BSID II score at 24 months in the intervention group was 0.37 points lower in the intervention group (1.47 lower to 0.76 higher)		MD -0.37 (-1.49 to 0.76)	1154 (4 RCTs)	⊕⊕⊖⊖ LOW[52]
Children of women randomised to omega-3 or no omega-3 during pregnancy	Omega-3 vs. no omega-3	**Cognition**: BSID III score at < 24 months	The mean BSID III score at 24 months in the intervention group was 0.04 points higher (1.59 lower to 1.68 higher)		MD 0.04 (-1.59 to 1.68)	809 (2 RCTs)	⊕⊕⊖⊖ LOW[53]
Children of women randomised to omega-3 or no omega-3 during pregnancy	Omega-3 vs. no omega-3	**IQ**: WASI at 7 years	The mean WASI at 7 years in the intervention group was identical to the mean in the control group (0.79 points lower to 2.79 higher)		MD 1.00 (-0.79 to 2.79)	543 (1 RCTs)	⊕⊕⊖⊖ LOW[53]
Children of women randomised to omega-3 or no omega-3 during pregnancy	Omega-3 vs. no omega-3	**IQ**: WISC-IV at 12 years	The WISC-IV at 12 years in the intervention group was identical to in the control group (5.16 points lower to 7.16 higher)		MD 1.00 (-5.16 to 7.16)	50 (1 RCTs)	⊕⊖⊖⊖ VERY LOW[54]

[48] Imprecision (-1): downgraded one level due to crossing line of no effect and/or wide confidence intervals.
[49] Design limitations: larger studies of high quality, but some smaller studies with unclear risk of selective reporting and some smaller studies with unclear or high attrition bias at the time of birth (not downgraded for study limitations).
[50] Design limitations: larger studies of higher quality, but several studies with unclear or high attrition bias at the time of birth, or baseline imbalances (not downgraded for study limitations).
[51] Imprecision (-1): downgraded one level due to crossing line of no effect and/or wide confidence intervals.
[52] Design limitations (-1): downgraded one level due to unclear randomisation in 3 studies (that contributed 40% to meta-analysis) and some studies at high risk of attrition bias; Imprecision (-1): downgraded one level for wide confidence intervals including line of no effect.
[53] Imprecision (-2): downgraded one level for confidence intervals including line of no effect; and one level for small number of studies/single study.
[54] Design limitations (-1): downgraded one level for unclear selection bias (not clear if random sequence generated), possible attrition and/or reporting bias; Imprecision (-2): downgraded two levels for wide confidence intervals including line of no effect and 1 study with small number of participants.

Population	Intervention and Comparator	Outcome	Assumed risk: risk with no omega-3	Corresponding risk: risk with omega-3 (95% CI)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
Children of women randomised to omega-3 or no omega-3 during pregnancy	Omega-3 vs. no omega-3	**Behaviour**: BSID III adaptive behaviour score at 12-18 months	The mean BSID III adaptive behaviour score in the intervention group at 12-18 months was 1.20 points lower (3.12 lower to 0.72 higher)		MD -1.20 (-3.12 to 0.72)	809 (2 RCTs)	⊕⊕⊖⊖ LOW[55]
Children of women randomised to omega-3 or no omega-3 during pregnancy	Omega-3 vs. no omega-3	**Behaviour**: SDQ Total Difficulties at 7 years	The mean SDQ total difficulties score at 7 years in the intervention group was 1.08 higher (0.18 higher to 1.98 higher)		**MD 1.08 (0.18 to 1.98)**	543 (1 RCTs)	⊕⊕⊖⊖ LOW[53]
Evidence Statement: *Maternal use of omega-3 fatty acids during pregnancy does not appear to be associated with a reduction in child cognition (assessed using BSID II or BSID III score) up to age 24 months (low certainty evidence).* *Maternal use of omega-3 fatty acids during pregnancy does not appear to be associated with a reduction in child IQ (assessed using WASI) at age 7 years (low certainty evidence).* *Maternal use of omega-3 fatty acids during pregnancy does not appear to be associated with a reduction in child IQ (assessed using WISC-IV) at age 12 years (very low certainty evidence).* *Maternal use of omega-3 fatty acids during pregnancy does not appear to be associated with adaptive behaviour in the child (assessed using BSID III) at age 12-18 months (low certainty evidence).* *Maternal use of omega-3 fatty acids during pregnancy may be associated with behavioural difficulties in the child (assessed using SDQ) at age 7 years (low certainty evidence).*							

Source: Middleton 2018, *with the addition of Evidence Statements*.

Abbreviations: BSID, Bayley Scales of Infant Development; CI, confidence interval; IQ, intelligence quotient; MD, mean difference; RCT, randomised controlled trial; RR, relative risk; SFGA/IUGR: small-for-gestational age/intrauterine growth restriction; SDQ, Strengths and Difficulties Questionnaire; WASI, Weschler Abbreviated Scale of Intelligence; WISC, Weschler Intelligence Scale for Children; vs., versus.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** we are very uncertain about the estimate.

[55] Design limitations (-1): downgraded one level for unclear randomisation (possible lack of allocation concealment), possible attrition and/or selective bias in 1 of the trials (contributing 15% to analysis); Imprecision (-1): downgraded one level for confidence intervals including line of no effect and few studies.