**Appendix 1 PRISMA checklist**

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| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | 1 |
| **ABSTRACT**  |  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | 2 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 3 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 3 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | 4 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 4 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 4 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | 4 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | 4 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 5 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | 4 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 5 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 5 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | 5 |

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| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 5 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | 5 |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | 6 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | 6 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | 6-9 |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 9 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 6-9 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 9 |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | 9 |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | 10 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 11-13 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 14 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | 14 |

**Appendix 2 Search term**

PubMed:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Key words | MeSH/ Pharmacological Action term | Terms as a free text | Search terms |
| A | Antipsychotics | Antipsychotic Agents | Agents, AntipsychoticAntipsychoticsMajor TranquilizersTranquilizers, MajorTranquillizing Agents, MajorAgents, Major TranquillizingMajor Tranquillizing AgentsNeuroleptic DrugsDrugs, NeurolepticNeurolepticsTranquilizing Agents, MajorAgents, Major TranquilizingMajor Tranquilizing AgentsAntipsychotic DrugsDrugs, AntipsychoticNeuroleptic AgentsAgents, NeurolepticAntipsychotic EffectEffect, AntipsychoticAntipsychotic EffectsEffects, Antipsychotic | ((((((((((((((((((((((“Antipsychotic Agents”[MeSH]) OR Antipsychotic Agent\*) OR Agents, Antipsychotic) OR Antipsychotics) OR Major Tranquilizers) OR Tranquilizers, Major) OR Tranquillizing Agents, Major) OR Agents, Major Tranquillizing) OR Major Tranquillizing Agents) OR Neuroleptic Drugs) OR Drugs, Neuroleptic) OR Neuroleptics) OR Tranquilizing Agents, Major) OR Agents, Major Tranquilizing) OR Major Tranquilizing Agents) OR Antipsychotic Drugs) OR Drugs, Antipsychotic) OR Neuroleptic Agents) OR Agents, Neuroleptic) OR Antipsychotic Effect) OR Effect, Antipsychotic) OR Antipsychotic Effects) OR Effects, Antipsychotic |
| B | Antipsychotics | Antipsychotic Agents |  | “Antipsychotic Agents”[Pharmacological Action] |
| C | Pregnancy | Pregnancy | Pregnancies Gestation | (((“Pregnancy”[MeSH]) OR Pregnan\*) OR Pregnancies) OR Gestation |
| D | Pregnancy complication | Pregnancy Complications | Complication, PregnancyPregnancy ComplicationComplications, Pregnancy | ((((“Pregnancy complications”[MeSH]) OR Pregnancy complication\*) OR Complication, Pregnancy) OR Pregnancy Complication) OR Complications, Pregnancy |
| E | Gestational Diabetes | Diabetes, gestational  | Diabetes, pregnancy-inducedDiabetes, pregnancy inducedPregnancy-induced diabetesGestational diabetesDiabetes mellitus, gestationalGestational diabetes mellitus | (((((((“Diabetes, gestational” [MeSH]) OR “Diabetes, pregnancy-induced”) OR “diabetes, pregnancy induced”) OR “Pregnancy-induced diabetes”) OR “Gestational diabetes”) OR “Diabetes mellitus, gestational”) OR “Gestational diabetes mellitus”) |

1. A OR B
2. D OR E
3. 1 AND C AND 2

EMBASE:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Key words | Map Term | Terms as a free text | Search terms |
| A | Antipsychotics | Neuroleptic Agent | Agents, AntipsychoticAntipsychoticsMajor TranquilizersTranquilizers, MajorTranquillizing Agents, MajorAgents, Major TranquillizingMajor Tranquillizing AgentsNeuroleptic DrugsDrugs, NeurolepticNeurolepticsTranquilizing Agents, MajorAgents, Major TranquilizingMajor Tranquilizing AgentsAntipsychotic DrugsDrugs, AntipsychoticNeuroleptic AgentsAgents, NeurolepticAntipsychotic EffectEffect, AntipsychoticAntipsychotic EffectsEffects, Antipsychotic | Neuroleptic Agent.mp. or Neuroleptic Agent/ OR (Antipsychotic Agent\* or Agents, Antipsychotic or Antipsychotics or Major Tranquilizers or Tranquilizers, Major or Tranquillizing Agents, Major or Agents, Major Tranquillizing or Major Tranquillizing Agents or Neuroleptic Drugs or Drugs, Neuroleptic or Neuroleptics or Tranquilizing Agents, Major or Agents, Major Tranquilizing or Major Tranquilizing Agents or Antipsychotic Drugs or Drugs, Antipsychotic or Neuroleptic Agents or Agents, Neuroleptic or Antipsychotic Effect or Effect, Antipsychotic or Antipsychotic Effects or Effects, Antipsychotic) |
| B | Pregnancy | Pregnancy | Pregnancies Gestation | Pregnancy.mp. or Pregnancy/ OR (Pregnan\* or Pregnancies or Gestation) |
| C | Pregnancy complication | Pregnancy Complication | Complication, PregnancyPregnancy ComplicationComplications, Pregnancy | Pregnancy complication.mp. or Pregnancy complication/ OR (Pregnancy complication\* or Complication, Pregnancy or Pregnancy Complication or Complications, Pregnancy) |
| D | Gestational Diabetes  | Pregnancy Diabetes Mellitus | Diabetes, pregnancy-inducedDiabetes, pregnancy inducedPregnancy-induced diabetesGestational diabetesDiabetes mellitus, gestationalGestational diabetes mellitus | Pregnancy diabetes mellitus.mp. or Pregnancy diabetes mellitus/ OR (Diabetes, pregnancy-induced OR Diabetes, pregnancy induced OR Pregnancy-induced diabetes OR Gestational diabetes OR Diabetes mellitus, gestational OR Gestational diabetes mellitus) |

1. C OR D
2. A AND B AND 1

Cochrane Library:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Key words | MeSH | Terms as a free text | Search terms |
| A | Antipsychotics | Antipsychotic Agents | Agents, AntipsychoticAntipsychoticsMajor TranquilizersTranquilizers, MajorTranquillizing Agents, MajorAgents, Major TranquillizingMajor Tranquillizing AgentsNeuroleptic DrugsDrugs, NeurolepticNeurolepticsTranquilizing Agents, MajorAgents, Major TranquilizingMajor Tranquilizing AgentsAntipsychotic DrugsDrugs, AntipsychoticNeuroleptic AgentsAgents, NeurolepticAntipsychotic EffectEffect, AntipsychoticAntipsychotic EffectsEffects, Antipsychotic | MeSH descriptor: [Antipsychotic Agents] explode all trees OR (Antipsychotic Agent\* or Agents, Antipsychotic or Antipsychotics or Major Tranquilizers or Tranquilizers, Major or Tranquillizing Agents, Major or Agents, Major Tranquillizing or Major Tranquillizing Agents or Neuroleptic Drugs or Drugs, Neuroleptic or Neuroleptics or Tranquilizing Agents, Major or Agents, Major Tranquilizing or Major Tranquilizing Agents or Antipsychotic Drugs or Drugs, Antipsychotic or Neuroleptic Agents or Agents, Neuroleptic or Antipsychotic Effect or Effect, Antipsychotic or Antipsychotic Effects or Effects, Antipsychotic) |
| B | Pregnancy | Pregnancy | Pregnancies Gestation | MeSH descriptor: [Pregnancy] explode all trees OR (Pregnan\*) OR (Pregnan\* or Pregnancies or Gestation) |
| C | Pregnancy complication | Pregnancy Complications | Complication, PregnancyPregnancy ComplicationComplications, Pregnancy | MeSH descriptor: [Pregnancy Complications] explode all trees OR (Pregnancy complication\* or Complication, Pregnancy or Pregnancy Complication or Complications, Pregnancy) |
| D | Gestational Diabetes | Diabetes, Gestational | Diabetes, pregnancy-inducedDiabetes, pregnancy inducedPregnancy-induced diabetesGestational diabetesDiabetes mellitus, gestationalGestational diabetes mellitus | MeSH descriptor: [Diabetes, Gestational] explode all trees OR ("diabetes, pregnancy-induced" or "diabetes, pregnancy induced" or "pregnancy-induced diabetes" or "gestational diabetes" or "diabetes mellitus, gestational" or "gestational diabetes mellitus") |

1. C OR D
2. A AND B AND 1

PsycINFO

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| --- | --- | --- | --- | --- |
|  | Key words | Map Term | Terms as a free text | Search terms |
| A | Antipsychotics | Neuroleptic Agent | Agents, AntipsychoticAntipsychoticsMajor TranquilizersTranquilizers, MajorTranquillizing Agents, MajorAgents, Major TranquillizingMajor Tranquillizing AgentsNeuroleptic DrugsDrugs, NeurolepticNeurolepticsTranquilizing Agents, MajorAgents, Major TranquilizingMajor Tranquilizing AgentsAntipsychotic DrugsDrugs, AntipsychoticNeuroleptic AgentsAgents, NeurolepticAntipsychotic EffectEffect, AntipsychoticAntipsychotic EffectsEffects, Antipsychotic | Neuroleptic Agent.mp. or Neuroleptic Agent/ OR (Antipsychotic Agent\* or Agents, Antipsychotic or Antipsychotics or Major Tranquilizers or Tranquilizers, Major or Tranquillizing Agents, Major or Agents, Major Tranquillizing or Major Tranquillizing Agents or Neuroleptic Drugs or Drugs, Neuroleptic or Neuroleptics or Tranquilizing Agents, Major or Agents, Major Tranquilizing or Major Tranquilizing Agents or Antipsychotic Drugs or Drugs, Antipsychotic or Neuroleptic Agents or Agents, Neuroleptic or Antipsychotic Effect or Effect, Antipsychotic or Antipsychotic Effects or Effects, Antipsychotic) |
| B | Pregnancy | Pregnancy | Pregnancies Gestation | Pregnancy.mp. or Pregnancy/ OR (Pregnan\* or Pregnancies or Gestation) |
| C | Pregnancy complication | Pregnancy Complication | Complication, PregnancyPregnancy ComplicationComplications, Pregnancy | Pregnancy complication.mp. or Pregnancy complication/ OR (Pregnancy complication\* or Complication, Pregnancy or Pregnancy Complication or Complications, Pregnancy) |
| D | Gestational Diabetes  | Pregnancy Diabetes Mellitus | Diabetes, pregnancy-inducedDiabetes, pregnancy inducedPregnancy-induced diabetesGestational diabetesDiabetes mellitus, gestationalGestational diabetes mellitus | Pregnancy diabetes mellitus.mp. or Pregnancy diabetes mellitus/ OR (Diabetes, pregnancy-induced OR Diabetes, pregnancy induced OR Pregnancy-induced diabetes OR Gestational diabetes OR Diabetes mellitus, gestational OR Gestational diabetes mellitus) |

1. C OR D
2. A AND B AND 1

**Appendix 3 Quality assessment of included articles**

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| **Study** | **Year of publication** | **Selection** | **Comparability** | **Outcome** | **Total** |
| **Representativeness of the exposed cohort** | **Selection of the unexposed cohort** | **Ascertainment of exposure** | **Demonstration that outcome of interest was not present at start of study** | **study controls for mother age, smoking, alcohol consumption** | **study controls for any additional factor**  | **Assessment of outcome**  | **Was follow-up long enough for outcomes to occur** | **Adequacy of follow up of cohorts** |
| McKenna et al. | 2005 | 1 | 1 | 1 | 1  | 0 | 0 | 1 | 1 | 0 | 6 |
| Reis and Kallen | 2008 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 8 |
| Boden et al.  | 2012 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 8 |
| Sadowski et al. | 2013 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 6 |
| Bellet et al. | 2015 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 6 |
| Vigod et al. | 2015 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 8 |
| Petersen et al. | 2016 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Frayne et al.  | 2017 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 7 |
| Panchaud et al. | 2017 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 8 |
| Park et al. | 2018 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 8 |

**Appendix 4 Summary of the included studies results**

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| --- | --- | --- | --- | --- |
| **Study** | **Results** | **Adjusted confounding factors** | **Adjustment method** | **Adjusted Results** |
| **McKenna et al. (2005)** | non-teratogenic agent: 6/93; Atypical Antipsychotic: 6/78 | N/A | N/A | N/A |
| **Reis and Kallen (2008)** | N/A | maternal (year of delivery, maternal age, parity, maternal smoking in early pregnancy, previous miscarriages, subfertility, maternal BMI, maternal cohabitation, work outside home, maternal country of birth) | Mantel Haenszel method and Miettinen's method  | dixyrazine or prochlorperazine: OR 1.37, 95% CI 0.94-2.01; other antipsychotics: OR 1.78, 95% CI 1.04-3.01 |
| **Boden et al. (2012)** | clozapine/olanzapine: OR 2.44, 95% CI 1.14-4.24; other antipsychotics: OR 2.53, 95% CI 1.48-4.34 | maternal country of origin, smoking, height, cohabitation status at the first antenatal visit, maternal age when giving birth, birth order of the infant. | Multivariate regression; 'women who had taken any other type of antipsychotics' as an active control group | clozapine/olanzapine: OR 1.71, 95% CI 0.82-3.56; other antipsychotics: OR 1.46, 95% CI 0.84-2.53 |
| **Sadowski et al. (2013)** | healthy comparison group: 5/133; exposed group: 11/133 | N/A | N/A | N/A |
| **Bellet et al. (2015)** | OR 1.15, 95% CI 0.33-4.04 | N/A | N/A | N/A |
| **Vigod et al. (2015)** | RR 1.15, 95% CI 0.82-1.61 | adjusting for additionally prescribed non-antipsychotic psychotropic medications (a prescribed selective serotonin reuptake inhibitor (SSRI), non-SSRI, mood stabiliser, or benzodiazepine during the index pregnancy) | PS method; regression model | RR 1.10, 95% CI 0.77-1.57 |
| **Petersen et al. (2016)** | RR 1.61, 95% CI 0.89-2.91 | age at delivery, calendar year of delivery, obesity, illicit drug use, alcohol problem, smoking status, pre-existing medical conditions (depression, epilepsy, psychosis, hypertension, diabetes), prescriptions of concomitant medication listed in the BNF chapter 4 including antidepressants, anxiolytics, hypnotics, anticonvulsant mood stabiliser and lithium. | PS method; 'discontinuers' as a control group | RR 0.95, 95% CI 0.53-1.69 |
| **Frayne et al. (2017)** | no medication: 4/67; antipsychotic medication: 13/87 | N/A | N/A | N/A |
| **Panchaud et al. (2017)** | OR 1.02, 95% CI 0.54-1.91 | maternal age, marital status, race, employment status, level of education, smoking, primary psychiatric diagnosis, BMI | PS method; regression model; 'pregnant women not exposed to SGAs but with a psychiatric condition' as a control group | OR 0.79, 95% CI 0.40-1.56 |
| **Park et al. (2018)** | aripiprazole: RR 1.06, 95% CI 0.65-1.72; ziprasidone: RR 1.12, 95% CI 0.48-2.61; quetiapine: RR 1.75, 95% CI 1.36-2.24; risperidone: RR 1.56, 95% CI 0.98-2.49; olanzapine: RR 2.55, 95% CI 1.44-2.04 | demographic data (age, race, and medicaid eligibility type), psychiatric diagnoses (anxiety disorders, attention deficit hyperactivity disorder, bipolar disorder, depression, schizophrenia or other psychoses, and other psychiatric disorders), comorbidity (pain disorders, hypertension, obesity, and dyslopidemia), other medication use (anticonvulsants, antidepressants, anxiolytics, benzodiazepines, mood stabilizers other than antipsychotics, opioids, other hypnotics, stimulants, and antihypertensives), history of gestational diabetes, and the duration of antipsychotic treatment received during the 3 months before the last menstrual period | PS method; regression model; 'discontinuers' as a control group | aripiprazole: RR 0.82, 95% CI 0.50-1.33; ziprasidone: RR 0.76, 95% CI 0.29-2.00; quetiapine: RR 1.28, 95% CI 1.01-1.62; risperidone: RR 1.09, 95% CI 0.70-1.70; olanzapine: RR 1.61, 95% CI 1.13-2.29 |

N/A: not applicable, OR: odds ratio; RR: risk ratio; 95 % CI: 95% confidence interval; PS method: Propensity score method