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SYSTEMATIC REVIEW AND META-ANALYSIS

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Prenatal exposure to antipsychotic agents and the risk of congenital malformations in children: A systematic review and meta-analysis

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Objective: To evaluate the association between antipsychotic use in pregnancy and the risk of congenital malformations in children.

Data sources: Searches of PubMed, EMBASE, PsycINFO and Cochrane Library were conducted from inception to 06 January 2020 using keywords: *antipsychotics*, *pregnancy*, *pregnancy complication* and *congenital abnormalities*.

Study selection: Of 38 reports initially identified as being of potential interest, 13 studies met our inclusion criteria: English observational studies that examined the association between gestational antipsychotic use and congenital malformations in children.

Data extraction: Data were extracted independently by 2 investigators including the publication year, study site, study period, data source, study design, sample size, medication exposure, exposure period and pregnancy definition, exposure as well as outcome ascertainment, selection of study and comparison group, confounding adjustment, statistical analysis, and method of linkage between mother and children. Risk estimates were pooled using a random-effect model and the I^2 statistic was used to evaluate the degree of heterogeneity.

Results: Thirteen studies met our systematic review inclusion criteria. Six studies with a total of 2 515 272 pregnancy episodes were included in our meta-analysis, which provided a pooled adjusted risk ratio of 1.23, 95% confidence interval: 0.96–1.58. The I^2 result showed moderate heterogeneity between studies (I^2 = 35.2%, P = .173).

Conclusion: We did not find strong evidence of an association between prenatal exposure to antipsychotic medications and the risk of congenital malformations in children. We recommend further studies investigate this association, focusing on

Abbreviations: aRR, adjusted risk ratio; **CI**, confidence interval; **FGA**, first-generation antipsychotic; **NOS**, Newcastle–Ottawa Scale; **OR**, odds ratio; **PS**, propensity score; **RR**, risk ratio; **SGA**, second-generation antipsychotic.

specific medication classes and dose responses, which would help clinicians decide whether to prescribe certain antipsychotics during pregnancy.

KEYWORDS
antipsychotics, congenital malformation, pregnancy

1 | INTRODUCTION

Antipsychotics are commonly used as first-line treatment for mental disorders such as schizophrenia and bipolar disorders.[1,2] Pregnancy can lead to physiological, hormonal and psychological variations[3,4] that may increase the risk of psychiatric disorders.[5] Moreover, treatment with antipsychotics during pregnancy can be necessary for women with pre-existing severe mental illness to reduce symptoms and to prevent relapse.[6] Discontinuation of treatment may not only increase maternal anxiety levels but also affect foetoplacental integrity and central nervous system development in offsprings.[7] Pharmacologically, antipsychotics can cross the placenta, thereby causing an unintended impact on neonatal development.[8] Clinicians should consider both the benefits and potential risks of gestational antipsychotics use, as well as any potential risks associated with discontinuation of on-going antipsychotic treatment. An increasing trend of antipsychotic use, in particular atypical antipsychotics, in pregnancies has been observed in the last 3 decades.[9–11] It is therefore important to investigate the safety of these medications.

Congenital malformations include single or multiple defects of the morphogenesis of organs or other body parts identifiable at birth or during the intrauterine life.[12] Malformation in the offspring can lead to long-term disability, illness and death.[13] The global prevalence of congenital malformations is around 2–3% and the most common severe congenital malformations are heart defects and neural tube defects. In addition to genetic and socioeconomic factors that may increase the risk of having a foetus affected by congenital malformations, other potential causes include maternal exposure to alcohol, tobacco, radiation and medications.[13,14]

The most recent systematic review and meta-analysis was published in 2015 and included articles published before 2013 with 1 640 357 pregnancy episodes.[15] Of the 7 studies included, 2 were literature reviews.[15] Coughlin *et al.* concluded that there was an increased risk of congenital malformations, based on crude results without confounding adjustments (odds ratio [OR]: 2.12, 95% confidence interval [CI]: 1.25–3.57) and thus the validity of the finding is questionable.[15] Since 2013, new research has been published, including observational studies using electronic healthcare databases or registries with advanced epidemiological methodologies.[16–20] We conducted this systematic review and meta-analysis including all literature published until January 2020 to provide a more precise risk estimate between the use of antipsychotic agents in pregnancy and congenital malformations in children.

2 | METHODS

2.1 | Search strategy and selection criteria

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, a systematic literature search was conducted in PubMed, EMBASE, PsycINFO and Cochrane Library databases from the inception to 6 January 2020 to search for all observational studies that investigated congenital malformations after antipsychotic exposure during pregnancy. The complete list of search terms is presented in Appendix A. Study protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42018095014).

Studies were included if they were observational studies (either a cohort or case–control design) reported the association between gestational antipsychotic use and congenital malformations in children. We excluded animal studies, case reports, conference abstracts, book chapters, reviews, and summaries or articles written in languages other than English.

Two investigators (Z.W. and B.A.) independently conducted screening for all articles returned from the literature search to identify studies that fulfilled our inclusion criteria with discrepancies resolved through discussion or, if necessary, with adjudication by a third researcher (P.M.). Two authors (Z.W. and P.M.) independently extracted relevant information from the included studies to the data collection form to ensure consistency and accuracy. The data collection form contains information on study publication year, study site, study period, data source (categorised with reference to previous methodological study[21]), study design, sample size, medication exposure, exposure period and pregnancy definition, exposure identification, selection of study and comparison group, confounding adjustment, outcome assessment, statistical analysis, and method of linkage between mother and children. Risk estimates such as risk ratio (RR), OR and the corresponding 95% CIs were extracted and included in the meta-analysis. If the relevant estimates were not directly available in the included studies but sufficient information was reported, we calculated the corresponding risk estimates accordingly.

2.2 | Quality assessment and data analysis

Two investigators (Z.W. and P.M.) independently assessed the quality of studies using the Newcastle–Ottawa Scale (NOS).[22] Selection (representativeness), comparability (controls or adjustment for confounding factors) and outcome (assessment and follow-up) are the

domains of the assessment. NOS rating score ranges from 0 to 9, a higher score indicating better quality. Studies with good quality, i.e. at least 1 score in each domain and a 5 or above score in total, were included in the meta-analysis.

Risk estimates with the corresponding 95% CI were pooled in the meta-analysis with a random-effect model[23] with further subgroup analyses based on the included studies reported outcomes with different generations of antipsychotics. Higgins' I^2 statistics was used to assess the heterogeneity with larger values indicate higher heterogeneity.[24] Cochran's Q test with 2-sided *P*-value less than the 0.1 cut-off was considered statistically significant for heterogeneity.[24] $P < .05$ was used for all other analyses. Study with the largest sample size was included in the meta-analysis if articles used the same data source or population. Additionally, we conducted sensitivity analyses: (i) we calculated E-values for each study using an online calculator to evaluate the impact of unmeasured confounding factors, while the E-value is defined as "the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome, conditional on the measured covariates, to fully explain a specific treatment–outcome association".[25–27] A large E-value indicates that considerable unmeasured confounding would be necessary to explain an effect estimate.[26,27] (ii) We conducted subgroup analysis according to the time of exposure during pregnancy. All meta-analyses were conducted using STATA 15.

2.3 | Role of the funding source

There was no funding source for this study. All authors had full access to the study data and the corresponding author had final responsibility for the decision to submit the report for publication.

3 | RESULTS

We identified 2210 records for screening after removing duplicates on 6 January 2020. Out of 38 full-text studies assessed for eligibility, 13 studies met our inclusion criteria for the systematic review, involving 2 612 385 pregnancy episodes. Figure 1 shows the search and selection process.

Tables 1 and 2 summarise the characteristics of the included studies. All studies were published in English: 8 prospective cohort studies,[16,18,28–32] 4 retrospective cohort studies[17,19,20,33] and 1 case–control study.[34]

Four studies assessed any antipsychotic exposure in mothers,[17,19,20,33] while 3 studies focused on first-generation antipsychotics (FGAs)[28,31,32] and 6 studies focused on any second-generation antipsychotics (SGAs).[16,18,28–30,34] However, only Habermann *et al.*[29] provided detailed descriptions as to whether the SGA-exposed group was administered concomitant medications alongside FGAs. It is therefore impossible to ascertain whether the effect is due to SGAs or

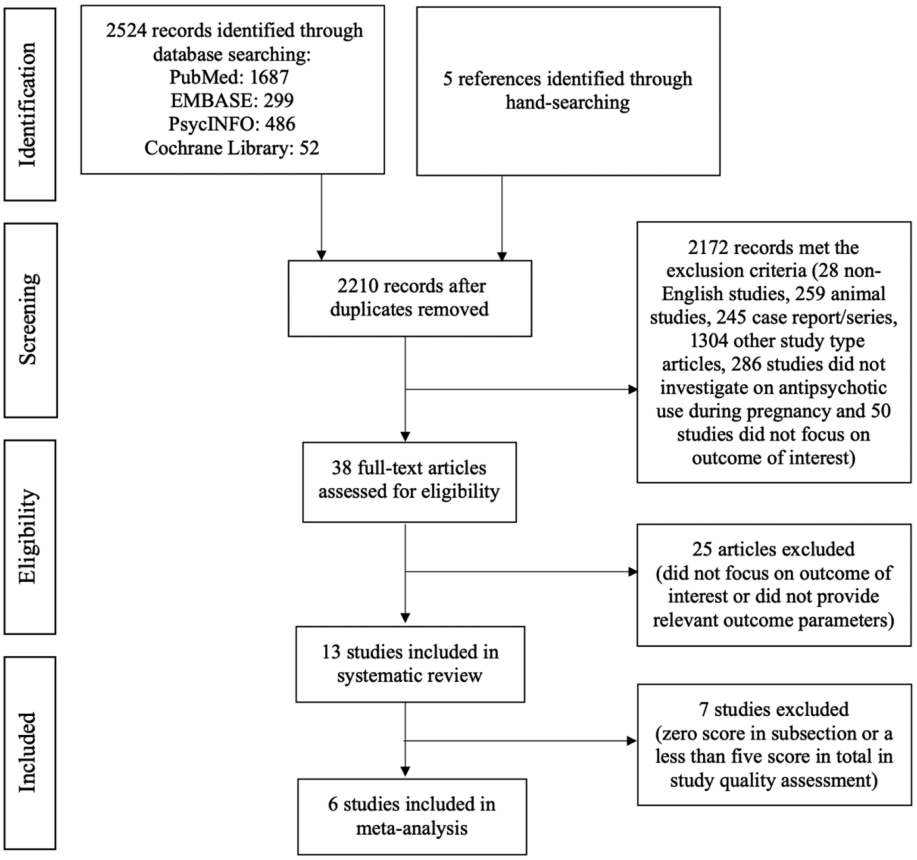

FIGURE 1 Study selection

TABLE 1 Summary of included studies (A)

Study	Study period	Country	Data source	Study design	Sample size[a]	Mother–baby linkage	Confounding adjustment
Rumeau-Rouquette *et al.*[31]	1963–1969	France	12 university hospitals Ad hoc clinical sample	Prospective, cohort	315 exposed, 11 099 unexposed	No data available	No adjustment
Slone *et al.*[32]	1959–1965	USA	Collaborative perinatal project, 12 hospitals Ad hoc clinical sample	Prospective, cohort	1309 exposed, 48 973 unexposed	No data available	No adjustment
Diav-Citrin *et al.*[35]	1989–2001	Israel, Germany, the Netherlands and Italy	ENTIS including 4 TISs Ad hoc disease registry	Prospective, cohort	179 exposed, 581 unexposed	No data available	No adjustment
McKenna *et al.*[28]	No data avaliable	Canada, Israel, UK	The Motherisk Program at the Hospital for Sick Children in Toronto; Israeli TIS; the drug safety research unit in Southampton Ad hoc disease registry	Prospective, cohort	151 exposed, 151 unexposed	No data available	No adjustment
Kallen[33]	1994–2005	Sweden	Swedish medical birth register and the register of congenital malformations and the hospital discharge register Administrative database/registry	Retrospective, cohort	958 729[b]	Yes, personal identification number	Yes
Habermann *et al.*[29]	1997–2009	Germany	TIS Ad hoc disease registry	Prospective, cohort	430 exposed, 1014 unexposed	Yes, interview	Yes
Sadowski *et al.*[30] (2013)	2005–2009	Canada	Motherisk Program at the Hospital for Sick Children in Toronto Ad hoc disease registry	Prospective, cohort	133 exposed, 133 unexposed	Yes, self-reported	No adjustment
Bellet *et al.*[16]	2004–2011	France	TIS Ad hoc disease registry	Prospective, cohort	71 exposed, 161 unexposed	Yes, interview	No adjustment
Vigod *et al.*[17]	2003–2012	Canada	Health administrative databases at ICES in Toronto Administrative database/registry	Retrospective, cohort	50 exposed, 1589 unexposed	98% yes, data records	Yes
Cohen *et al.*[18]	2008–2014	USA	Massachusetts general hospital Centre for Women's mental health and the Centre's website Ad hoc disease registry	Prospective, cohort	214 exposed, 89 unexposed	Yes, interview	Yes

TABLE 1 (Continued)

Study	Study period	Country	Data source	Study design	Sample size[a]	Mother–baby linkage	Confounding adjustment
Huybrechts *et al.*[19]	2000–2010	USA	Nationwide Medicaid analytic extract database Administrative database/registry	Retrospective, cohort	9991 exposed, 1 331 910 unexposed	Yes, state, Medicaid case number (family identifier) and delivery/birth dates	Yes
Petersen *et al.*[20]	1995–2012	UK	THIN and CPRD Administrative database/registry	Retrospective, cohort	290 exposed, 210 996 unexposed	Yes, household identifier and same general practice	Yes
Anderson *et al.*[34]	1997–2011	USA	NBDPS Ad hoc disease registry	Retrospective, case control	22 387 cases, 11 470 controls	Yes, interview	No adjustment

ENTIS: The European Network of Teratology Information Services; TIS: Teratology information service; ICES: Institute for Clinical Evaluative Sciences; THIN: The Health Improvement Network; CPRD: Clinical Practice Research Datalink; NBDPS: National Birth Defects Prevention Study.

[a]Sample size represents the number of pregnancy episodes.

[b]Details are not available.

the comedications i.e. other antipsychotic agents in any of the included studies, except the Habermann *et al.*[29] study.

Six studies[16,19,20,30,33,35] reported the daily dose of antipsychotics or dose effect but only Huybrechts *et al.*[19] evaluated the effect using dose–response analysis and reported no evidence of a dose–response association for any of the individual antipsychotics except for risperidone. Dosage of risperidone of at least 2 mg/d was associated with an increased risk of cardiac malformation (RR: 2.08, 95% CI: 1.32–3.28).

Six included studies used at least 1 approach to deal with confounders,[17–20,29,33] such as multivariable adjustments in regression model, restriction in control group selection or using a propensity score (PS) method. Except for simply comparing the outcome estimate between exposure and nonexposure, 2 studies applied additional control groups in order to control for confounding by indication: Petersen *et al.*[20] used *discontinuers* (women who had taken medications before pregnancy but had no dispensed record for an antipsychotic medication during pregnancy) as a negative control group (which indicated that the risk of congenital malformations was associated with potential maternal psychiatric disorders rather than exposure to antipsychotics in pregnancy); while Habermann *et al.*[29] chose women who took other types of antipsychotics (e.g. less anabolic or other generation antipsychotics) as an active control group.

The outcomes in included studies were assessed through either database records, physician reports, or by a structured questionnaire or interview. Four out of 13 studies did not provide details of those lost to follow-up.[16,28,31,32] Nine out of 13 studies referred to the linkage method between mother and children.[16–20,29,30,33,34]

Six studies were deemed to be of good quality according to NOS assessment and were included in the meta-analysis[17–20,29,33] (Appendix B and C). Others were excluded due to their poor quality, with a score of zero in the NOS comparability assessment section. All included studies in the meta-analysis were considered to have a low risk of bias. As there were <10 studies included in the meta-analysis, we did not examine the publication bias for included studies.[36]

Appendix D summarise the individual study results. Overall, there was no statistically significant association between the risk of congenital malformations and prenatal exposure to any antipsychotics (adjusted RR [aRR]: 1.23, 95% CI: 0.96–1.58, I^2 = 35.1%, P = .173; Figure 2)[17–20,29,33] as well as SGAs subgroup (aRR: 1.35, 95% CI: 0.73–2.47, I^2 = 65.4%, P = .056; Figure 3).[18,19,29]

We conducted a sensitivity analysis according to the timing of exposure during pregnancy. Four studies limited an exposure time to the first or second trimester rather than anytime during pregnancy with an aRR of 1.05 (95% CI: 0.96–1.15)[17,19,20,33] (Appendix E). No observed heterogeneity was found (I^2 = 0.0%, P = .581).

4 | DISCUSSION

Overall, this systematic review and meta-analysis suggests that there is no strong evidence to demonstrate an association between prenatal exposure to any antipsychotics or, in particular SGAs, and

TABLE 2 Summary of included studies (B)

Study	Medication exposure	Exposure period	Exposure identification	Selection of study group	Selection of comparison group	Outcome assessment	Type or definition of malformation
Rumeau-Rouquette *et al.*[31]	FGAs	The first 3 mo of pregnancy after the last menstrual period	Interview using standardised questionnaire by a physician	Women who came to these hospitals for examination during the first 3 mo of their pregnancy and who delivered in these hospitals	Women without exposure to phenothiazines by interview	Infants were examined during the first 5 d of life by paediatricians	An abnormality of appearance or function evident at birth, or within the first 4 wk of life
Slone *et al.*[32]	FGAs	The first 4 lunar mo of pregnancy	Data on drug use were recorded at each antenatal visit and confirmed, with few exceptions, by the attending physician or by review of the hospital or clinic record	Women with antenatal exposure to phenothiazines, no details	Women without antenatal exposure to phenothiazines, no details	No data available	Uniform malformations including major, central nervous, cardiovascular, musculoskeletal, respiratory, gastrointestinal, hypospadias, other genitourinary, eye and ear, syndromes, tumours; nonuniform malformations including inguinal hernia and clubfoot.
Diav-Citrin *et al.*[35]	FGAs	Pregnancy, no detailed description for pregnancy definition	Structured questionnaire	Butyrophenone-exposed pregnant women in the registries	Women who had been counselled during pregnancy in regard to exposures known to be nonteratogenic from the 4 TISs	Telephone interview and/or mailed questionnaire	Severe bullous emphysema, lung hypoplasia; absent left 4th finger, common wrist of left first and second fingers; cystic hygromas; upper limb reduction defect and foot deformity; carbamazepine syndrome, developmental delay, congenital heart defect; ventricular septal defect, genu varum

TABLE 2 (Continued)

Study	Medication exposure	Exposure period	Exposure identification	Selection of study group	Selection of comparison group	Outcome assessment	Type or definition of malformation
McKenna *et al.*[28]	SGAs	Within 3 mo of pregnancy or during pregnancy, no detailed description for pregnancy definition	Questionnaire	SGAs within 3 mo of pregnancy or during pregnancy, no detailed descriptions for whether comedication with FGAs	Women without psychiatric diagnosis/medication, matched for maternal age ± 2 y, with nonteratogenic exposures including cold medications, hair dyes, antibiotics, paracetamol, antacids, antihistamines, etc.	Telephone contact and physician report	No detailed definition
Reis and Kallen[33]	FGAs +SGAs	Early pregnancy (usually before the end of the first trimester), no detailed description for pregnancy definition	Recorded from interviews performed by the midwife at the first antenatal care visit	Women who had reported the use in early pregnancy of antipsychotics	All other pregnancy women in register	National health registers	Congenital malformation including major and mild. Major congenital malformation such as ectopic anus, hand/finger reduction, spina bifida, ventricular septum defect
Habermann *et al.* [29]	SGAs	Any time between conception (defined as 2 wk of gestation) and delivery	Structured questionnaires at the first contact	Women exposed to at least 1 SGA during pregnancy, comedication with FGAs was allowed	Women exposed to FGAs, teratogenic, fetotoxic, or insufficiently studied agents were excluded in comparison cohort, a random sample of all available cases from comparison cohort was matched for a 2:1 ratio	Structured questionnaires at 8 wk after the estimated date of birth	Major birth defects were defined as structural abnormalities of medical, surgical, and/or cosmetic relevance. Major malformations in different organ systems were reported
Sadowski *et al.*[30] (2013)	SGAs	A minimum of 4 wk during pregnancy, no detailed description for pregnancy definition	Self-report	Women who confirmed the use of SGAs for a minimum of 4 wk of pregnancy, no detailed descriptions for whether comedication with FGAs	Women who reported exposure to nonteratogenic agents	Telephone follow-up interview, cross-referenced by physicians	No detailed definition

(Continues)

TABLE 2 (Continued)

Study	Medication exposure	Exposure period	Exposure identification	Selection of study group	Selection of comparison group	Outcome assessment	Type or definition of malformation
Bellet *et al.*[16]	SGAs	During embryogenesis (gestational wk, i.e. wk after the last menstrual period)	Standardised questionnaires at initial telephone contact	Women exposed to aripiprazole during embryogenesis, coexposed to known teratogens during embryogenesis were excluded, no detailed descriptions for whether comedication with FGAs or other SGAs	Women without exposure or exposed to agents known to be nonteratogenic; excluded if coexposed to known teratogens as well	Structured questionnaires after birth	According to the European surveillance of congenital anomalies (EUROCAT) guide
Vigod *et al.*[17]	FGAs +SGAs	Prior to 27 wk gestation, corresponding to the first or second trimester of pregnancy	Prescriptions filled record	At least 2 consecutive antipsychotic drugs filled between the conception date and the delivery date	Nonusers were 1:1 matched by means of an HDPS algorithm	Database	According to ICD-10-CA codes
Cohen *et al.*[18]	SGAs	Pregnancy, no detailed description for pregnancy definition	Interview	Women who used 1 or more SGAs during first trimester, no detailed descriptions for whether comedication with FGAs	Women with a history of psychiatric illness being treated with a variety of psychotropic medications other than SGAs	Postpartum interview	Abstracted from medical records. A major malformation is defined as a structural abnormality with surgical, medical, or cosmetic importance
Huybrechts *et al.*[19]	FGAs +SGAs	During the first 90 d of pregnancy (first trimester), pregnancy period was calculated by last menstrual period to delivery date	Prescriptions filled record	At least 1 prescription during the first 90 d of pregnancy	Women who did not fill an antipsychotic prescription during the 3 mo before the start of pregnancy or during the first trimester	Database	ICD-9 in the maternal (1st mo after delivery) or infant (first 3 mo after date of birth), 13 specific malformations: CNS, ear, eye, cardiovascular, other vascular, respiratory, oral cleft, gastrointestinal tract, genital, urinary, musculoskeletal, limb, other

TABLE 2 (Continued)

Study	Medication exposure	Exposure period	Exposure identification	Selection of study group	Selection of comparison group	Outcome assessment	Type or definition of malformation
Petersen *et al.*[20]	FGAs +SGAs	Between 31 and 105 d (inclusive) after the start of pregnancy (the 1st d of last menstrual period or 280 d before delivery if no records suggested a different duration of pregnancy)	Prescriptions filled record	Women exposed to antipsychotics in pregnancy	Women not exposed to antipsychotics	Database	According to read codes, including ventricular septal defect, hypospadias, cleft palate, duplex kidneys
Anderson *et al.*[34]	SGAs	From the mo before pregnancy to the 3rd mo of pregnancy (early pregnancy)	Maternal report via interview	Infants with birth defects medical records	Liveborn infants without major birth defects	Registry	Any heart defect including Conotruncal defects, tetralogy of Fallot, LVOTO, RVOTO, septal defects, atrial septal defect. Any orofacial cleft including cleft palate, cleft lip ± cleft palate, anorectal atresia/stenosis, hypospadias, 2/3rd degree, craniosynostosis, gastroschisis

FGAs: first-generation antipsychotics; SGAs: second-generation antipsychotics; TIS: Teratology Information Service; HDPS: High dimensional propensity score; ICD-9: International Classification of Diseases, Ninth Revision; ICD-10-CA: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada; CNS: central nervous system; LVOTO: left ventricular outflow tract obstruction; RVOTO: right ventricular outflow tract obstruction.

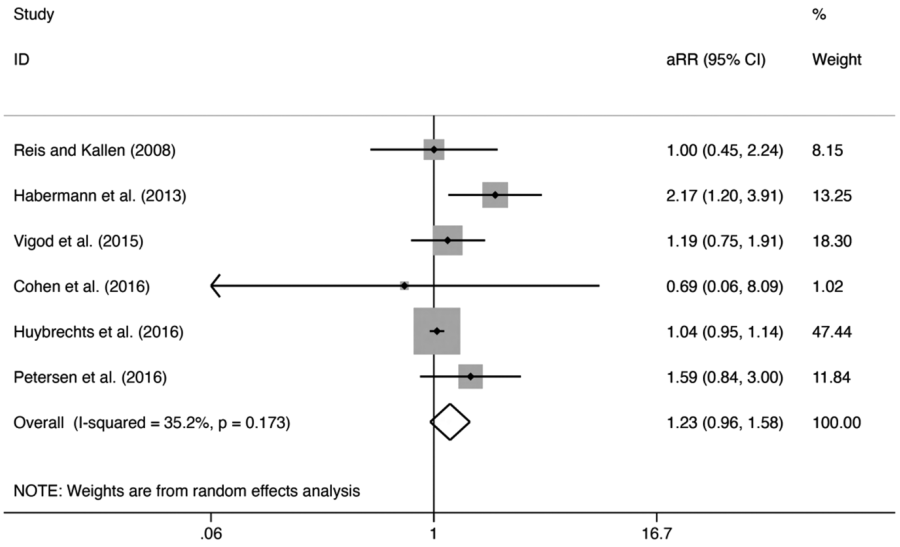

FIGURE 2 Forest plot of the meta-analysis for congenital malformation. aRR: adjusted risk ratio; CI: confidence interval

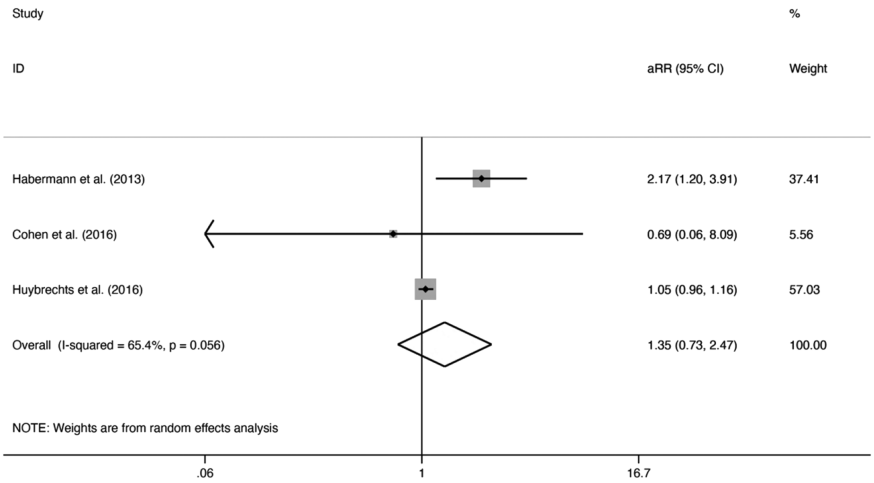

FIGURE 3 Forest plot of the meta-analysis for congenital malformation (second-generation antipsychotic subgroup). aRR: adjusted risk ratio; CI: confidence interval

congenital malformations in children. Also, there is no evidence to supported an association between exposure to antipsychotics within the first or second trimester and congenital malformations in children. As we focused solely on overall congenital malformations, we cannot report on the risk of individual malformation types. Our result differs to the findings of a previous systematic review study,[15] which be due to the fact that Coughlin *et al.*[15] used crude results rather than adjusted estimates which could have affected the validity of the pooled estimates. Also, we included current studies with larger sample sizes in our meta-analysis and we suggest that, if there is an increased risk, the effect size is probably smaller than that reported previously.

We estimated an E-value of 3.76 for Habermann *et al.*[29], which implies their results are unlikely to be affected by unmeasured confounding factors, unless there are unadjusted factors with a magnitude as strong as 3.76 (Appendix F).

Three of 6 meta-analyses studies reported outcomes following SGAs exposure,[18,19,29] while only 1 focused on FGAs[19] which may be partly explained by the changing trend of antipsychotic use in pregnancy (SGA use increased over time).[11] Although our systematic review did not include sufficient studies to conduct a meta-analysis for the FGA subgroup, the only study that compared SGAs to FGAs exposure after the first trimester reported no significant differences for the rate of major malformations.[29]

In this systematic review, there were some methodological challenges.

Firstly, although it would be ideal to investigate the adverse outcomes in FGAs and SGAs respectively, even to examine the risks of specific antipsychotics individually, it is still a practical challenge due to the limited number of patients who are exposed. Additionally, use of concomitant medications, such as lithium and valproate, may be a potential confounder. It is noted that subgroup analysis conclusion was based on studies reporting outcomes following SGAs exposure rather than mutually exclusive SGAs users. It is not able to conduct FGAs subgroup analysis due to insufficient studies. Further studies may consider using mutually exclusive comparison cohorts (i.e. exclusively FGAs and exclusively SGAs subgroups) to address this by having multicentre databases with larger sample sizes.

Moreover, although an administrative database/registry is normally considered as a good first choice for a representative study sample,[21] misclassification is still a significant limitation. An accurate exposure assessment is important to minimize bias, studies should select women with continuous usage of antipsychotics for a period or at least 2 prescriptions like Sadowski *et al.*[30] and Vigod *et al.*[17] to minimize any exposure misclassifications. Measurement of medication concentration in maternal blood could potentially be an ideal method to validate exposure status, although it is not available in most data sources.[21] Additionally, some administrative databases/registries, such as The Health Improvement Network database, do not contain prescriptions from specialists, which may cause underestimation of exposure duration or overall exposure episodes.[20] Furthermore, poor antipsychotic adherence among patients with schizophrenia is common,[37,38] and we cannot confirm whether the patient collected or took prescribed medication in database studies, which may influence the accuracy of actual medicine records.

Exposed time in different gestation periods may lead to distinct results relevant to the pathogenesis, e.g. the critical period for neural tube development is 17–30 days of gestation.[21] Petersen *et al.*[20] limited the study period for occurrence of the outcome of interest to 31–105 days after the start of pregnancy, and only 6 out of 13 included studies[17,19,31–34] specified the exposure period to early pregnancy rather than general pregnancy. Further studies should stratify specifically for different trimesters.

Observational studies are the only practical study designs to investigate the association between antenatal medication exposure and foetal risk, mainly due to the ethical implications of conducting a clinical trial.[21] Confounding bias, 1 of the main types of bias in observational studies, can influence the validity of obtained estimates. Among the included studies, multivariable adjustments were still the most common method to manage potential confounders (5 out of 6).[18–20,29,33] Maternal age, smoking and alcohol consumption are considered the most relevant factors that can influence pregnancy complications and birth outcomes.[39–41] However, in our meta-analysis, only 3 studies considered all 3 of these factors as covariates.[19,20,29] Habermann *et al.* adjusted for alcohol consumption in the final model.[29] Three studies applied PS methods to address the effect of confounding,[17–19] whereas only 1 study used negative control analysis, which can address alternative factors rather than the exposure factor being studied.[20] No study used sibling-matched analysis, which could address confounding factors such as genetic and socioeconomic status as well as family disease history.[21] It is also noted that, although there is no way to address confounding by indication, its effect could be minimized by selecting an active comparator control group e.g. antidepressants. It is essential to address confounding factors in a comprehensive manner in future studies in order to minimize the potential for bias.

We found that studies rarely stated precisely which malformation outcomes were included[19,20,28,29,32–34] and this needs to be improved. Good examples are Petersen *et al.*[20], Reis and Kallen,[33] and Anderson *et al.*[34] which provided a list of congenital malformations included; by contrast, only Huybrechts *et al.*[19] presented the risk for a specific malformation (cardiac malformation with no evidence of an association). It is vital for future studies to identify the effect on specific malformations as specific patterns of malformation can potentially reveal the mechanism of teratogenicity, such as sodium valproate and neural defects.[42] It is noted that the reviewed studies included only live births and therefore early terminations (either selective or spontaneous abortions/miscarriages) are not included, which may underestimate the rate of malformation. Additionally, this study did not include other adverse obstetric and offspring outcomes (such as gestational hypertension, pre-eclampsia, preterm delivery, small or large for gestational age) in the benefit–risk consideration.

The potential consequences of untreated psychotic episodes may be severe and lead to a higher risk of relapse or exacerbation of symptoms, antipsychotics should be continued prescribing during pregnancy if there is a clinical need.[3] For pregnant women with schizophrenia and/or related disorders, it is necessary to weigh the risk and benefit of potential adverse outcomes of antenatal exposure to medications against the potential risk of untreated illness. Also, we would not advise clinicians to switch treatment from SGAs to FGAs or FGAs to SGAs in the absence of an increased risk associated with the use of different drug classes.

We have included all relevant literature on the risk of congenital malformations in children with prenatal antipsychotic use in this systematic review and meta-analysis. Reviewer selection bias was minimised by using a comprehensive search strategy, independent text screening and data extraction. All included studies in our meta-analyses were conducted with administrative databases/registries or ad hoc disease registries which provided a relatively large sample size and good generalisability in the corresponding population.[21] All studies were based in western countries, and we cannot determine if the effect is similar in different ethnic populations (e.g. Asian). Methodological differences in study designs, the selection of the exposure and control groups, duration of follow-up, and exposure and outcome definitions, may all have influenced the risk estimates. We observed moderate heterogeneity (I^2 = 35.2%) in overall adjusted pooled estimates. This could represent the consistency of the findings but it may also be due to the small number of included studies.[43] Future studies should be conducted using an appropriate exposure period, adequate follow-up time, a larger sample size and address potential covariates with a more comprehensive approach, such as using the PS method and sibling-matched analysis. Studies focusing on individual agents, dose response and specific congenital malformations are also recommended in the future.

5 | CONCLUSIONS

This systematic review and meta-analysis suggests that there is no strong evidence of an association between women exposed to antipsychotic agents during pregnancy and overall congenital malformations in children. Future studies are recommended that should focus on typical or atypical antipsychotics, dose response and specific congenital malformations using a large sample size

with a comprehensive study design in order to help clinicians to decide whether to continue antipsychotic prescriptions during pregnancy.

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COMPETING INTERESTS

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CONTRIBUTORS

Z.W., I.C.K.W., K.K.C.M. and R.B. designed the study. Z.W., B.A. and P.M. conducted articles screening, data extraction and meta-analyses. Z.W. wrote the first draft of the manuscript. R.B., K.K.C.M, B.A., P.M. and I.C.K.W. critically reviewed the manuscript. All authors participated in the interpretation of the study results and approved the final version of the manuscript.

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APPENDIX A: SEARCH TERMS

PubMed:

	Keywords	MeSH/pharmacological action term	Terms as a free text	Search terms
A	Antipsychotics	Antipsychotic agents	Agents, antipsychotic Antipsychotics Major tranquilizers Tranquilizers, major Tranquillizing agents, major Agents, major tranquillizing Major tranquillizing agents Neuroleptic drugs Drugs, neuroleptic Neuroleptics Tranquilizing agents, major Agents, major tranquilizing Major tranquilizing agents Antipsychotic drugs Drugs, antipsychotic Neuroleptic agents Agents, neuroleptic Antipsychotic effect Effect, antipsychotic Antipsychotic effects Effects, 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, pregnancy Pregnancy complication Complications, pregnancy	((("pregnancy complications"[MeSH]) OR pregnancy complication*) OR complication, pregnancy) OR pregnancy complication) OR complications, pregnancy
E	Congenital abnormalities	Congenital abnormalities	Abnormality, congenital Congenital abnormality Deformities Deformity Congenital defects Congenital defect Defect, congenital Defects, congenital	((((((((((((("congenital abnormalities"[MeSH]) OR congenital Abnormalit*) OR abnormality, congenital) OR congenital abnormality) OR deformities) OR deformity) OR congenital defects) OR congenital defect) OR defect, congenital) OR defects, congenital) OR abnormalities, congenital) OR birth defects) OR birth defect) OR defect, birth) OR defects, birth

	Keywords	MeSH/pharmacological action term	Terms as a free text	Search terms
			Abnormalities, congenital	
			Birth defects	
			Birth defect	
			Defect, birth	
			Defects, birth	

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

EMBASE:

	Keywords	Map term	Terms as a free text	Search terms
A	Antipsychotics	Neuroleptic agent	Agents, antipsychotic Antipsychotics Major tranquilizers Tranquilizers, major Tranquillizing agents, major Agents, major tranquillizing Major tranquillizing agents Neuroleptic drugs Drugs, neuroleptic Neuroleptics Tranquilizing agents, major Agents, major tranquilizing Major tranquilizing agents Antipsychotic drugs Drugs, antipsychotic Neuroleptic agents Agents, neuroleptic Antipsychotic effect Effect, antipsychotic Antipsychotic effects Effects, 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, pregnancy Pregnancy complication Complications, pregnancy	Pregnancy complication. Mp. Or pregnancy complication/OR (pregnancy complication* or complication, pregnancy or pregnancy complication or complications, pregnancy)
D	Congenital abnormalities	Congenital disorder	Abnormality, congenital	Congenital disorder. Mp. Or congenital disorder/OR (congenital Abnormalit* or abnormality, congenital or

(Continues)

	Keywords	Map term	Terms as a free text	Search terms
			Congenital abnormality Deformities Deformity Congenital defects Congenital defect Defect, congenital Defects, congenital Abnormalities, congenital Birth defects Birth defect Defect, birth Defects, birth	congenital abnormality or deformities or deformity or congenital defects or congenital defect or defect, congenital or defects, congenital or abnormalities, congenital or birth defects or birth defect or defect, birth or defects, birth)

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

Cochrane Library:

	Keywords	MeSH	Terms as a free text	Search terms
A	Antipsychotics	Antipsychotic agents	Agents, antipsychotic Antipsychotics Major tranquilizers Tranquilizers, major Tranquillizing agents, major Agents, major tranquillizing Major tranquillizing agents Neuroleptic drugs Drugs, neuroleptic Neuroleptics Tranquilizing agents, major Agents, major tranquilizing Major tranquilizing agents Antipsychotic drugs Drugs, antipsychotic Neuroleptic agents Agents, neuroleptic Antipsychotic effect Effect, antipsychotic Antipsychotic effects Effects, 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)

	Keywords	MeSH	Terms as a free text	Search terms
C	Pregnancy complication	Pregnancy complications	Complication, pregnancy Pregnancy complication Complications, pregnancy	MeSH descriptor: [pregnancy complications] explode all trees OR (pregnancy complication* or complication, pregnancy or pregnancy complication or complications, pregnancy)
D	Congenital abnormalities	Congenital abnormalities	Abnormality, congenital Congenital abnormality Deformities Deformity Congenital defects Congenital defect Defects, congenital Defect, congenital Abnormalities, congenital Birth defects Birth defect Defect, birth Defects, birth	MeSH descriptor: [congenital abnormalities] explode all trees OR (congenital Abnormalit* or abnormality, congenital or congenital abnormality or deformities or deformity or congenital defects or congenital defect or defect, congenital or defects, congenital or abnormalities, congenital or birth defects or birth defect or defect, birth or defects, birth)

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

PsycINFO

	Key words	Map term	Terms as a free text	Search terms
A	Antipsychotics	Neuroleptic agent	Agents, antipsychotic Antipsychotics Major tranquilizers Tranquilizers, major Tranquillizing agents, major Agents, major tranquillizing Major tranquillizing agents Neuroleptic drugs Drugs, neuroleptic Neuroleptics Tranquilizing agents, major Agents, major tranquilizing Major tranquilizing agents Antipsychotic drugs Drugs, antipsychotic Neuroleptic agents Agents, neuroleptic Antipsychotic effect	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)

(Continues)

	Key words	Map term	Terms as a free text	Search terms
			Effect, antipsychotic Antipsychotic effects Effects, antipsychotic	
B	Pregnancy	Pregnancy	Pregnancies Gestation	Pregnancy. Mp. Or pregnancy/OR (Pregnan* or pregnancies or gestation)
C	Pregnancy complication	Pregnancy complication	Complication, pregnancy Pregnancy complication Complications, pregnancy	Pregnancy complication. Mp. Or pregnancy complication/OR (pregnancy complication* or complication, pregnancy or pregnancy complication or complications, pregnancy)
D	Congenital abnormalities	Congenital disorder	Abnormality, congenital Congenital abnormality Deformities Deformity Congenital defects Congenital defect Defect, congenital Defects, congenital Abnormalities, congenital Birth defects Birth defect Defect, birth Defects, birth	Congenital disorder. Mp. Or congenital disorder/OR (congenital Abnormalit* or abnormality, congenital or congenital abnormality or deformities or deformity or congenital defects or congenital defect or defect, congenital or defects, congenital or abnormalities, congenital or birth defects or birth defect or defect, birth or defects, birth)

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

APPENDIX B: QUALITY ASSESSMENT OF INCLUDED ARTICLES (COHORT STUDY)

		Selection				Comparability		Outcome			
Study	Year of publication	Representativeness of the exposed cohort	Selection of the nonexposed 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	Total
Rumeau-Rouquette *et al.*[31]	1977	1	1	1	1	0	0	1	1	0	6
Slone *et al.*[32]	1977	1	1	1	1	0	0	0	0	0	4
Diav-Citrin *et al.*[35]	2005	1	1	1	1	0	0	0	1	1	6
McKenna *et al.*[28]	2005	1	1	1	1	0	0	1	1	0	6
Reis and Kallen[33]	2008	1	1	0	1	0	1	1	1	1	7
Habermann *et al.*[29]	2013	1	1	1	1	1[a]	1[a]	0	1	1	8
Sadowski *et al.*[30]	2013	1	0	0	1	0	0	1	1	1	5
Bellet *et al.*[16]	2015	1	1	1	1	0	0	0	1	0	5
Vigod *et al.*[17]	2015	1	1	1	1	0	1	1	1	1	8
Cohen *et al.*[18]	2016	0	1	1	1	0	1	1	1	1	7
Huybrechts *et al.* [19]	2016	1	1	1	1	1	1	1	1	1	9
Petersen *et al.*[20]	2016	1	1	1	1	1	1	1	1	1	9

[a] Habermann *et al.*[29] included potential confounders (maternal age, alcohol consumption, smoking habits, body mass index [BMI], previous spontaneous abortions, and previous malformed children) in a start model for adjustment through logistic regression to define the relevant confounders for major malformations. However, only alcohol consumption was shown to have a significant influence and, therefore, was considered in the final analysis. We gave the scores due to authors acknowledged the confounders that might confound the outcomes even if they were not considered in the final model.

APPENDIX C: QUALITY ASSESSMENT OF INCLUDED ARTICLES (CASE–CONTROL STUDY)

	Selection				Comparability		Outcome			
Study	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Study controls for mother age, smoking, alcohol consumption	Study controls for any additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	Total
Anderson *et al.*[34]	1	1	1	1	0	0	0	1	1	6

APPENDIX D: SUMMARY OF THE INCLUDED STUDIES RESULTS

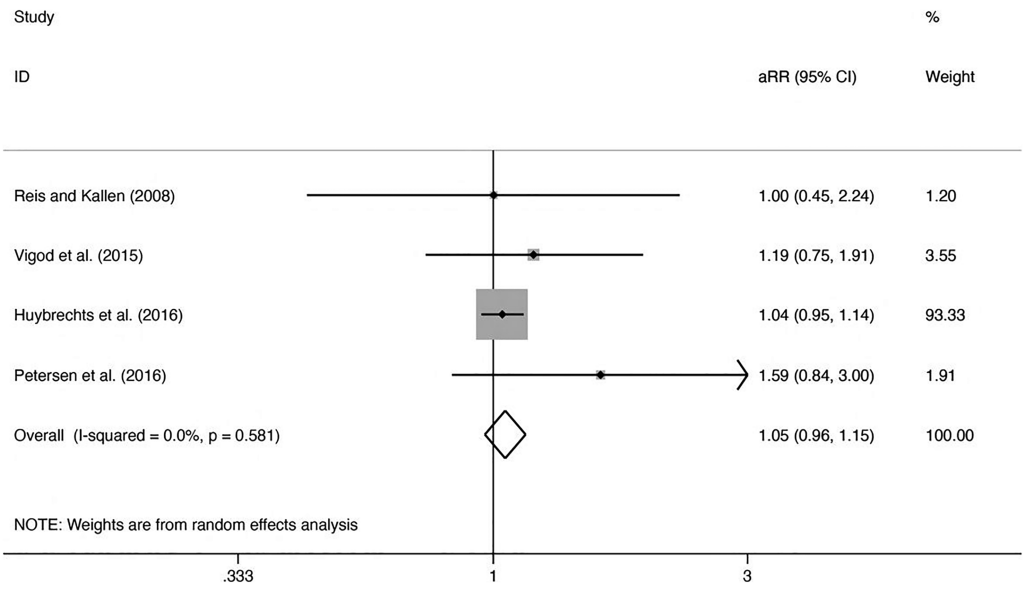
Study	Unadjusted results	Adjusted confounding factors	Adjustment method	Adjusted results
Rumeau-Rouquette *et al.*[31]	Rate of malformation in unexposed group = 1.6%, Rate of malformation in exposed group = 3.5%	N/A	N/A	N/A
Slone *et al.*[32]	Uniform malformation: Exposed group = 5%, Unexposed group = 4.5%, RR 1.07; Major malformation: Exposed group = 3.6%, Unexposed group = 2.7%, RR 1.16.	N/A	N/A	N/A
Diav-Citrin *et al.*[35]	Butyrophenone group: 6/179; controls group: 22/581	N/A	N/A	N/A
McKenna *et al.*[28]	SGAs group: 1/151; Non-teratogenic agent group: 2/151	N/A	N/A	N/A
Reis and Kallen[33]	N/A	Maternal (y of delivery, maternal age, parity, maternal smoking in early pregnancy, previous miscarriages, subfertility, maternal BMI, maternal cohabitation, work outside home, maternal country of birth), delivery and infant (infant sex, number of infants at birth, gestational duration, birth weight, intrauterine growth, infant survival, congenital malformations, maternal pregnancy diagnoses, infant neonatal diagnoses)	Mantel–Haenszel method and Miettinen's method	Dixyrazine or prochlorperoxine: OR 0.67, 95% CI 0.49–0.90; other antipsychotics: OR 1.52, 95% CI 1.05–2.19
Habermann *et al.*[29]	OR 2.13, 95% CI 1.19–3.83	Maternal age, alcohol consumption, smoking habits, number of previous spontaneous abortions, number of previous malformed children, gestational wk at delivery. However, only alcohol consumption (91 drink/d) was shown to have a significant influence and, therefore, was considered in the final analysis.	Logistic regression	OR 2.17, 95% CI 1.20–3.91
Sadowski *et al.*[30]	Exposed group: 7/133; Healthy comparison group: 3/133	N/A	N/A	N/A
Bellet *et al.*[16]	OR 2.30, 95% CI 0.32–16.7	N/A	N/A	N/A
Vigod *et al.*[17]	RR 1.10, 95% CI 0.72–1.69	Adjusting for additionally prescribed nonantipsychotic psychotropic medications (a prescribed SSRI, non-SSRI, mood stabiliser, or benzodiazepine during the index pregnancy)	Propensity score method	RR 1.19, 95% CI 0.75–1.91
Cohen *et al.*[18]	OR 1.25, 95% CI 0.13–12.19	Diagnosis and severity of illness; whether the pregnancy was		OR 0.69, 95% CI 0.06–8.09

(Continues)

Study	Unadjusted results	Adjusted confounding factors	Adjustment method	Adjusted results
		planned; maternal age; health and lifestyle indicators, such as BMI; and first trimester use of other psychotherapeutic drugs, prenatal vitamins, alcohol, and cigarettes	Adjusted regression, propensity score method	
Huybrechts *et al.*[19]	FGAs: RR 1.17, 95% CI 0.81–1.68; SGAs: RR 1.36, 95% CI 1.24–1.50	Calendar y, age, race, smoking, multiple gestation, indications for antipsychotics, other maternal morbidity, concomitant medication use, and general markers of the burden of illness	Adjusted regression, propensity score method	FGAs: RR 0.90, 95% CI 0.62–1.31; SGAs: RR 1.05, 95% CI 0.96–1.16
Petersen *et al.*[20]	RR 1.74, 95% CI 0.93–3.25	Age at delivery, calendar y of delivery, obesity, illicit drug use, alcohol problem, smoking status, pre-existing medical conditions, prescriptions of concomitant medication	Propensity score method	RR 1.59, 95% CI 0.84–3.00
Anderson *et al.*[34]	Any heart defect: OR 1.5, 95%CI 0.7–3.0; Conotruncal defects: OR 2.3, 95% CI 0.9–6.1; tetralogy of fallot: OR 2.5, 95% CI 0.7–8.8; LVOTO: OR 1.8, 95% CO 0.6–5.5; RVOTO: OR 1.4, 95% CI 0.4–5.0; septal defects: OR 0.8, 95% CI 0.3–2.6; atrial septal defect: OR 1.3, 95% CI 0.6–3.7; any orofacial cleft: OR 1.4, 95% CI 0.6–3.7; cleft palate: OR 2.5, 95%CI 0.8–7.6; cleft lip ± cleft palate: OR 0.9 95% CI 0.3–3.3; anorectal atresia/stenosis: OR 2.8, 95% CI 0.8–9.9; hypospadias, 2/3rd degree: OR 0.8, 95% CI 0.2–2.9; Craniosynostosis: OR 1.8, 95% CI 0.5–6.5; Gastroschisis: OR 2.1 95% CI: 0.6–7.3	N/A	N/A	N/A

N/A: not applicable; FGAs: first-generation antipsychotics; SGAs: second-generation antipsychotics; RR: risk ratio; OR: odds ratio; CI: confidence interval; LVOTO: left ventricular outflow tract obstruction; RVOTO: right ventricular outflow tract obstruction; SSRI: selective serotonin reuptake inhibitor.

APPENDIX E: FOREST PLOT OF THE SUBGROUP ANALYSIS - LIMITED EXPOSURE TIME WITHIN FIRST OR SECOND TRIMESTER RATHER THAN GENERAL PREGNANCY



aRR: adjusted risk ratio; CI: confidence interval.

APPENDIX F: ADJUSTED RESULTS AND E-VALUES FOR META-ANALYSES INCLUDED STUDIES

Study	aRR (95% CI)	E-value for estimates
Reis and Kallen[33]	1.00 (0.45–2.24)	1.00
Habermann *et al.*[29]	2.17 (1.20–3.91)	3.76
Vigod *et al.*[17]	1.19 (0.75–1.91)	1.67
Cohen *et al.*[18]	0.69 (0.06–8.09)	2.26
Huybrechts *et al.*[19]	1.04 (0.95–1.14)	1.24
Petersen *et al.*[20]	1.59 (0.84–3.00)	2.56

aRR: adjusted risk ratio; CI: confidence interval.