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Association between prenatal antipsychotic exposure and the risk of attention-deficit/hyperactivity disorder and autism spectrum disorder: a systematic review and meta-analysis

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ABSTRACT

The paucity of evidence regarding the safety of gestational antipsychotic exposure has led to treatment discontinuation in pregnant women with severe mental health conditions. This systematic review and meta-analysis aimed to summarise the current evidence on the association between gestational antipsychotic exposure and attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in children (Study protocol registered in PROSPERO:CRD42022311354). Five studies included in our meta-analysis with around 8.6 million pregnancy episodes in nine different countries/regions. Results from our meta-analysis indicate that the heightened risks of ASD and ADHD in children gestationally exposed to antipsychotics appear to be attributable to maternal characteristics, rather than having a causal relationship with the antipsychotic exposure during pregnancy. The results underscore the importance of meticulously monitoring the neurodevelopment of children born to mothers with mental illnesses, which can facilitate early interventions and provide requisite support.

1. Introduction

Antipsychotics are the basis of pharmacotherapy to treat several psychiatric disorders (Crystal et al., 2009). They exhibit the clinical effects by blocking dopamine receptors, and their indications range from schizophrenia, bipolar disorder, sleeping problems, major depression, and severe anxiety (Crystal et al., 2009). Antipsychotics have been increasingly prescribed for women who are pregnant and of childbearing age over recent years, largely driven by the increase use of atypical antipsychotics which have received approvals for broader indications (e.g., mood stabilisation in bipolar disorder and adjunct therapy for major depressive disorder) (Camsarı et al., 2014; Park et al., 2017; Toh et al., 2013).

Furthermore, decisions on using antipsychotics to treat psychiatric disorders during pregnancy are complex. Untreated maternal mental illness is associated with poor health outcomes for both mothers and

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children (Bonari et al., 2004; Moore and Pytlarz, 2014), but pregnant women may not want to expose their foetus to any medications which may lead to unwanted effects. Antipsychotics can cross the placenta and the foetus can be exposed to higher concentrations than the mother's serum level in some cases (Newport et al., 2007). As dopamine receptors play a role in foetal development, concerns have been raised regarding potential neurodevelopmental impairment through alteration of dopaminergic system (Brisch et al., 2014; Moody et al., 1993; Popolo et al., 2004), which may increase risks for attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), two major neurodevelopmental disorders (NDDs).

ADHD and ASD are both debilitating conditions that can pose notable morbidity and mortality risks to individuals who suffer from them (Simonoff et al., 2008). Several observational studies have recently investigated the risks of ADHD and ASD in children with prenatal exposure to antipsychotics (Halfdanarson et al., 2020; Petersen et al., 2016; Straub et al., 2022; Wang et al., 2021; Yeh et al., 2021; Momen et al., 2021). However, due to infrequent prenatal use of antipsychotics, these were limited by small sample sizes, leading to imprecise risk estimates. To date, no systematic review and meta-analysis was conducted on this topic, and the clinical decision about whether or not to continue antipsychotic treatment in patients who become pregnant has remained inconclusive.

The objective of this systematic review and meta-analysis of observational studies was to provide a summary of current evidence on the safety of gestational antipsychotic exposure with respect to the incidence of ADHD and ASD in children.

2. Methods

2.1. Search strategy and selection criteria

A systematic literature search was conducted on PubMed, EMBASE, APA PsycINFO, and Cochrane Library databases up to 12th March, 2023 since inception, following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and checklist (Appendix 1). We searched for all cohort or case-control studies that evaluated the association between gestational antipsychotic exposure (regardless of maternal psychiatric status) and the risk of ADHD and/or ASD using comprehensive search terms (Appendix 2). Only full-text original articles written in English were considered for review inclusion. If two or more articles had overlapping datasets, the article with the largest dataset, or longest follow-up period was retained for the meta-analysis. Our study protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42022311354).

2.2. Data extraction

All searched articles were screened independently by three investigators (ZW, KW and ASCY) to identify relevant studies based on titles, abstracts as well as full-text contents. Discrepancies were resolved through discussion and consensus. Information from eligible articles was extracted independently by two authors (ZW and KW) using a standardised data collection form including study design (cohort or case-control), data source, study period, details of the study population, details of exposure and outcome ascertainment, follow-up, confounding adjustment, and statistical analysis.

2.3. Quality assessment

Three investigators (ZW, KW and ASCY) independently assessed the quality of included studies using two tools: Newcastle-Ottawa Scale (NOS), a tool assessing the methodological quality (Higgins, 2008; Stang, 2010) and Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I), a tool for assessing risk of bias in non-randomized studies (Sterne et al., 2016).We only included studies rated as good (a score of at least one in each major section and a total score of six or above) in NOS and with overall bias other than 'critical risk' in ROBINS-I (Appendix 3).

2.4. Outcomes and outcome metrics

The primary outcomes are diagnosis of ADHD and/or ASD. NDD was considered as proxy if ADHD and/or ASD were/was captured. Outcome metrics such as adjusted risk ratios (RRs), odds ratios (ORs), hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were extracted and included in the meta-analysis, if appropriate.

2.4.1. Primary comparisons

We pooled data comparing children with prenatal antipsychotic exposure to the unexposed in the primary analysis.

2.4.2. Other comparisons

We conducted several additional analyses according to the gestational antipsychotic exposure at different risk windows. First, we narrowed exposure period to the first trimester (early gestational exposure), which is the critical time for foetal neurological development (Stiles and Jernigan, 2010). Second, we compared those with gestational exposure versus gestational non-exposure of the sibling from the same mother (sibling-matched analysis), for addressing shared genetic and social factors at the family level. Third, we compared those with gestational exposure versus past exposure to address potential confounding by maternal psychiatric disorders. Fourth, as a negative control analysis, we compared those with past exposure versus never exposed to assess the impact of maternal psychiatric disorders.

2.4.3. Subgroup comparisons

Subgroup analysis by different classes of antipsychotics was performed for first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs).

2.5. Statistical analysis

Adjusted estimates from five studies, details for confounding adjustment in each included study are presented in Appendix 4 (Table S7), were pooled using a random-effect model with the corresponding 95% CI for each outcome in the analyses (DerSimonian and Laird, 1986). We presented results as RRs with 95% CIs. Heterogeneity among included studies was evaluated using I^2, where a value of 0% is considered as no observed heterogeneity and a larger value indicates increasing heterogeneity (Higgins et al., 2003).

All analyses were conducted using STATA 15 and STATA/MP 17.

3. Results

3.1. Study selection

A total of 1,943 records were identified for screening after removing 88 duplicates on 12 March 2023. Out of 12 full-text articles that were assessed for eligibility, six studies met the inclusion criteria for this systematic review (Halfdanarson et al., 2020; Petersen et al., 2016; Straub et al., 2022; Wang et al., 2021; Yeh et al., 2021; Momen et al., 2021). However, two studies (Halfdanarson et al., 2020; Momen et al., 2021) included the same population and only Halfdanarson et al., 2020 was included in the quantitative analysis of results due to a longer follow-up duration (Fig. 1).

3.2. Characteristics of included studies

All studies were published in English from 2016 onwards; one was conducted in the United States of America (USA) (Straub et al., 2022),

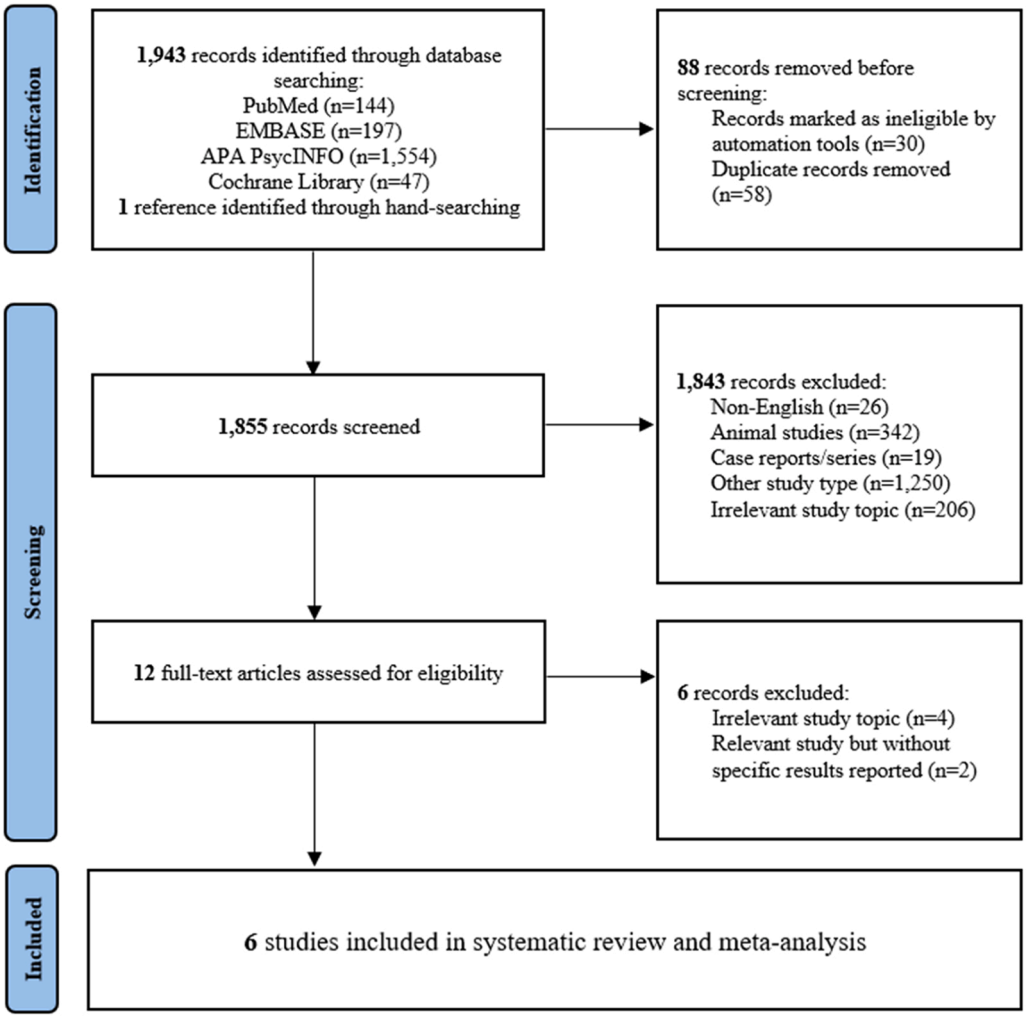

Fig. 1. Study selection flow diagram.

three in Europe (Halfdanarson et al., 2020; Momen et al., 2021; Petersen et al., 2016), and two in Asia (Wang et al., 2021; Yeh et al., 2021). All included studies utilised administrative databases/registries; four studies adopted a retrospective cohort study design, and one study implemented a case-control design (Yeh et al., 2021). Five studies evaluated any antipsychotic exposure in pregnancy (with either FGAs or SGAs) (Halfdanarson et al., 2020; Petersen et al., 2016; Straub et al., 2022; Wang et al., 2021; Momen et al., 2021), while one focused on SGAs only (Yeh et al., 2021). Five studies indicated the risks of ADHD and ASD separately (Halfdanarson et al., 2020; Straub et al., 2022; Wang et al., 2021; Yeh et al., 2021; Momen et al., 2021) and one study only identified NDDs generally (Petersen et al., 2016). Three studies offered adequate follow-up time for the outcomes of interest: at least 5 years for ADHD and 2 years for ASD (Momen et al., 2021; Wang et al., 2019; Yeh et al., 2021). Table 1 and Table S7 (Appendix 4) summarise the characteristics of the included studies.

3.3. Risk of bias of included studies

All studies were considered as of good quality according to NOS quality assessment (at least 8 scores) and moderate risk of bias based on ROBINS-I assessment, except for Yeh et al. (2021) (Yeh et al., 2021) – 'serious risk' as the study only included psychiatrically healthy individual as comparator group. Appendix 3 (Table S4-S6) shows the results of quality assessment. All included articles have dealt with confounding factors either using multivariable adjustments in the regression models, restriction in control group selection or propensity score (PS) methods (Halfdanarson et al., 2020; Petersen et al., 2016; Straub et al., 2022; Wang et al., 2021; Yeh et al., 2021). In addition to comparing the outcome rates between the gestationally exposed and unexposed groups, and in consideration of potential confounding effects related to maternal psychiatric status, all studies used additional methods to address confounding by indication: (1) 'discontinuers/past exposure' (mothers who had filled antipsychotic prescriptions prior to pregnancy but discontinued during pregnancy) used as a control group (Halfdanarson et al., 2020; Petersen et al., 2016; Straub et al., 2022; Wang et al., 2021; Yeh et al., 2021; Momen et al., 2021); (2) analyses stratified by different types or severity of maternal psychiatric disorders (Halfdanarson et al., 2020; Yeh et al., 2021); (3) sibling-matched analysis (Halfdanarson et al., 2020; Wang et al., 2021); and (4) paternal exposure during the same window (Momen et al., 2021).

3.4. Summary of results

3.4.1. Primary comparisons

Fig. 2 shows the forest plots of the primary analyses. Four studies (8,087,966 pregnancy episodes) contributed to data of the primary outcomes. The pooled adjusted RR was 1.11 (95% CI, 1.03–1.19; I^2=0.0%) for ADHD, and 1.10 (95% CI, 0.98–1.24; I^2=0.0%) for ASD when comparing children with gestational antipsychotic exposure to the unexposed. One study only evaluated the risk of NDDs as a composite outcome (Petersen et al., 2016), with an adjusted RR of 1.22 (95% CI,

Table 1
Characteristics summary of included studies.

Study	Country	Data source	Study Population	Study period	Antipsychotics	Pregnancy episodes	Follow-up	Outcomes
Petersen et al. (2016)	UK	THIN and CPRD	All pregnant women	1995–2012	Any antipsychotic, FGA, SGA	495,953 pregnancies	2–3 years	NDDs
Halfdanarson et al. (2020)	Denmark, Finland, Iceland, Norway, Sweden	Nationwide registers in five Nordic countries	All pregnant women and their live-born singletons	Denmark (1997–2017), Finland (1996–2016), Iceland (2004–2017), Norway (2004–2017), Sweden (2006–2016).	Any antipsychotic, FGA, SGA,	4324,086 children	ADHD: at least 3 years; ASD: at least 1 year	ADHD, ASD
Wang et al. (2021)	Hong Kong	CDARS	All pregnancy women aged 15–50 who delivered a live birth	2001–2019	Any antipsychotic, FGA, SGA	411,251 pairs of mother-child records for ASD, 333,749 for ADHD	ADHD: at least 6 years; ASD: at least 3 years	ADHD, ASD
Yeh et al. (2021)	Taiwan	Taiwan National Health Insurance Research Database	All people registered in Taiwan since 2002	2002–2011	SGA	5669 pregnant women with bipolar disorder and 5669 psychiatrically healthy controls	Up to 10 years	ADHD, ASD
Straub et al. (2022)	USA	MAX, MarketScan	Mothers (12–55 years old),	2000–2015[a]	Any antipsychotic, FGA, SGA, individual[b]	9551/2034,883 in MAX, 1221/ 1306,408 in MarketScan	ADHD: at least 2 years; ASD: at least 1 year	ADHD, ASD, NDD
Momen et al. (2021)	Denmark	Danish Registries and Statistics	Live-born singletons	1998–2015	Any antipsychotic	9011 liveborn singletons	At least 15 years	ADHD, ASD

Abbreviation: ADHD: Attention-Deficit/Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CPRD: Clinical Practice Research Datalink; CDARS: Clinical Data Analysis and Reporting System; FGAs: First-Generation Antipsychotics; MarketScan: IBM Health MarketScan Research Database; MAX: Medicaid Analytic eXtract; NDD: Neurodevelopmental disorders; SGAs: Second-generation Antipsychotics; THIN: The Health Improvement Network; UK: United Kingdom; USA: United States of America

[a] Straub et al. (2022) only stated cohort time - MAX (2000–2014), MarketScan (2003–2015)

[b] Aripiprazole, olanzapine, quetiapine, risperidone and haloperidol

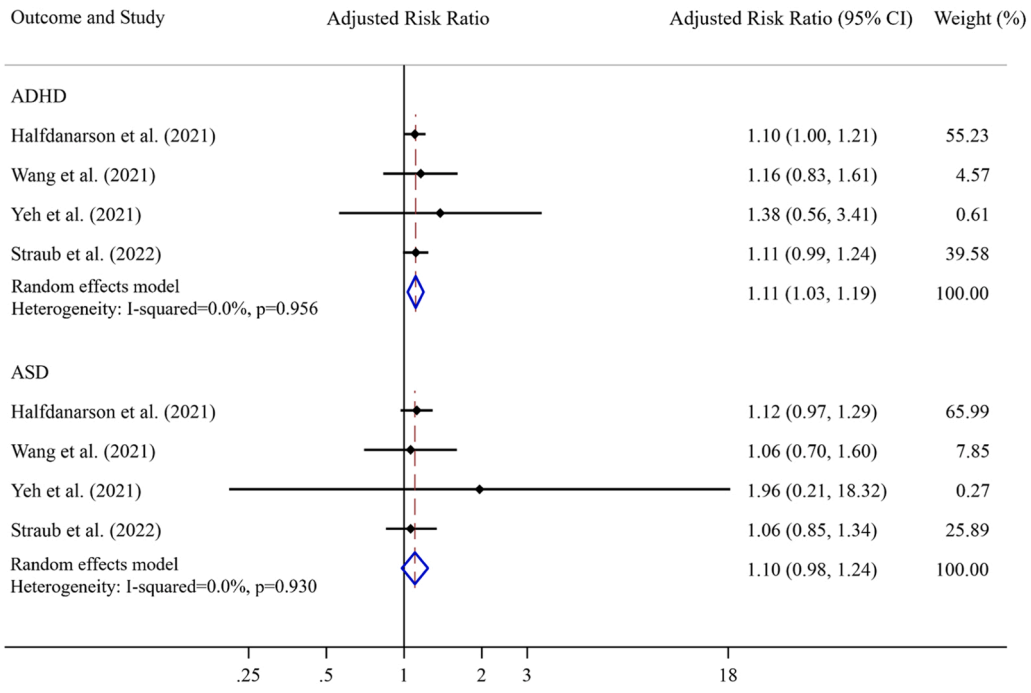

Fig. 2. Forest plot demonstrating individual and pooled relative risks of primary analysis for the gestational antipsychotic exposure versus gestational non-exposure. ADHD: Attention-Deficit/Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CI, confidence interval.

0.80–1.84) when compared to the gestationally unexposed. Table S8-S10 shows detailed results for each outcome from all five studies (Appendix 4).

3.4.2. Other comparisons

Results from three studies that evaluated the risks of ADHD and ASD with early gestational antipsychotic exposure (Halfdanarson et al.,

2020; Wang et al., 2021; Yeh et al., 2021), showed similar results to the main analysis (ADHD: pooled adjusted RR 1.07; 95% CI 0.93–1.23; I^2=0.0%; ASD: pooled adjusted RR 1.09; 95% CI 0.56–2.14; I^2=18.4%) (Fig. 3; Appendix 5 Figure S1). A post-hoc analysis was conducted to test the associations of antipsychotics exposure in the second trimester or the third trimester only, which showed consistent results to the first trimester only – no evidence supporting the causal association between antipsychotics exposure and ADHD/ASD development (Appendix 5 Figure S2). Similarly, similar findings were observed within sibling comparisons (ADHD: pooled adjusted RR 1.11; 95% CI 0.78–1.60; I^2=0.0%; ASD: pooled adjusted RR 1.17; 95% CI 0.73–1.87; I^2=0.0%) (Halfdanarson et al., 2020; Wang et al., 2021) (Fig. 3; Appendix 5 Figure S3).

In exploring the potential confounding effect of maternal underlying psychiatric conditions, we found no increased risk with gestational exposure when compared to past exposure for ADHD (pooled adjusted RR 0.78; 95% CI 0.63–0.96; I^2=16.3%) and ASD (pooled adjusted RR 0.90; 95% CI 0.73–1.12; I^2=0.0%) (Fig. 3; Appendix 5 Figure S4). While, increased risks with past exposure when compared to never exposed were identified for both ADHD and ASD (ADHD: pooled adjusted RR 1.96; 95% CI 1.05–3.66; I^2=95.8%; ASD: pooled adjusted RR 1.38; 95% CI 1.20–1.60; I^2=0.0%) (Fig. 3; Appendix 5 Figure S5).

3.4.3. Subgroup comparisons

In relation to the class of antipsychotics, we observed small increased risks of ADHD and ASD associated with the gestational exposure to both FGAs and SGAs, which are broadly consistent with the main analysis (Appendix 5 Figure S6).

4. Discussion

This study summarised the latest available evidence on the safety of gestational exposure to antipsychotics regarding developing ADHD or ASD. Considering the five observational studies which met our inclusion criteria, our meta-analyses showed slightly elevated risks of ADHD and ASD in gestationally exposed children compared to their unexposed counterparts. However, the results of our further analyses showed lower risks of ADHD and ASD when comparing gestational exposure to past exposure, and higher risks of ADHD and ASD when comparing past exposure to never exposed. The overarching results indicate that the association between gestational exposure to antipsychotics and development of ADHD and ASD is unlikely to be causal as this seems to be confounded by maternal characteristics.

4.1. Interpretation of results

Our study showed consistent results across comparison analyses between gestational exposure towards antipsychotics and non-exposure, including sibling-matched and early gestational exposure analyses (Fig. 3). We observed slightly increased RRs for ADHD and ASD in children with gestational exposure to antipsychotics. However, the results are different when we implemented different comparison groups, considering antipsychotic exposure 'before pregnancy'. We observed no increased risks of ADHD and ASD with gestational antipsychotic exposure versus past exposure analysis, and notably increased risks when comparing past exposure to never exposed (Fig. 3). In other words, children who were born to mothers who used antipsychotics before pregnancy but not during pregnancy, were at higher risks of developing ADHD and ASD than children who were born to mothers who had never been exposed to antipsychotics. This indicates an association between the risks of ADHD and ASD in children and underlying maternal characteristics rather than gestational exposure to antipsychotics. In addition, previous studies have identified increased risks of ADHD and ASD were associated with maternal psychiatric disorders (Fairthorne et al., 2016; Nidey et al., 2021; Vizzini et al., 2019), and may also be associated with poorly managed psychiatric conditions, which could arise from either the abrupt discontinuation of ongoing antipsychotic treatment during pregnancy or the decision to withhold starting such treatment when a new psychiatric condition emerged during pregnancy.

However, as there are ethical challenges for interventional studies to explore the risk of ADHD and ASD in children associated with gestational exposure to antipsychotics, all included studies in this meta-analysis are observational studies, and some possess several limitations which warrant methodological considerations. Four studies were assigned a moderate risk of bias (Halfdanarson et al., 2020; Petersen et al., 2016; Straub et al., 2022; Wang et al., 2021), and one study was assigned a serious risk of bias (Yeh et al., 2021) when using the ROBINS-I tool (Table S6). Potential limitations identified in the selected studies include residual confounding, bias from missing data, exposure misclassification, and short follow-up time. The major limitations were

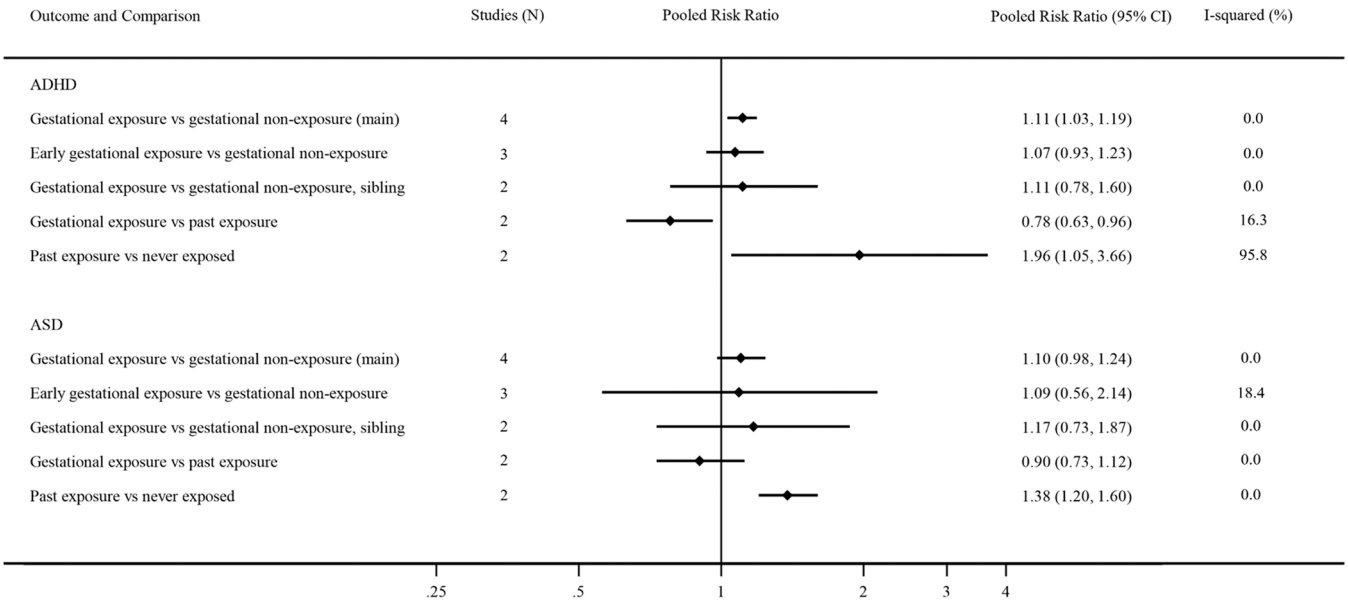

Fig. 3. Results of meta-analyses of different comparisons with varying gestational exposure to antipsychotics. ADHD: Attention-Deficit/Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CI, confidence interval; RR, adjusted risk ratio.

confounding by indication and/or severity of maternal psychiatric disorders which is related to previous exposure to antipsychotics. Although most studies considered maternal factors in their statistical model, the genetic liability for ADHD and ASD were not adequately controlled for. Furthermore, sibling-matched analysis, in order to control for many maternal factors, was performed only in two studies (Halfdanarson et al., 2020; Wang et al., 2021), and only three studies compared antipsychotic exposure during and before pregnancy (Halfdanarson et al., 2020; Petersen et al., 2016; Wang et al., 2021).

4.2. Strengths and limitations

Our study has many strengths. This is the first meta-analysis to summarise available literature evaluating the association between gestational antipsychotic exposure and the risk of ADHD and ASD in children. Second, selection bias was minimised by using a comprehensive search strategy as well as independent article screening and data extraction. Third, we used validated tools assessing the quality and risk of different biases of the included studies, such as selection bias and confounding, to enable interpretation of our results in the context of potential limitations of these studies. Fourth, the overall sample size of all included studies for the meta-analysis was over 8 million pregnancy episodes across nine different regions which allows us to extrapolate our findings to the broader population through west to east. However, this study does have some limitations. First, our review is influenced by the limitations inherent in the included studies, such as residual confounding due to the nature of observational studies, and relatively short follow-up periods when considering the age range at ASD and ADHD diagnosis. Second, methodological differences in the included studies could affect the accuracy of the pooled RRs. Nevertheless, we observed no or low heterogeneity in the pooled RRs which indicate consistency in the results.

4.3. Clinical implications and future directions

Overall, our findings support the safety of gestational antipsychotic use with respect to the risk of ADHD and ASD development in offspring. Therefore, antipsychotic treatment during pregnancy could be considered when clinically indicated. However, risks of ADHD and ASD related to individual antipsychotics and different dosing regimens are yet to be explored in the included studies. In addition, the association between the different types and severities of maternal psychiatric disorders and the development of ADHD and ASD in offsprings remains unclear. Future studies are warranted to investigate the effect of different antipsychotics, their dosing regimens and the types and severities of maternal psychiatric conditions. Future studies should also adopt a longer follow-up duration, extending into adolescence or adulthood, to assess the long-term outcomes of prenatal antipsychotic exposures.

5. Conclusion

Our systematic review and meta-analysis of observational studies indicates that the heightened risks of ADHD and ASD observed in children gestationally exposed to antipsychotics appear to be attributable to maternal characteristics, rather than having a causal relation to the antipsychotic itself. Hence, current evidence highlights the significance of close observation the neurodevelopment of offspring born to mothers with mental disorders, as this can enable early interventions and ensure the necessary support is provided. Additionally, this evidence emphasizes the importance of carefully considering antipsychotic treatment during pregnancy, which is crucial for managing maternal mental health while also taking into account the well-being of the offspring.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105635.

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