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REVIEW PAPER

Autism Spectrum Disorders in Offspring Exposed to Maternal Gestational Diabetes: a Meta-Analysis and Systematic Review

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Abstract

The association between maternal diabetes and risk of autism spectrum disorder in offspring was not completely consistent. We performed an updated and systematic review and meta-analysis with relevant studies published until 6 August 2020. We included 17 publications, describing 15 studies, including 1,751,537 participants. Exposure to maternal diabetes in utero was correlated to an increased risk of ASD (effect estimate 1.30 [95% CI: 1.16–1.46]). Offspring exposure to maternal diabetes with antidiabetic medication has a heightened risk of ASD by 48% than offspring with a non-diabetic mother, and 42% than offspring with diabetic mother not receiving medical treatment. Exposure to maternal diabetes in utero increases the risk of ASD in offspring, especially exposure to maternal diabetes with antidiabetic medication.

Keywords Maternal diabetes · Antidiabetic · Autism spectrum disorders (ASD) · Offspring · Meta

Introduction

Autism spectrum disorder (ASD), occurring in early childhood development, is a group of neurodevelopmental disorders characterized by social interaction and communication deficiencies and stereotyped repetitive behaviors or interests. Since it was first reported in 1943, accompanied by a steady increase in the incidence of ASD (Baio et al., 2018), the understanding of this disorder has increased, but the specific pathogenesis remains unknown. ASD is likely a multifactorial disease (Lyall et al., 2014), resulting from the interaction of genes and environment. Intrauterine exposure to various pregnancy complications might be critical environmental factors playing a role in the pathogenesis (Alderete et al., 2018; Estes & McAllister, 2016; Maimburg & Vaeth, 2006).

Gestational diabetes is a common complication of pregnancy that has serious adverse effects on the mother and the pregnancy outcome. It can lead to perinatal mortality (Ornoy et al., 2015), preterm delivery (Ornoy et al., 2015), miscarriage (Greene et al., 1989), cardiovascular system abnormality (congenital heart defects) (Greene, 2001), and neurocognitive abnormalities (intellectual disability (Bytoft et al., 2016; Fraser et al., 2012; Clausen et al., 2011), attention-deficit/hyperactivity disorder (ADHD), (Xiang et al., 2018a; Instanes et al., 2017), ASD (Xiang et al., 2018b)). An increasing number of studies have explored the association between maternal diabetes and the risk of ASD. Several relevant meta-analyses and reviews have been conducted, but results were inconsistent, resulting in a lack of correlation between antidiabetic medication exposure in utero and the occurrence of ASD. We performed an updated meta-analysis and explored the effect of antidiabetic medication exposure in utero.

Material and Methods

Search Strategy and Selection Criteria

We conducted this meta according to the general standards in the Preferred Reporting Items for Systematic Reviews

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and Meta-Analyses (PRISMA) (Supplementary Table 1). We searched the literature for ASD and other developmental disabilities, such as attention-deficit/hyperactivity disorder (ADHD), depression, intellectual disability, and Tourette syndrome in five electronic databases, including Web of Science, PubMed, Embase, and Wanfang, for studies published until January 2019 without a language restriction (removed the search of Cochrane database, the others are the same as our published article (Guo et al., 2020)). Then, we conducted an extended search of ASD-related literature in PubMed until 6 August 2020.

The article selection process was performed as published previously (Guo et al., 2020). After eliminating duplicates, titles and abstracts were reviewed for eligibility. Full texts of eligible studies were checked for inclusion criteria: original article; cohort study, or case-control study; exploring the association between maternal diabetes and ASD in offspring; contain data on the relative risk (RR), hazard ratio (HR), or odds ratio (OR), with 95% confidence interval (95% CI), or data that allow calculation of one of these effect indicators. Furthermore, we screened references listed in the included articles. We included data from the latest publication if a study was repeated in multiple publications. Two independent investigators performed all selection; any disagreement was settled through discussion.

Data Extraction and Quality Assessment

We extracted necessary data from the included articles (shown in Table 1, Supplementary Tables 2 and 3). The risk estimate for the relationship between maternal diabetes exposure and risk of ASD in offspring was chosen preferentially and was adjusted for the most confounding factors. Data about different types of diabetes or differences in time of diabetes diagnosis were extracted separately and used as independent data for the final calculation.

The quality of included articles was assessed using the Newcastle-Ottawa Scale (Stang, 2010), (totaling three broad perspectives: four stars for the selection of the study groups; two stars for the comparability of the groups; and three stars for the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively). The results were represented as low quality for 0–3 stars, moderate quality for 4–6 stars, and high quality for 7–9 stars.

Data Synthesis and Analysis

We pooled all risk estimates for cohort and case-control studies. Since the prevalence of ASD is low for the rare disease assumption (< 10%), the use of OR is assumed to be approximately the RR. Data of different types of diabetes and different times of diabetes diagnosis in the same study were calculated as independent data. We performed a meta-analysis using a fixed-effect model if the I^2 statistic showed a P value for heterogeneity of > 0.1 and an $I^2 < 50\%$; otherwise, a random-effect model was used (Higgins & Thompson, 2002). We conducted sensitivity analyses to assess the effect of each study. Publication bias was estimated by graphical aids and the Egger linear regression test (Egger et al., 1997). Additionally, subgroup analyses of possible confounders were performed.

Stata version 12.0 was used for all statistical analyses. P value < 0.05 was considered statistically significant, except for the I^2 statistic, which was assessed at a significance of 0.10.

Results

Literature Search Results

After omitting duplicates, 3017 potential articles were entered into the screening process. After screening, 58 studies met our inclusion criteria, including 17 publications about ASD. The study population of one article (Xiang et al., 2015) was the same as another publication (Xiang et al., 2018b). Considering they contain different subgroup data, these were all included in this study for overall analysis and subgroup analysis, respectively. The same applied to two other articles (Kong et al., 2018; Kong et al., 2020). Therefore, there were 17 publications (including 15 studies) available for the final analysis. Figure 1 shows our selection process.

Characteristics of Studies Included in the Meta-Analysis

The characteristics of included articles are listed in Table 1 and Supplementary Tables 2 and 3. We included 17 articles (including 15 studies) with 1,751,537 participants in this meta-analysis, of which nine studies were designed as a cohort study (Xiang et al., 2018b; Kong et al., 2018; Burstyn et al., 2010; Dodds et al., 2011; Lyall et al., 2012; Connolly et al., 2016; Li et al., 2016; Nahum Sacks et al., 2016; Jo et al., 2019) and six as a case-control study (Hultman et al., 2002; Croen et al., 2005; Buchmayer et al., 2009; Krakowiak et al., 2012; Chien et al., 2019; Cordero et al., 2019). The number of participants in each study ranged from a few hundred to nearly 420,000. Studies were conducted in different regions around the world. Eight studies (Xiang et al., 2018b; Lyall et al., 2012; Connolly et al., 2016; Li et al., 2016; Jo et al., 2019; Croen et al., 2005; Krakowiak et al., 2012; Cordero et al., 2019) were performed in the USA, two in Sweden (Hultman et al., 2002; Buchmayer et al., 2009),

Table 1 Characteristics of the included studies

Study	Country	Study design	Sample size	Maternal diabetes criteria	ASD criteria	Effect size (95% CI)	Controlled variables
Hultman et al. (2002) Score 7[a]	Sweden	Case-control study	15/2433	ICD-8 code 250 and ICD-9 codes 250, 648A, and 648W	ICD-9 code 299A	OR DM: 1.80 (0.60, 5.70)	None
Croen et al. (2005) Score 7	USA	Case-control study	14/2488	ICD-9-CM code	ICD-9-CM code 299.0, 299.8	OR T1D: 2.60 (0.80, 7.90)	Maternal age, maternal education, maternal race/ethnicity, and plurality
Buchmayer et al. (2009) Score 7	Sweden	Case-control study	98/7198	ICD-9/ICD-10	ICD-9/ICD-10	OR DM: 0.90 (0.49, 1.67)	Age, gender, birth year, birth hospital through matching, maternal age, smoking, maternal country of birth, whether the mother lived with the father, and maternal schizophrenia
Burstyn et al. (2010) Score 8	Canada	Cohort study	(1)GDM: 7507/208835 (2)PGDM: 1661/214681	ICD-9	ICD-9 codes 299.0, 299.8	RR (1)GDM: 1.24 (0.94, 1.65) (2)PGDM: 1.65 (1.01, 2.71)	NA
Dodds et al. (2011) Score 8	Canada	Cohort study	(1)GDM: 3474/126259 (2)PGDM:533/129200	ICD-9 or ICD-10 codes	ICD-9 code 299 or ICD 10 code F84	RR (1)GDM: 1.29 (0.90, 1.83) (2)PGDM: 1.98 (0.94, 4.16)	None
Krakowiak et al. (2012) Score 7	USA	Case-control study	63/763	The CHARGE Environmental Exposure Questionnaire, birthfiles, and medical records	The Autism Diagnostic Interview, Revised (ADI-R)29 and the Autism Diagnostic Observation Schedule (ADOS)	OR T2D or GDM : 1.52 (0.82, 2.83)	Mother's age at delivery, race/ethnicity, education level, delivery payer, calendar time, child's age at enrollment and gender, and catchment area
Lyall et al. (2012) Score 5	USA	Cohort study	2169/64276	Questionnaire	Questionnaire	OR GDM: 1.76 (1.34, 2.32)	Race, marital status, income, and spouse education, as well as age, AFB, and parity, and, when not being assessed as the complication of interest, twin births, pregnancy complications, induced abortions, and miscarriages

Table 1 (continued)

Study	Country	Study design	Sample size	Maternal diabetes criteria	ASD criteria	Effect size (95% CI)	Controlled variables
Connolly et al. (2016) Score 8	USA	Cohort study	2596/36717	The birth record data	ICD9 codescodes, and using natural language processing (NLP) techniques to gleam clinical concepts (including diagnoses) from free-text office visit notes	OR GDM: 1.56 (1.14, 2.11)	Maternal age at birth, maternal race, year of birth, and BMI
Li et al. (2016) Score 8	USA	Cohort study	(1) GDM: 87/1685 (2) PGDM:76/1685	Maternal medical records	ICD-9	HR (1) GDM: 1.86 (0.92, 3.76) (2) PGDM: 2.25 (1.14, 4.42)	Child year of birth, child gender, maternal age, parity, smoking during pregnancy, and preterm birth
Nahum Sacks et al. (2016) Score 8	Israel	Cohort study	12642/218629	ICD-9	ICD-9	OR GDM: 4.44 (1.55, 12.69)	Maternal age, obesity, preeclampsia, fertility treatment, gestational week, and time-to-event
Kong et al. (2018) Score 8	Finland	Cohort study	GDM: 33179/349150 PGDM: 1840/349150	(1) GDM: ICD-10 (2) PGDM: the Finnish Register on Reimbursement Drugs (RRD)	ICD-10	HR (BMI: 18.5–25) (1) GDM: 1.06 (0.88, 1.28) (2) PGDM: 0.54 (0.20, 1.44)	Offspring birth year, sex, perinatal problems, number of fetuses, cesarean delivery, maternal age group at delivery, parity, unmarried mother at birth, mother's country of birth, maternal smoking, maternal psychiatric disorder, maternal systemic inflammatory disease
Xiang et al. (2018b) Score 8	USA	Cohort study	GDM ≤ 26 wk: 11922/372924 GDM > 26 wk: 24505/372924 PT1D: 621/372924 PT2D: 9453/372924	ICD-9, antidiabetic medication use, and glucose values and/or oral glucose tolerance tests	ICD-9 codes299.x or equivalent KPSC codes	HR (1) GDM ≤ 26 wk: 1.26 (1.08, 1.47) (2) GDM > 26 wk: 0.98 (0.87, 1.10) (3) PT1D: 2.33 (1.29, 4.21) (4) PT2D: 1.26 (1.18, 1.62)	Birth year, maternal age, parity, education, median household income based on census tract of residence, self-reported race/ethnicity, history of comorbidity (≥ 1 diagnosis of heart, lung, kidney, or liver disease; cancer); and sex of the child
Chien et al. (2019) Score 5	China	Case-control study	15/1812	100 g glucose tolerance test	DSM-IV	OR GDM: 1.78 (0.52, 6.12)	Sex, age, and maternal age upon delivery

Table 1 (continued)

Study	Country	Study design	Sample size	Maternal diabetes criteria	ASD criteria	Effect size (95% CI)	Controlled variables
Cordero et al. (2019) Score 8	USA	Case-control study	143/1529	Prenatal care records; telephone interview; self-administered checklists of the mother's medical history	Screened for autism symptoms using the social communication Questionnaire; developmental assessments; the Autism Diagnostic Observation Schedule; the Autism Diagnostic Interview-Revised	OR GDM: 0.96 (0.67, 1.38)	Maternal age, BMI, maternal race/ethnicity, maternal education, maternal smoking, and study site
Jo et al. (2019) Score 8	USA	Cohort study	GDM ≥ 24 wk: 16112/221330 GDM < 24 wk: 4893/221330 PT2D: 4085/221330	ICD-9 codes, antidiabetic medication use, and glucose values from 1-hour 50-g glucos challenge tests and/or oral glucose tolerance tests administered during pregnancy	ICD-9 codes 299.x or equivalent KPSC codes from the KPSC electronic medical records	HR (1) GDM ≥ 24 wk: 0.92 (0.77, 1.09) (2) GDM < 24 wk: 1.24 (0.95, 1.62) (3) PT2D: 1.45 (1.11, 1.91)	Birth year, KPSC medical center service areas, maternal age, parity, maternal race/ethnicity, maternal education, census tract median household income, maternal history of comorbidities before pregnancy (≥ 1 diagnosis of heart, lung, kidney, liver disease or cancer), child sex, and family

ASD autism spectrum disorders; *CI* confidence interval; *ICD* the International Classification of Diseases; *OR* odds ratio; *DM* diabetes mellitus; *ICD-9-CM* the International Classification of Diseases, Ninth Revision, Clinical Modification; *T1D* type 1 diabetes mellitus; *GDM* gestational diabetes mellitus; *PGDM* pregestational diabetes mellitus; *RR* relative risk; *NA* not available; *CHARGE* Childhood Autism Risks from Genetics and the Environment; *ADI-R* Autism Diagnostic Interview, Revised; *T2D* type 2 diabetes mellitus; *HR* hazard ratio; *BMI* body mass index; *PT1D* preexisting type 1 diabetes mellitus; *PT2D* preexisting type 2 diabetes mellitus; *KPSK* Kaiser Permanente Southern California; *DSM* Diagnostic and Statistical Manual of Mental Disorders; *KPSC* Kaiser Permanente Southern California

[a]The score represents study quality which was assessed by Newcastle-Ottawa Scale

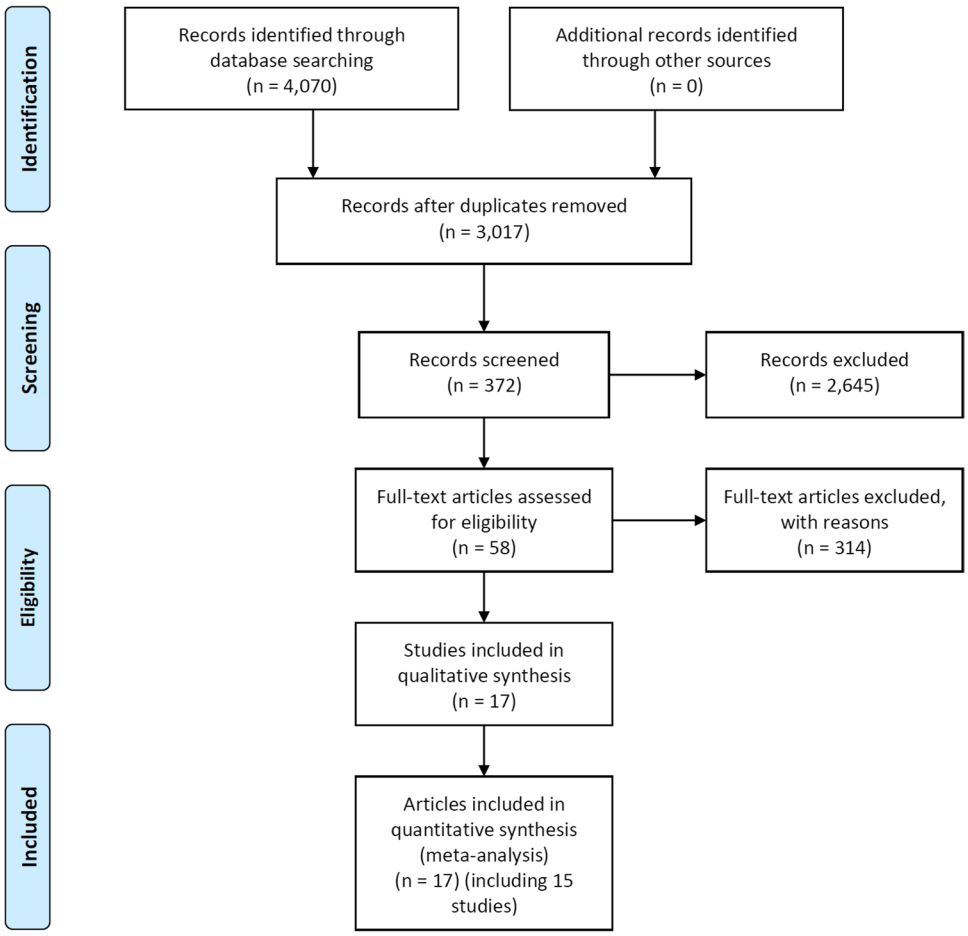

Fig. 1 Flow chart of the study selection

two in Canada (Burstyn et al., 2010; Dodds et al., 2011), and others were in Israel (Nahum Sacks et al., 2016), Finland (Kong et al., 2018), and China (Chien et al., 2019). Each study explored the effect of different diagnosis time of maternal diabetes exposure during pregnancy on the occurrence of ASD in offspring, including those diagnosed during pregnancy (Lyall et al., 2012; Connolly et al., 2016; Nahum Sacks et al., 2016; Chien et al., 2019), mixed diagnosed before and during pregnancy (Hultman et al., 2002; Buchmayer et al., 2009; Krakowiak et al., 2012; Cordero et al., 2019), data of two diagnosis time presented separately (Xiang et al., 2018b; Kong et al., 2018; Burstyn et al., 2010; Dodds et al., 2011; Li et al., 2016; Jo et al., 2019), and some were not differentiated (Croen et al., 2005). The quality of included studies was at the upper-middle level based on the Newcastle-Ottawa Scale. Thirteen articles were considered high quality with 7–9 stars (Xiang et al., 2018b; Kong et al., 2018; Burstyn et al., 2010; Dodds et al., 2011; Connolly et al., 2016; Li et al., 2016; Nahum Sacks et al., 2016; Jo et al., 2019; Hultman et al., 2002; Croen et al., 2005; Buchmayer et al., 2009; Krakowiak et al., 2012; Cordero et al., 2019), while the other two were of moderate quality with 4–6 stars (Lyall et al., 2012; Chien et al., 2019). The specific score of study quality assessed by the Newcastle-Ottawa Scale, diagnostic criteria for maternal diabetes, diagnostic criteria of ASD, the risk estimate, and the covariates adjusted during calculation are listed in Table 1 and Supplementary Table 2 and 3.

Maternal Diabetes and Risk of ASD in Offspring

As Fig. 2 shows, the overall analysis found maternal diabetes increased the risk of ASD (the pooled risk estimate was 1.30 (95% CIL 1.16–1.46), with significant heterogeneity ($I^2 = 62.8\%$, $P < 0.001$)). There was no publication bias based on the funnel plot and the Egger test ($P = 0.835$). We conducted a sensitivity analysis and found the result did not change substantially when studies were eliminated one by one (data not shown).

Based on the subgroup analysis by study design, cohort studies showed a positive relationship (1.32, 1.17–1.49), with significant heterogeneity ($I^2 = 69.9\%$, $P < 0.001$)), while case-control studies showed a negative result (1.17, 0.89–1.55) with no significant heterogeneity ($I^2 = 7.3\%$, $P = 0.370$)) (Supplementary Fig. 1).

Then, after removing studies with mixed diagnosed before and during pregnancy and with undifferentiated

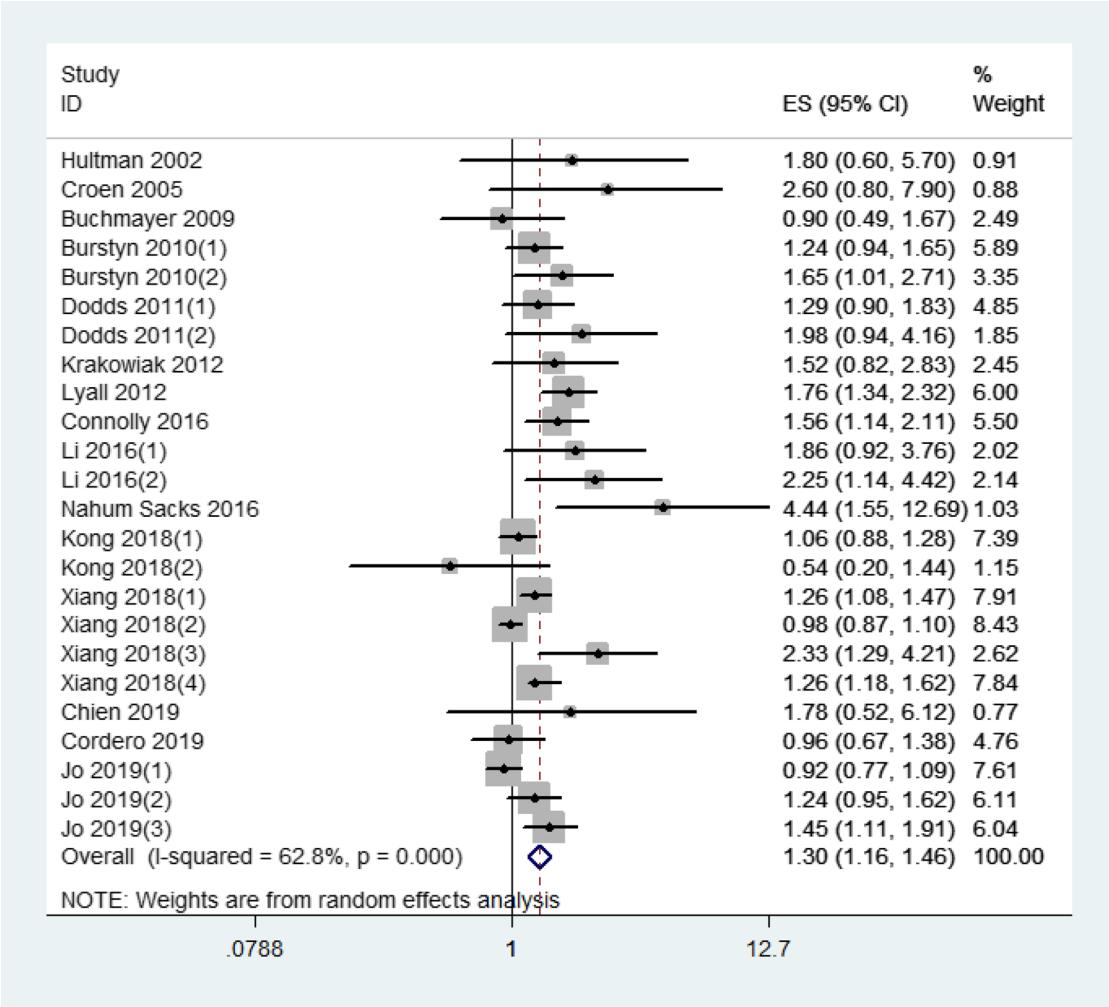

Fig. 2 Forest plot of overall analysis (including cohort studies and case-control studies) about ASD in offspring of mothers with maternal diabetes (including both pregestational diabetes and gestational diabetes). Each point represents a separate study for the indicated association

diagnosis time, we conducted a subgroup analysis by diagnosis time of maternal diabetes. We found that diabetes diagnosed before pregnancy heightened the risk of ASD in offspring by 51% (95% CI: 1.20–1.89), and diagnosis after pregnancy increased the risk by 25% (95% CI: 1.09–1.44) (Supplementary Fig. 2). The results are consistent with analysis results in cohort studies (before pregnancy: 1.51, 95% CI: 1.20–1.89; after pregnancy: 1.25, 95% CI: 1.08–1.44) (Supplementary Fig. 3).

Antidiabetic Medication Exposure and Risk of ASD in Offspring

We explored the relationship between antidiabetic medication exposure and risk of ASD in offspring, although the number of relevant studies assessing this was relatively small. Compared with controls not exposed to maternal diabetes in utero, antidiabetic medication exposure increased the risk of ASD in offspring by 48% (95% CI: 1.05–2.08) (Fig. 3A). Additionally, compared with the group exposed to maternal diabetes in utero but without antidiabetic medication, antidiabetic medication exposure also increased the risk of ASD in offspring by 42% (95% CI: 1.15–1.76) (Fig. 3B).

Discussion

We found that maternal diabetes (both pregestational and gestational diabetes) is associated with a heightened risk of ASD in offspring in this meta-analysis. This positive association was only shown in cohort studies and not in case-control studies. Since the sample size of each case-control study included was only in the thousands, while cohort

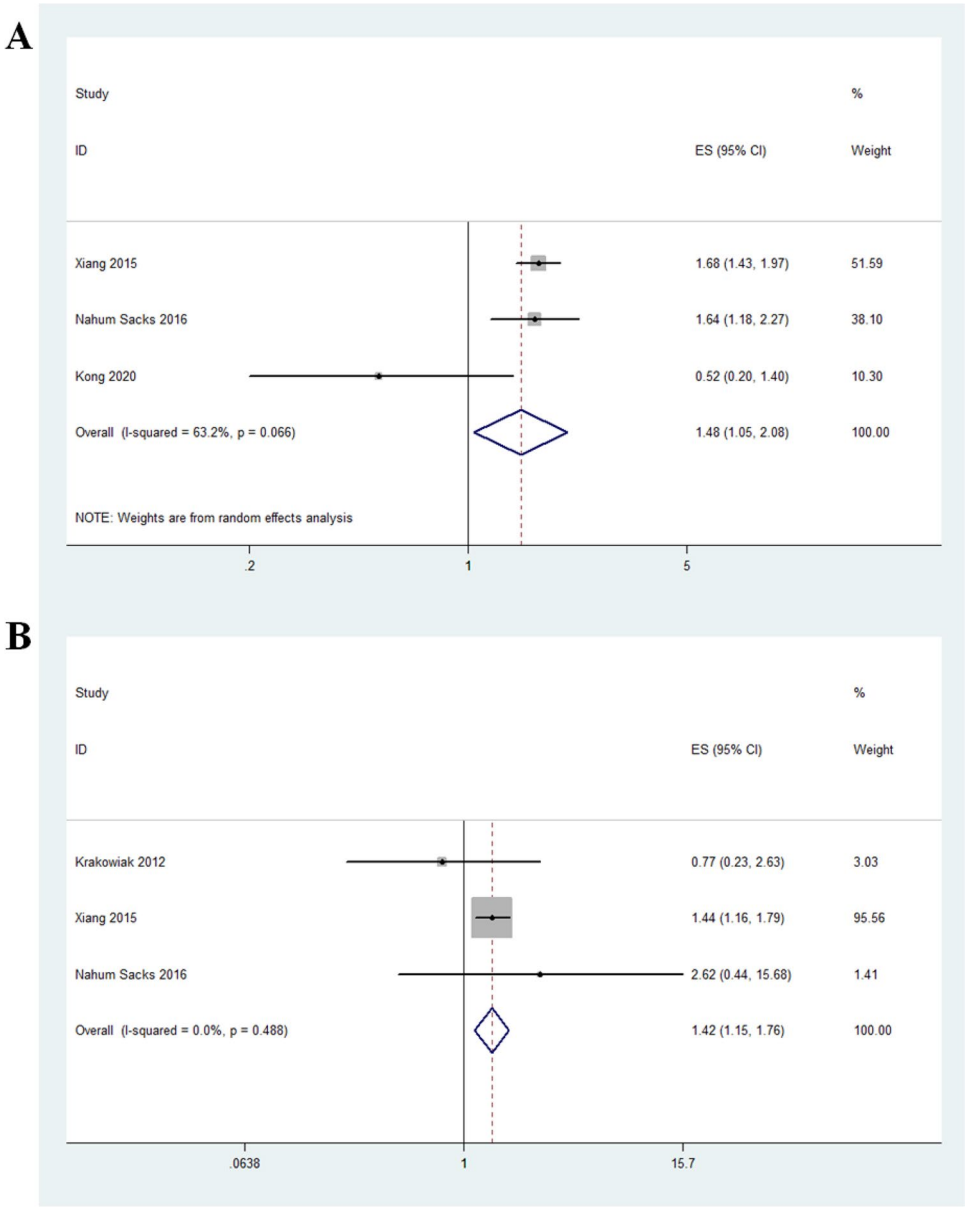

Fig. 3 Forest plot of ASD in offspring of mothers with maternal diabetes treated with antidiabetic medication compared to others. **A** Compared to controls not exposed to maternal diabetes. **B** Compared to a group exposed to maternal diabetes without antidiabetic medication

studies can reach hundreds of thousands, we hypothesize that sample size may be an important factor for the negative result of case-control studies. Of course, more large-sample population studies are needed for further verification.

Our results are consistent with previously published meta-analyses (Xu et al., 2014; Wan et al., 2018; Yamamoto et al., 2019). Wan et al. reported the relationship between ASD in offspring and maternal diabetes and analyzed all types as a whole, and they also found a positive result in case-control studies (Wan et al., 2018). Yamamoto et al. only explored the effect of exposure to pre-existing maternal diabetes in pregnancy (Yamamoto et al., 2019). Xu et al. showed results based on the type of study (cohort or case-control study) and the time of diabetes diagnosis (before or during pregnancy) (Xu et al., 2014). The difference between that study and ours is that they also showed an association between ASD in offspring and maternal diabetes during pregnancy in case-control studies. The mixed cases of maternal diabetes diagnosed before and during pregnancy presented a negative result in our study (Xu et al., 2014).

In addition, this study revealed that exposure to maternal diabetes with antidiabetic medication in pregnancy increased the risk of ASD in offspring, although the number of included literature was limited. Xiang et al. reported a similar result and showed that gestational diabetes (GDM) requiring antidiabetic medication increased the risk of ADHD in offspring (Xiang et al., 2018a). Unless bound to antibodies, insulin, as a leading drug in the treatment of diabetes, does not pass the placental barrier (Menon et al., 1990). Therefore, it is unlikely to affect the development of

the fetus directly. It has been reported that insulin is associated with the development of ASD by activating specific biological signaling pathways in neurons (Khanh et al., 2014). From another perspective, maternal diabetes requiring medical treatment represents a more severe condition than relatively severe hyperglycemia. Thus, in essence, this positive correlation might be caused by exposure to maternal diabetes. More in-depth research is required to explore the mechanisms involved in this process.

Our research confirmed the 'DOHaD' (the Developmental Origins of Health and Disease) concept, which states that the occurrence of many adult diseases is closely related to early life development, especially during some intrauterine critical and sensitive periods (Barker & Osmond, 1986). Maternal diabetes during pregnancy creates a hypoglycemia environment in utero, which may increase the possibility of ASD in offspring. Several underlying biological mechanisms have been proposed to explain this association. First, intrauterine hyperglycemia can lead to apoptosis, hypoxia, chronic inflammation, oxidative stress, and free-radical production (Reece et al., 2005; Eidelman & Samueloff, 2002; Biri et al., 2006). Besides, antidiabetic mediation, such as insulin used to regulate blood sugar levels, may also contribute to developmental disabilities, as mentioned above (Khanh et al., 2014). An animal study found chronic hyperglycemia in pregnancy may change the offspring's normal hippocampal development and behavior through increasing RAGE signaling in the brain (Chandna et al., 2015). In addition, epigenetics may be another potentially important mechanism. It has been reported that DNA methylation variations in some genes can affect neurodevelopmental and peroxisomal processes, thereby participating in the stability and maturity of cortical circuits (Walton et al., 2017). On the other hand, the epigenome of the embryo itself is also a critical affected aspect, which can increase the disease susceptibility of the offspring (Fujiki et al., 2009). What is more, neonatal composite caused by maternal diabetes may also be important: prematurity, neonatal hypoglycemia (Owens et al., 2015), as well as overweight and obesity (Kahathuduwa et al., 2019), which remains to be explored.

This meta-analysis benefits from a standard protocol for review, broad inclusion criteria, and rigorous information collection and methodology, enabling a comprehensive estimation of relevant literature. Some limitations of our study should be acknowledged. Limited by the data source only derived from published articles (the conference articles were not included), there might be a negative impact on our analysis. Firstly, the risk estimates used in each article are not the same, including three forms (OR with 95% CI, RR with 95% CI, and HR with 95% CI). Secondly, the types of considered covariates were inconsistent in different studies. Potential covariates that may lead to large deviations were also not taken into account in some studies, especially for paternal factors. Family studies found that ASD aggregates in families, and both parental factors affect the development of ASD (Sandin et al., 2014). Paternal mental illness was significantly associated with ASD, although paternal diagnosis seemed to have less effect than maternal psychiatric diagnosis (Yu et al., 2022). What is more, paternal IQ and age also be potential factors for ASD in offspring (Reichenberg et al., 2006; Gardner et al., 2020). Unfortunately, the available data did not allow us to consider paternal factors, which may have an impact on the results of our study. It is expected that more original studies will further explore this issue. Thirdly, the diagnostic criteria of diabetes and ASD and information sources were different in each study. Fourthly, considering the pathological mechanisms are not precisely the same, the type of diabetes should also be used as an important grouping basis for subgroup analysis. Examples of that included type 1 and type 2 diabetes, which should be separately assessed and discussed. Lastly, few studies reported the relationship between antidiabetic mediation and the occurrence of ASD in offspring, and the role of glycemic control has not been explored extensively, which could be a modifiable risk factor during nursing and treatment, as well as the postnatal care of the children.

Conclusions

In conclusion, exposure to maternal diabetes (both pregestational and gestational diabetes) is associated with an increased risk of ASD in offspring, as assessed by cohort studies. Antidiabetic medication may be another potential risk factor for ASD in offspring. However, limited by the amount of reliable information, these findings must be interpreted with caution. More studies are needed to explore this topic, especially considering controllable factors, such as anti-diabetic medication and glycemic control.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40489-023-00380-8.

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Declarations

Competing Interest The authors declare no competing interests.

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