Association of maternal diabetes with autism spectrum disorders in offspring

A systematic review and meta-analysis

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Abstract

Studies on the association of maternal diabetes with autism spectrum disorders (ASDs) in offspring provide inconsistent findings; therefore an updated and comprehensive literature review and meta-analysis is necessary to perform in order to evaluate the available evidences.

After searching databases systematically, we established the inclusion criteria and selected the eligible studies. In both overall and stratified analyses, the estimated effects were synthesized dependent on the presence or absence of heterogeneity.

Twelve articles involving 16 studies were included and synthesized, demonstrating a significant association of maternal diabetes with ASDs among children (relative risk [RR]=1.48). However, high heterogeneity was observed ($I^2=56.3\%$) and publication bias was identified. In terms of the analyses on reliable evidences from case-control studies, heterogeneity and publication bias disappeared, and the risk of ASDs was increased by 62% among diabetic mothers compared with non-diabetic mothers.

Maternal diabetes, especially gestational diabetes mellitus, is associated with ASDs in offspring based on a limited number of convincing case-control studies. More large-scale population-based prospective studies are still needed to draw firm conclusions.

Abbreviations: ASDs = autism spectrum disorders, GDM = gestational diabetes mellitus, PDDs = pervasive developmental disorders, RR = relative risk.

Keywords: autism spectrum disorders, maternal diabetes, meta-analysis, risk factor

1. Introduction

Autism spectrum disorders (ASDs) are defined as neurodevelopmental disorders manifested with persistent impairments in social interaction and communications and restricted and repetitive patterns of behaviors, interests, or activities.[1] In addition to these common manifestations, a series of pilot studies has innovatively revealed significant deficits in executive functions,[2] sensory perception,[3] sleep habits,[4] and autonomic regulation[5] among children with ASDs. Autistic disorder, including Asperger syndrome and pervasive developmental disorders (PDDs), is the most severe form of ASDs. A recent meta-analysis reports an estimated 52 million cases of ASDs in 2010, indicating a prevalence of 7.6 per 1000.[6] The diagnosis of ASDs has increased substantially over time.[7] Although this increment may be caused by increased public awareness and changing diagnostic standard, it is also possible that a true rise is occurring.[8] The causes and contributing factors for autism are poorly understood. Conventional knowledge indicates autism is a neurobiological disorder of development with strong genetic basis.[9] Furthermore, accumulating evidences provide a novel insight that prenatal environmental factors are associated with ASD via affecting fetal brain development.[10,11]

During gestation, a hyperglycemic environment of intrauterine negatively impacts the development of fetal brain.[12] With the constantly growing prevalence of maternal diabetes,[13] it is plausible to observe a parallel rise in ASD diagnosis over years. The association of maternal diabetes with ASD in offspring has been evaluated by several case-control or cohort studies, with controversial conclusions.[1,14–24] For example, a prospective birth study in 2016 (N=2743 mother–child pair) showed a weak association of gestational diabetes mellitus (GDM) with ASD (hazard ratio [HR] 1.86; 95% confidence interval [CI] 0.92–3.76) after adjusting crucial variables.[21] On the contrary, a retrospective longitudinal cohort study based on larger sample size (N=322,323) revealed that GDM was not related to ASD (HR, 1.04; 95% CI, 0.91–1.19).[31] Therefore, it is necessary to obtain more data to evaluate the relationship between maternal diabetes and ASD in offspring. In this study, we comprehensively searched electronic databases until June 2017 to identify all the available investigations, and conducted a meta-analysis to reassess the possible risk of ASD in offspring conferred by maternal diabetes.

2. Methods

The study doesn’t involve any patients and animals. Ethical approval and patient consent is not applicable.
2.1. Literature search and identification of eligible studies

A comprehensive literature search in the electronic databases (PubMed and Web of Science) was performed to identify all the relevant studies. The key words were “autism,” “autism spectrum disorder,” “ASD,” “Asperger syndrome,” “pervasive developmental disorder,” “PDD,” and “maternal diabetes.” Initially, the irrelevant records were removed according to title and abstract screening. The remaining articles were manually checked based on the inclusion criteria. The inclusion criteria were: original article; case-control study or cohort study aimed to investigate the relationship between risk of ASD in offspring and maternal diabetes; effect size such as odds ratio (OR), relative risk (RR), or hazard ratio (HR), with 95% confidence interval (95% CI) was provided, otherwise the number of participants in exposure/non-exposure group for cohort study, or in case/control group for case-control study must be presented. When a cohort was reported in articles repeatedly, the newest publication was selected in order to avoid inclusion of overlapping data. Review, editorial, conference article, or comment were excluded.

2.2. Data extraction and quality assessment

The following items were extracted by 2 investigators independently: first author, publication year, study design, characteristics of the participants, diagnostic standards of ASD and maternal diabetes, effect size with 95% CI (preferentially adjusted effect size), and controlled covariates. Effect size was manually calculated from the original data when necessary. Any disagreement was resolved by further discussion.

The quality of eligible study was evaluated based on Newcastle-Ottawa Scale.[23] A “star system” was used to judge the quality of study on 3 broad perspectives: the selection of the study groups (4 stars); the comparability of the groups (2 stars); and the ascertainment of either the exposure for case-control study, or of the outcome of interest for cohort study (3 stars). Studies with 0 to 3, 4 to 6, or 7 to 9 stars were designated as low, moderate, and high quality, respectively.

2.3. Data synthesis

The heterogeneity within studies was assessed with Q-statistic, in which the significance level was defined as 0.1.[26] The extent of the inconsistency was measured by I² value, which indicated the percent of the total variance across studies due to heterogeneity rather than chance. Heterogeneity was classified into high, medium, or low, represented as odds ratio (OR), relative risk (RR), or hazard ratio (HR), with 95% confidence interval (95% CI) was provided, otherwise the number of participants in exposure/non-exposure group for cohort study, or in case/control group for case-control study must be presented. When a cohort was reported in articles repeatedly, the newest publication was selected in order to avoid inclusion of overlapping data. Review, editorial, conference article, or comment were excluded.

The overall analysis demonstrated that gestational diabetes increased the risk of ASD by 48% (RR: 1.48; 95% CI: 1.26–1.75) (Table 2, Fig. 2). However, this result was unstable due to presence of inconsistency (I² = 56.3%, P = .003) and publication bias (P = .001). In order to find more stable results, we subsequently performed several stratified analyses, as shown in Table 2. The data pooling of the 8 articles that reported OR as effect size[15,17,19,20,22–24,33] did not show heterogeneity (I² = 31.8%, P = .174), nor publication bias (P = .351). In this strata, the risk was relatively higher, accounting for OR of 1.67 (95% CI: 1.40–1.99). However, the combinations of the studies reporting RR values[16,18] or HR values[1,21] presented either heterogeneity or publication bias. In addition, we also performed subgroup analyses based on type of diabetes, study design, country, and study quality. For more details, see Table 2.

3. Results

3.1. Selection of eligible studies and characteristics of the included studies

As illustrated in Fig. 1, 188 records were initially found through database searching. After removal of duplicated records, 79 studies were screened according to titles and abstracts and 61 of them were excluded. Then the remaining 18 articles were reviewed. Two of them[29,30] were excluded due to insufficient data; 2 of them[15,21] reported the same Swedish population, therefore dropping the older one[31]; and another 2 studies[14,32] were excluded because the entire national populations were chosen as control groups. Finally, a total of 12 eligible articles[11–14,17–24,31,33] were selected in the meta-analysis.

Among the 12 articles, 7 were case-control studies[15,17,19,20,22,24,31] and 5 were cohort study.[11,16,18,21,23] Most of the studies were conducted in USA[1,17,19,21,22,24] and the rest were from Sweden,[15] Israel,[23] Australia,[20] and Egypt.[33] Therefore, findings in the present study might be restricted to specific populations. The majority of the included studies reported estimated effects after adjusting crucial variables, except studies of Dodds et al.[18] Elhameed et al.[33] and Piven et al.[24] The diagnostic criteria of ASD and maternal diabetes were clarified in each study (Table 1).

3.2. Meta-analyses on maternal diabetes and risk of ASD in offspring

3.3. Meta-analyses on maternal diabetes and risk of ASD in offspring based on moderate and high-quality case-control studies

Of note, based on the stratified analyses, the pooled case-control studies did not present inconsistent and publication bias. But the strata combining cohort studies showed both of them. Therefore,
| Study                      | Participants’ characteristics                                                                 | ASD diagnosis                                                                 | Diabetes diagnosis                                                                 | Effect size (95% CI) | Controlled variables                                                                 |
|---------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------|--------------------------------------------------------------------------------------|
| Buchmayer et al [5]       | Score 9: Cases were from records in the SHD between 1987 and 2005 (N = 1216). For each case subject, 5 controls from SHD who were matched individually regarding sex, birth year and birth hospital were randomly selected (N = 6080). | National screening for developmental disorders, further confirmation by child psychiatric specialist unit. | Maternal medical records                                                      | OR diabetes: 0.90   | (0.49, 1.67)                                                             | Maternal age, smoking, maternal country of birth, whether the mother lived with the father, and maternal schizophrenia                                        |
| Burstyn et al [6]         | Score 6: Children who were unambiguously matched in the AHPI files to AHPI records were follow-up by AHPI until March 31, 2008 (N = 218,890). Lost to follow-up rate was 10.4%. | ICD-9 codes 299.0, 299.8                                                     | AHPH records                                                                     | RR PGDM: 1.65 (1.01, | 2.11)                                                                                  | Maternal age, BMI, bleeding, smoking, poor weight gain, parity, socioeconomic status of mother, type of labor, gestational age, birth weight, age, and catchment area |
| Connolly et al [7]        | Score 6: Cases were selected from medical records of CCHMC from 2009 to 2014 (N = 503). Controls were from Ohio state birth records from 1989 to 2013 (N = 36,810). | Comprehensiveness and multidisciplinary evaluation                           | Birth record data                                                                | OR DM: 2.32           | (1.93, 2.77)                                                             | Maternal age, race, BMI                                                                 |
| Dodds et al [8]           | Score 7: All live births from the Nova Scotia After Perinatal Databases, which included all hospital births of ≥500g, or 20 weeks gestation or greater, between January 1, 1990 and December 31, 2002 (N = 129,733). | ICD-9 code 299 or ICD-10 code F84 from a primary or secondary field in database. | Optimally scale                                                                  | RR PGDM: 1.98 (0.94, | 4.16)                                                                                  | None                                                                                   |
| Elnaamde et al [9]        | Score 3: Cases were autistic children attending the JBAO in Minia, Egypt (N = 16). Controls were the siblings of those autistic children (N = 28). | CARS                                                                           | Questionnaire                                                                    | OR DM: 6.33 (0.24, | 165.89)                                                                 | None                                                                                   |
| Krakowiak et al [10]      | Score 7: This study was based on the CHARGE study. Cases were children with ASD identified through multiple centers (N = 517). Controls were identified from state birth files, frequency-matching to age, sex, and region (N = 315). | ADI-R and ADOS by trained clinicians                                            | CHARGE environmental exposure questionnaire                                        | OR DM: 1.52 (0.82, | 2.63)                                                                                  | Mother’s age at delivery, race, ethnicity, education level, delivery payer, calendar time, child’s age at enrolment and sex, and catchment area |
| Leonard et al [11]        | Score 6: Cases were ASD children identified from multiple sources (N = 191). The children considered to have biomedical cause for intellectual disability were included. Controls were children without intellectual disability between 1983 and 1992 and alive in 2002 (N = 236,964). | DSM-V                                                                          | ICD-9 codes for GDM (6488) and PGDM (350, 6480)                                  | OR DM: 2.95 (1.30, | 6.73)                                                                                  | Infant sex, birth order, maternal ethnicity, age group, marital status, income, education, parity, gestational age, and birth weight, and catchment area |
| Li et al [12]             | Score 6: Two thousand seven hundred thirty four mother–child pairs, a subset from BBC from 1998 to 2014 who had at least 1 prenatal follow-up. The median length follow-up time was 6.9 years. | Electronic medical records, ICD-9 codes 299.x                                 | Maternal medical records                                                      | HR PGDM: 2.25 (1.14, | 4.45)                                                                                  | Child year of birth, child sex, maternal age, parity, smoking during pregnancy, preterm birth |
| Lyall et al [13]          | Score 4: The NHS II cohort consists of female nurses (N = 66,445) aged 25 to 42 recruited in 1989. A total of 793 mothers reported having a child with ASD. | Questionnaire report of having a child with ASD                               | Questionnaire                                                                    | OR DM: 1.76 (1.34, | 2.32)                                                                                  | Race, marital status, income, education, parity, age-at-first-birth                       |
| Nahum et al [14]          | Score 5: Non-selective population-based cohort from the solo hospital of the Southern region of Israel from 1991 to 2014 (N = 231,271). GDM exposure = 12,642; comparison = 218,629. | ICD-9 codes 299.x                                                             | Not specified                                                                     | OR DM: 4.44 (1.55, | 12.69)                                                                                  | Maternal age, obesity, preclampsia, fertility treatment, gestational week, time-to-event |
| Piven et al [15]          | Score 5: Autistic probands (N = 53) and their siblings (N = 63), who were consecutively enrolled in a study were included. | ADI and ADOS                                                                   | Standard questionnaire and delivery record                                         | OR DM: 3.08 (0.12, | 77.91)                                                                                  | None                                                                                   |
| Xiang et al [16]          | Score 7: Singleton children born at 28 to 44 weeks’ gestation in KPSC hospitals between January 1, 1995 and December 31, 2009 (N = 322, 323). GDM exposure = 25,035; PGDM exposure = 6486; comparison = 290,792. | Pediatric developmental specialist evaluations                                  | Laboratory tests                                                                | HR PGDM: 1.33 (1.07, | 1.66)                                                                                  | Maternal age, parity, education, household income, race, history of comorbidity, child sex |

ADI-R = Autism Diagnostic Interview, Revised (ADI-R); ADOS = Autism Diagnostic Observation Schedule; GDM = Gestational Diabetes; PGDM = Pregestational Diabetes; BMI = Body Mass Index; HR = Hazard Ratio; GDM = Gestational Diabetes Mellitus; P-value = P-value for entry into model; NA = Not Available; OR = Odds Ratio; CI = Confidence Interval; APHP = Alberta Perinatal Hospital Program; BBC = British Birth Cohort; CARS = Childhood Autism Rating Scale; CC = Cincinnati Children’s Hospital Medical Center; CHARGE = Childhood Autism Risks From Genetics and the environment; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-V = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; G8DS = Autism Spectrum Disorder; G8DS = Autism Spectrum Disorder; SCA = Social Communication Assessment; SCA = Social Communication Assessment; SHDR = Shanghai Women and Children’s Hospital; Screening Questionnaire OR GDM: 4.44 (1.55, 12.69); Screening Questionnaire OR GDM: 4.44 (1.55, 12.69); Screening Questionnaire OR GDM: 4.44 (1.55, 12.69); Screening Questionnaire OR GDM: 4.44 (1.55, 12.69).
the case-control studies seemed to be an ideal source of reliable and consistent evidences, from which we could draw a more robust conclusion.

Thus, another group of meta-analyses synthesized case-control studies with moderate\[17,20,22,24\] or high quality.\[15,19\] Generally, the combined data indicated that maternal diabetes could increase the risk of ASD by 62% (RR: 1.62; 95% CI: 1.35–1.94) (Table 3, Fig. 3), without detecting significant heterogeneity ($I^2=0.0\%$, $P=0.859$), while the estimated effect was higher (RR: 1.72; 95% CI: 1.34–2.21; Table 3).

**4. Discussion**

In the present study, it was demonstrated that maternal diabetes was associated with an increased risk of ASD in offspring (RR: 1.48; 95% CI: 1.26–1.75). This was consistent with the results of 2 previous meta-analyses.\[34,35\] However, moderate heterogeneity ($I^2=56.3\%$) and significant publication bias ($P<.001$) were also observed, therefore, we conducted several subgroup analyses to find more rigorous and reliable results. On the one hand, the combined data from retrospective studies revealed an unfavorable effect of gestational diabetes (RR: 1.62; 95% CI: 1.36–1.94), without detecting heterogeneity and publication bias. This result was in line with other retrospective studies based on large sample size. For example, a study involving 231,271 individuals demonstrated that GDM was associated with 3.44-fold higher risk of ASD in offspring and this impact was independent of crucial covariates such as maternal age, obesity, and gestational week.\[23\] Another retrospective study recruited >40,000 participants and consistently found an adverse effect, showing a 0.56-fold increased risk among mothers with GDM.\[17\] The studies reporting null results were often based on small sample size and flawed design.\[24,33\] On the other hand, in the subgroup combining prospective studies, both heterogeneity ($I^2=59.0\%$) and publication bias ($P<.001$) were detected. Hence, a robust conclusion was unlikely to be drawn by synthesizing cohorts. Nevertheless, each high-quality prospective study is capable to provide us with reliable evidences that support the association and clarify the temporal relationship of it. A large cohort included 322,323 individuals and found significant risks of ASD among women with pre-existing DM (HR = 1.21) and GDM by 26 weeks’ gestation (HR = 1.39) after adjustment of crucial variables.\[11\]

The majority of the included studies clarified the time of DM diagnosis and separated pregestational DM from GDM. Thus, we further evaluated whether the temporal relationship between DM diagnosis and conception was a determinant for higher ASD risk. Surprisingly, we found that both pregestational (RR = 1.63; $I^2=75.2\%$) and gestational DM (RR = 1.63; $I^2=59.0\%$) were associated with ASD. Since heterogeneity and publication bias were detected, we did not believe the result was reliable, so we reassessed the results derived from trustworthy (moderate and high quality) case-control studies. In this scenario, GDM was identified as a risk factor (RR = 1.72), without detecting heterogeneity and publication bias. No quality case-control study aimed to investigate the role of pregestational DM.

Since the history of gestational complications was commonly obtained by questionnaires, recall bias might occur. Fortunately, the majority of the convincing case-control studies used medical record data,\[11,17,20,24\] thus recall bias was probably prevented. Regarding the studies using questionnaires,\[19,25\] a recent validation study demonstrated that, for etiological study, self-
reported diabetes during periconception showed high validity among mothers compared with medical records. In addition, diabetic mothers should be aware of the intensive management of this disease during pregnancy, the changes in diet and lifestyle, and the medication for glycemic control. Therefore, we were confident that the quality case-control studies provided with rigorous diagnosis of pregnant complications.

Although robust epidemiological evidences are limited and findings are controversial, several biological mechanisms are proposed in order to elucidate how DM may cause brain malformation and aberrant neurodevelopment, which in turn supports our findings. In a diabetic mouse model that mimicking pregestational DM, abnormal morphogenesis, and histological structure of brain in mouse fetuses were identified. Enhanced cell apoptosis and activated oxidative stress were detected in mouse fetal brains, where Nrf2 signaling played a crucial role. The role of oxidative stress on pathogenesis of autism was further supported by idiopathic autism mouse model. It was demonstrated that gestational exposure to chemical trigger of oxidative stress strengthened some of the autistic-like traits, including delayed motor maturation and increased vocalization rate. Apart from oxidative stress, dysregulated immune responses during fetal neurodevelopment are also believed to participate in pathogenesis of ASD. A case-control study, as a part of the CHARGE (Childhood Autism Risks from Genetics and Environment) study, described a direct relationship between maternal autoantibodies and the risk of developing of autism. The presence of autoantibodies to fetal brain proteins at 37 and 73 kDa occurred significantly more often among mothers of autism children, compared with 2 distinct control populations. Further, the presence of autoantibodies correlated with the specific behaviors within autism, including expressive language and irritability.

The present study should be treated with caution because of some limitations. First, the included case-control studies were commonly based on hospital. Only a few investigations recruited controls from possible source population. For example, Connolly et al recruited control individuals from the birth records of Ohio state. Similarly, Krakowiak et al selected controls from state birth files. However, the representativeness of state birth data was unknown. So more community-based studies are encouraged. Second, several included studies did not consider potential covariates when analyzing the association. If these univariate studies were excluded, the overall estimated effect was still statistically significant (RR: 39%; 95% CI: 1.17–1.65), but relatively lower than the result given above (1.39 vs 1.48). It is noteworthy that some of the variables are strongly correlated to risk of ASD. For example, maternal obesity was related to an increased risk of ASD in offspring, according to recent meta-analytic studies. Furthermore, the risk of ASD was greater when obesity and diabetes occurred concomitantly. So studies that took potential covariates into account were more likely to reveal the true effect of maternal diabetes. To overcome this obstacle, we extracted the estimated effects that were adjusted by controlled variables. Third, the severity and type of maternal diabetes was ignored by the majority of the studies. Regarding to the effect of severity, 1 included study revealed that the risk of ASD conferred by mild diabetes (OR = 1.83, 95% CI = 1.53–2.19) was greater than that conferred by severe diabetes (OR = 1.64, 95% CI = 1.18–2.27). Considering the number of mild diabetes cases (N = 10,076) was nearly 4 times larger than that of severe diabetes cases (N = 2,566), this result needs to be confirmed by further studies. Regarding the type of diabetes, there were only 2 studies clearly reported the recruited cases were diagnosed with type 2 DM. Due to insufficient evidences we could not perform data synthesis, so we expect more studies reporting these characteristics and believe that introduction of biological markers that are capable to accurately describe severity, such as insulin and glucose level, would be of assistance.

In conclusion, convincing case-control studies suggest that maternal diabetes, especially GDM, is associated with an increased risk of ASD in offspring. Given the limited number of reliable evidences, more well-designed prospective studies,

Figure 2. Meta-analysis of all included studies. (A) Forest plot of the meta-analysis; (B) funnel plot of the meta-analysis; (C) sensitivity analysis.
with standardized recruitment criteria, and rigorous diagnostic process, are needed to confirm this finding.

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