

The association of maternal diabetes with attention deficit and hyperactivity disorder in offspring: a meta-analysis

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Objective: Recent controversial evidence suggests that maternal diabetes may increase the risk of attention deficit and hyperactivity disorder (ADHD) in offspring. To examine this potential association, a systematic literature search and meta-analysis was performed.

Methods: OR or risk ratio (RR) from each study was obtained and combined for evaluating the risk. Six cohort studies and three case-control studies were included in the present study.

Results: The meta-analysis of the highly heterogeneous case-control studies did not find significant association between maternal diabetes and ADHD risk (OR: 1.20, 95% CI: 0.96–1.49). The combining of the cohort studies demonstrated that offspring of diabetic mothers were at higher risk of ADHD (RR: 1.40, 95% CI: 1.27–1.54); however, publication bias was identified. When exposure was specified as gestational diabetes mellitus (GDM), GDM exposure increased the risk of ADHD for children by 164% (95% CI: 1.25–5.56) in a Caucasian population. Neither heterogeneity nor publication bias was detected.

Conclusion: Maternal diabetes, especially GDM, is probably a risk factor for ADHD in the Caucasian population. More studies based on large sample size and different ethnicities are needed to confirm this association.

Keywords: maternal diabetes, attention deficit hyperactivity disorder, meta-analysis

Introduction

Attention deficit and hyperactivity disorder (ADHD) is an early-onset neurodevelopmental disorder combining overactivity and impulsivity with the inability to concentrate, resulting in functional impairment in academic, family, and social settings. A systematic review including 175 studies has demonstrated that ADHD affects up to 7.2% (95% CI: 6.7–7.8) of children worldwide.¹ A recent investigation in the UK has demonstrated a marked increase in ADHD prevalence, incidence, and medication.² Therefore, this disorder is of particular public health concern. The etiology of ADHD is complex since it is clear that ADHD has a strong genetic component,³ while environmental risk factors are also implicated.⁴ For psychiatric disorders in children, exposure to risk factors in utero plays an important role.⁵ For example, a hyperglycemic intrauterine environment may exert a negative impact on the development of fetal brain.⁶

Diabetes before pregnancy is known as pregestational diabetes mellitus (PGDM). Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second and third trimesters of pregnancy. Experiments in animal models of diabetic pregnancies have demonstrated that maternal hyperglycemia usually creates an inflammatory environment by promoting oxidative stress via production of reactive oxygen species

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within the embryo and fetus.⁷ Intriguingly, it has been hypothesized that ADHD may be due to central nervous system inflammatory response in the fetus caused by maternal inflammation and immune response.⁸ In addition, murine models have showed that maternal diabetes induces imbalance in the epigenetic mechanisms, alters transcriptional factors and signaling pathways, and thereby contributes to neurodevelopmental disorders.⁹

In line with the experimental evidence mentioned earlier, population studies have suggested a possible association between maternal diabetes and the risk of ADHD for children. Several observational studies in the Caucasian and Chinese populations have revealed that maternal diabetes was related to higher risk of ADHD among children.^{10–13} However, some retrospective studies based on large sample size have reported statistically insignificant results,^{8,14} indicating that offspring from diabetic mothers may be vulnerable to ADHD. Because results from population investigations are currently controversial, we systematically searched the electronic databases, identified all the relevant studies, and performed meta-analyses to quantitatively synthesize all the available data. This is, to our knowledge, the first meta-analysis to study the association between maternal diabetes and risk of ADHD in offspring.

Materials and methods

Literature search

This meta-analysis followed the recommended PRISMA guidelines.¹⁵ A comprehensive literature search was conducted on PubMed, Web of Science, Embase, PsycINFO, WanFang, and China National Knowledge Infrastructure (CNKI) database. The most recent search was conducted in November 2018. The detailed search syntax for PubMed was as follows: (((maternal OR pregestational OR gestational) AND (diabetes OR “diabetes mellitus” OR hyperglycemia))) AND (“ADHD” OR “attention deficit” OR “hyperactivity syndrome” OR “attention deficit hyperactivity disorder”). The corresponding Chinese characters were used in CNKI database searching.

After the primary records were retrieved from databases, duplicated studies were removed. Then, the remaining records were checked according to titles and abstracts. Irrelevant studies were excluded during this step. After that, the full texts of the rest of the studies were obtained and reviewed in detail for eligibility according to the inclusion criteria. Finally, the qualified studies were included for further analyses.

Inclusion criteria

The inclusion criteria were established as follows: 1) original observational studies investigating the association between

maternal diabetes and risk of ADHD in offspring, and 2) effect size (usually OR or risk ratio [RR]) and its 95% CI were reported, or the distribution of subjects in each comparison group was given so that the effect size was able to be calculated. Only English and Chinese literature was included. No restriction on diabetes subtype and study design was imposed. Review, editorial, and conference articles were excluded.

Data extraction

The following items were extracted independently by two reviewers from each study: first author, publication year, study design, characteristics of the participants, diagnostic criteria of ADHD and maternal diabetes, effect size with its 95% CI (preferentially adjusted effect size), and adjusted confounders. If the effect size was not reported, it was manually calculated from the original data. Any disagreement was resolved by further discussion. Since Caucasian usually includes modern population of Europe and white people in the US, we roughly classified participants from Europe and the US into Caucasian population when performing subgroup analyses.

Statistical analyses

The heterogeneity across studies was evaluated with Q -statistic, and the significance level was defined as 0.1.¹⁶ Heterogeneity was further measured by I^2 value and classified into high, medium, or low when $I^2 \geq 50\%$, $50\% > I^2 \geq 25\%$, or $25\% > I^2$, respectively.¹⁷ If an I^2 was smaller than 25%, Mantel–Hansel’s method in fixed-effect model was used to pool outcomes, otherwise data were pooled based on DerSimonian and Laird method in random-effect model.¹⁸ The effect size and its lower and higher CIs were natural logarithm transformed before data combining, and the result was natural exponential transformed and displayed. The publication bias was evaluated by the Egger’s linear regression test statistically.¹⁶ Sensitivity analysis was performed with omitting each study and observing whether the synthesized result altered significantly. All statistical analyses were conducted by Stata 9.0 (StataCorp LP, College station, TX, USA). All P -values were two-sided and identified as significant if <0.05 , unless otherwise specified.

Results

Characteristics of the included studies

As illustrated in Figure 1, a total of nine studies^{8,10–14,19–21} involving 7,218,903 participants were included in the present analysis. The majority of them^{8,12–14,19,20} were published in the recent 2 years. For baseline information, six studies^{10–13,19,20}

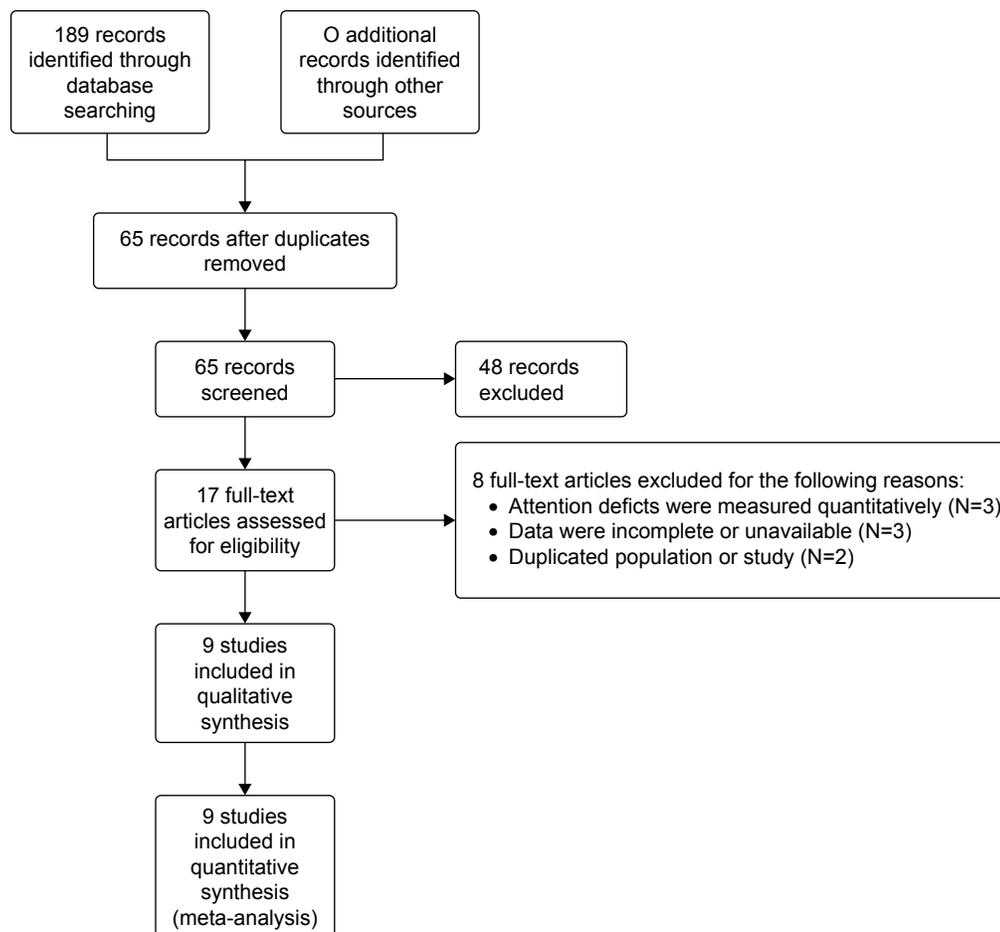


Figure 1 Flow diagram of the identification of the eligible studies.

were cohort design and used RR or HR to measure the effect size. The remaining three studies^{8,14,21} were case-control studies, using OR to describe the risk. Over half of the studies were conducted in Nordic Europe,^{8,12–14,19} benefiting from the excellent local nationwide registry system. The rest of the studies were from China,¹¹ Greece,²⁰ Germany,²¹ and USA.¹⁰ Maternal type 1 diabetes (T1D) was investigated in five studies,^{8,12–14,19} while four studies did not give the accurate type of diabetes.^{10,11,20,21} Only one study recruited mothers with type 2 diabetes (T2D).⁸ Three of the studies^{10,11,19} did not use multivariate analysis in order to consider the potential bias induced by confounders (for details see Table 1). The quality of each study was assessed in Table 2 using Newcastle-Ottawa Scale for nonrandomized studies. The overall quality levels were evaluated using the GRADE approach in Table 3.

Data synthesis of the case-control studies

The pooling of data from case-control studies^{8,14,21} demonstrated that maternal diabetes was not associated with ADHD in offspring (OR: 1.20, 95% CI: 0.96–1.49). Since all the

case-control studies were conducted among Caucasian population, the findings should be applied to this race exclusively. High heterogeneity was detected ($I^2=74.5\%$) (Figure 2A). Sensitivity analysis indicated that omission of a given study would not reverse the insignificant result (Figure 2B). Egger's test showed that no publication bias existed ($t=1.67$, $P=0.194$) (Table 4).

Data synthesis of the cohort studies

In terms of cohort studies,^{10–13,19,20} the meta-analysis demonstrated that maternal diabetes increased the risk of ADHD in offspring by 40% (RR: 1.40, 95% CI: 1.27–1.54) (Figure 2C). Sensitivity analysis confirmed that the results were stable (Figure 2D). Unfortunately, publication bias was identified according to Egger's test ($t=6.56$, $P=0.003$) (Table 4), indicating that the estimated effect was probably overstated due to publication of positive results. Since only the Li et al's¹¹ study investigated the effect of maternal diabetes in Chinese, the remaining studies^{10,12,13,19,20} that were conducted in Caucasian population demonstrated the risk in

Table 1 Basic information of the included studies

Study	Ethnicity	Study design	Exposed/case	Unexposed/control	Diabetes diagnosis	ADHD diagnosis	Effect size	Confounder adjustment
Bytoft et al, 2017 ¹⁹	C	A prospective nationwide cohort from Denmark	Adolescents with mothers who had T1D during 1993–1997 (n=269)	Gender, age, and SES matched background individuals (n=293)	GDM, data from Danish Diabetes Association	Self-reported use of ADHD medication	RR: 14.16, 95% CI: 0.80–250.08	No adjustment
Nielsen et al, 2017 ¹²	C	A Danish cohort based on nationwide register systems	Exposed children born in Denmark from 1990 to 2007 (n=190)	All unexposed children born in Denmark from 1990 to 2007 (n=983,490)	T1D, ICD-8 code 249 and ICD-10 code E10	Psychiatric admission for a diagnosis of ADHD (ICD code F90.x+ F98.8)	RR: 1.36, 95% CI: 1.17–1.56	Age, gender, the interaction of gender with age, and parental history of psychiatric admission
Daraki et al, 2017 ²⁰	C	A part of prospective pregnancy cohort from Greece	Exposed children had neurodevelopment assessment at 4 years of age from Oct 2011 to Jan 2013 (n=56)	All unexposed children had neurodevelopment assessment at 4 years of age from October 2011 to January 2013 (n=716)	GDM screen between 24 and 28 weeks of gestation according to criteria proposed by ADA (2008)	Standardized child scale	RR: 10.18; 95% CI: 0.22–473.43	Child gender, maternal age, origin, education, parity, smoking and pre-pregnancy BMI
Nomura et al, 2012 ¹⁰	C	A cohort study from New York	Exposed children at 6 years of age (n=21)	Unexposed children at 6 years of age (n=191)	GDM, face-to-face interview	Semi-structured child psychiatric interview	RR: 2.20; 95% CI: 1.00–4.82	No adjustment
Li et al, 2014 ¹¹	A	A hospital-based cohort study from China	Children exposed to maternal diabetes and hypertension (n=302)	Children unexposed to maternal diabetes and hypertension (n=668)	GDM, blood and oral glucose tolerance test	Standardized child scale	RR: 1.86; 95% CI: 1.27–2.73	No adjustment
Ji et al, 2018 ¹³	C	A retrospective cohort study based on Swedish register system	Exposed children born in Denmark from 1970 to 2012 (n=15,615)	Matched control subjects (n=1,380,829)	T1D, ICD-8 code 250, ICD-9 code E10 and ICD-10 code E10	ICD-9 code 314 and ICD-10 code F90	HR: 1.35; 95% CI: 1.18–1.55	Year of birth, gender, parental history of ADHD, education, income, small for gestational age, maternal smoking, and low Apgar score
Schmitt and Romanos 2012 ²¹	C	A case control study based on German nationwide survey	Children with ADHD (n=660)	Children without ADHD (n=12,828)	Self-reported physician diagnosed GDM	Medical or psychological exam reported in standardized interview	OR: 1.91; 95% CI: 1.21–3.01	Age, gender, SES, maternal smoking, breastfeeding, atopic eczema, and perinatal health problems
Hegvik et al, 2018 ¹⁴	C	A cross-sectional study based on a Norwegian cohort	Children with ADHD during 2004–2015 (n=63,721)	All remaining individuals (n=2,436,397)	T1D, ICD-10 code E10 or ICPC T89	ADHD medication	OR: 1.00; 95% CI: 0.84–1.20	Age and maternal education
Instanes et al, 2017 ⁸	C	A population-based nested case-control study based on longitudinal Norwegian registers	Children with ADHD during 2004–2012 (n=47,944)	All remaining individuals (n=2,274,713)	PGDM, data from registry system	ADHD medication	T1D: OR: 1.5; 95% CI: 1.2–1.9; T2D: OR: 1.1; 95% CI: 0.7–1.8	Age, parity, maternal age, education, marital status, ADHD medication, birth weight, and gestation age

Abbreviations: A, Asian; ADA, American Diabetes Association; ADHD, attention deficit hyperactivity disorder; BMI, body mass index; C, Caucasian; GDM, gestational diabetes mellitus; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; PGDM, pregestational diabetes mellitus; RR, risk ratio; SES, socioeconomic status; T1D, type 1 diabetes; T2D, type 2 diabetes.

Table 2 Quality of the included studies

Study	Selection score	Comparability score	Outcome score	Total score	Quality
Bytoft et al, 2017 ¹⁹	4	2	3	9	High
Nielsen et al, 2017 ¹²	3	2	3	8	High
Daraki et al, 2017 ²⁰	4	2	3	9	High
Nomura et al, 2012 ¹⁰	4	2	3	9	High
Li et al, 2014 ¹¹	3	0	2	5	Moderate
Ji et al, 2018 ¹³	3	2	3	8	High
Schmitt and Romanos, 2012 ²¹	4	2	2	8	High
Hegvik et al, 2018 ¹⁴	3	2	3	8	High
Instones et al, 2017 ⁸	4	2	2	8	High

this race (RR: 1.37, 95% CI: 1.24–1.51). Subgroup analyses revealed that T1D increased the risk by 36% (RR: 1.36, 95% CI: 1.23–1.50).^{12,13,19} No heterogeneity between studies were found in either overall or subgroup analyses.

Subgroup analysis of the cohort studies investigating mothers with GDM

Since the participants in the cohort studies consisted of mothers with GDM and mothers with a history of diabetes (the onset of diabetes was not specified), we further narrowed the scope and investigated the effect of GDM on risk of ADHD for children. The combining of four studies^{10,11,19,20} demonstrated that GDM heightened the risk of ADHD by onefold (RR: 2.00; 95% CI: 1.42–2.81), without detecting inconsistency between studies ($I^2=0\%$) (Figure 3A). Publication bias was also identified regarding this analysis. We next excluded Li et al's study¹¹ and ensured all the included studies^{10,19,20} were from Caucasian population. The risk of ADHD conferred by GDM in Caucasian was as much as 1.64-fold (95% CI: 1.25–5.56) higher compared with controls (Figure 3B). Besides, neither heterogeneity nor publication bias was detected (Table 4).

Discussion

The present study is, to our knowledge, the first meta-analysis to evaluate the risk of ADHD for children induced by maternal diabetes. We systematically searched the databases and some of the included studies were nationwide investigations, and the number of subjects was large enough to obtain sufficient study power.^{12,13} The analyses generally consisted of two parts. On the one hand, combining of case-control studies demonstrated that the offspring of diabetic mothers were not at a heightened risk of ADHD (OR: 1.20, 95% CI: 0.96–1.49). All the case-control studies recruited Caucasian participants. Therefore, this finding

should be restricted to this population. Of note, it has been suggested that some minority groups, such as obese or older Caucasian women, are at a greater risk for maternal diabetes than the overall Caucasian women.²² This indicates that management of the high-risk subgroups by maternal DM intervention could be more beneficial for ADHD prevention. On the other hand, cohort studies altogether indicated that maternal diabetes was a risk factor for ADHD (RR: 1.40, 95% CI: 1.27–1.54). However, this result was not reliable considering publication bias was identified.

Since higher functions of brain develop during the second half of pregnancy, we hypothesized that GDM may exert adverse effects on offspring more profoundly in this period. When the participants were specified as offspring of mothers with GDM in Caucasian population from cohort studies, data pooling suggested that they were more vulnerable to ADHD and the risk was increased as much as by 1.64-fold (95% CI: 1.25–5.56). Although the sample size was relatively smaller (number of subjects in exposure group was 515, number of subjects in non-exposure group was 984,499) in this subgroup analysis, neither inconsistency nor publication bias was detected, indicating the reliability of this result. This result emphasizes the importance of good glycemic control in diabetic mothers throughout pregnancy and not only in the first trimester.

It has been hypothesized that ADHD may be due to inflammatory response to the central nervous system in the fetus caused by maternal inflammation and immune response. A nationwide study demonstrated that several immune system diseases, including maternal multiple sclerosis, rheumatoid arthritis, asthma and hypothyroidism, were more frequently observed among mothers of offspring with ADHD compared with mothers of controls.⁸ Apart from the association regardless of gender, another large cross-sectional study reported that inflammatory bowel disease was associated

Table 3 Evaluation of overall quality levels using the GRADE approach

Quality assessment		No of patients				Effect		Quality	Importance			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Case	Control	Relative (95% CI)	Absolute		
Association between maternal diabetes and ADHD (case-control study)												
3	Observational studies	No serious risk of bias	Serious ^a	No serious indirectness	No serious imprecision	Very strong association ^b	2531/112,325 (2.3%)	5,534/72,393 (0.12%)	RR 1.20 (0.96–1.49)	0 more per 1,000 (from 0 fewer to 1 more)	★★★★ Moderate	Critical
Association between maternal diabetes and ADHD (cohort study)												
6	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias ^c Very strong association ^b	2,372/16,453 (14.4%)	1,159/23,661 (4.9%)	RR 1.40 (1.27–1.54)	20 more per 1,000 (from 13 more to 26 more)	★★★★ Moderate	Critical
Association between GDM and ADHD (better indicated by lower values)												
4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias ^d Very strong association ^b	782	984,642	–	ES 2.00 higher (1.42–2.81 higher)	★★★★ Moderate	Important

Notes: ^aSignificant heterogeneity ($I^2=76.5\%$) was observed among the included studies. ^bA large sample size was observed among the included studies. ^cPublication bias was identified according to Egger's test ($t=6.56, P=0.003$). ^dPublication bias was identified regarding this analysis.

Abbreviations: ADHD, attention deficit hyperactivity disorder; ES, effect size; GDM, gestational diabetes mellitus; RR, risk ratio.

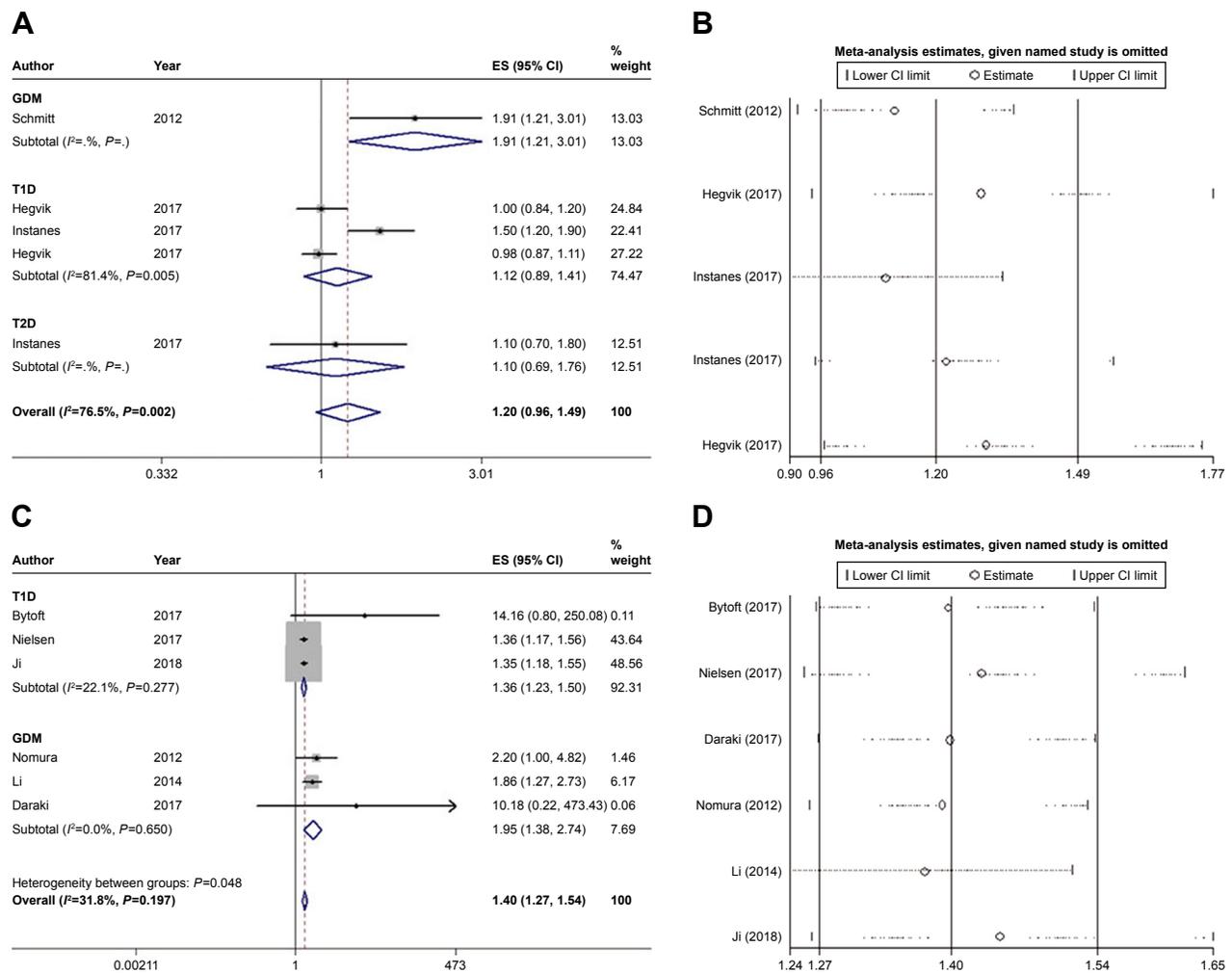


Figure 2 Main results of the meta-analyses.

Notes: (A) Data combination of case-control studies; (B) sensitivity analysis on case-control studies; (C) data combination of cohort studies; and (D) sensitivity analysis on cohort studies. Weights are from random-effects analysis.

Abbreviations: ES, effect size; GDM, gestational diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes.

with ADHD, particularly in females.¹⁴ Considering that ADHD has an approximate sex ratio of 3:1 during childhood and displays sex-specific manifestations,²³ a sex-specific mechanism may underlie the relationship between ADHD and maternal immune disease, such as diabetes. Among the included studies, only one investigation¹⁴ separately reported the association of maternal diabetes with ADHD in males and

females. Although insignificant findings were shown in both males and females,¹⁴ further studies exploring the difference between gender are encouraged for a better understanding of ADHD etiology.

Social factors have been suggested to play a crucial role on maternal diabetes and glycemic control, thus mediating the onset of ADHD. Most the included studies^{8,13,14,20,21}

Table 4 Main results of the meta-analyses

Analysis	No of subjects	Statistical model	Data pooling			Heterogeneity		Publication bias		Sensitivity analysis
			Effect size	t-value	P-value	I^2 (%)	P-value	t-value	P-value	
Overall OR	4,836,263	Random	1.20 (0.96–1.49)	1.62	0.105	76.5	0.002	1.67	0.194	Stable
Overall RR	2,382,640	Fixed	1.40 (1.27–1.54)	6.89	<0.001	31.8	0.197	6.56	0.003	Stable
GDM RR	985,984	Fixed	2.00 (1.42–2.81)	4.00	<0.001	0.0	0.446	4.99	0.038	Stable
GDM in Caucasian RR	985,014	Fixed	2.64 (1.26–5.56)	2.56	0.011	0.0	0.369	3.30	0.187	Stable

Abbreviations: GDM, gestational diabetes mellitus; RR, risk ratio.

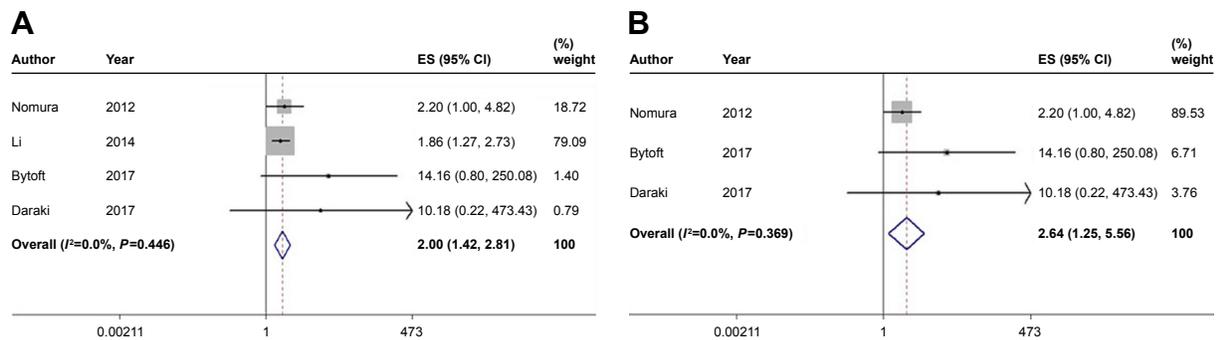


Figure 3 Meta-analyses of the subjects from (A) mothers with GDM or (B) Caucasian mothers with GDM.

Abbreviations: ES, effect size; GDM, gestational diabetes mellitus.

considered family socioeconomic status (SES), such as parental income, occupation, education, and single parent status, as a confounding variable and thereby adjusted the result. It is widely accepted that parental socioeconomic disadvantage is a risk factor for ADHD in children,²⁴ which is likely mediated by factors linked to low SES such as parental mental disorders. Diabetic mothers, especially for those with complications, are linked to low SES because those women might have limited ability to work and have lower disposable income, resulting in a relatively deprived environment for children. Apart from socioeconomic deprivation, lifestyle, access to health food, regular physical activity, public insurance, etc, are also linked to glycemic control.²⁵ Overall, it is recommended to record social factors and consider them as confounders when examining the true effect of maternal diabetes on ADHD in children. So the adjusted results were extracted and combined if available.

A new insight into the impact of in utero hyperglycemia on fetus brain development emphasizes that maternal diabetes may increase the vulnerability to psychiatric disorder later in life by interacting with other environmental insult during pregnancy. Animal model study has demonstrated that GDM and viral infection concurrently produce a novel transcriptional profile, and these novel transcriptional changes are associated with pathways implicated in psychiatric disorders.²⁶ This finding indicates that GDM may have the potential to prime the fetus for an exacerbating response to infection, which is a common environmental stress during pregnancy.

The mechanism of ADHD also has some endocrinological components. It has been shown that patients with T1D are more likely to receive ADHD diagnosis.²⁷ Interestingly, adolescents and young adults with ADHD are reportedly to be more likely than non-ADHD controls to develop T2D in later life.²⁸ There is an ongoing discussion whether thyroid hormone system is involved in the development of ADHD,

and there is a link between thyroid hormones and diabetes risk.²⁹ It has been observed that thyroid-stimulating hormone levels are slightly increased among ADHD patients.³⁰ This finding is further validated by transgenic mouse that expresses a human mutant thyroid receptor $\beta 1$, which manifests typical syndromes of ADHD such as impulsive and inattentive.³¹

The National Institute for Health and Care Excellence accredited guidelines for ADHD management emphasized the importance of a holistic approach to managing ADHD.³² A comprehensive shared treatment plan should address psychological, behavioral, and occupational or educational needs.³² The guideline recommends an ADHD-focused group parent-training program to parents or carers as first-line treatment for children under 5 years with ADHD. Pharmacological medication is offered to children aged 5 years and over, young people, and adults, only if ADHD symptoms are still causing a significant impairment in interpersonal relationships, education and occupational attainment, or risk awareness.³² However, a network meta-analysis of randomized trials indicated that the therapeutic effects of cognitive training, neurofeedback, antidepressants, antipsychotics, dietary therapy, fatty acids, and other complementary and alternative medicine were uncertain due to limited evidences.³³

The present studies consisted of cohort, cross-sectional, and case-control studies. Heterogeneity existed as a significant limitation for this review because of differences in ADHD definition, ethnicity, type of maternal diabetes, and methodology used. In order to reduce the heterogeneity between studies included in the review, the studies that were similar regarding design and measurement were combined. Another noteworthy fact was that we included the studies in which prescriptions were used as proxy for the diagnosis of ADHD,^{8,14,19} and thus selection bias might occur. Due to various health care systems and policies in different countries, medications are accepted by different subgroups of children who may have

been diagnosed with ADHD. However, medication for ADHD does not necessarily mean a clinical diagnosis has been given. Therefore, the identification of ADHD cases in further studies should be based on a standardized scale so that the selection bias could be diminished.

Conclusion

Maternal diabetes, especially for GDM, is probably a risk factor for ADHD in Caucasian race. This result emphasizes the importance of good glycemic control in diabetic mothers throughout pregnancy and not only in the first trimester. The attention on gender difference, the clear record of significant confounders, and the accurate diagnosis of ADHD cases are urgently needed in the further studies.

Disclosure

The authors report no conflicts of interest in this work.

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