Association of Maternal Diabetes and ADHD in Offspring: A Systematic Review and Meta-Analysis

Batool Okhovat Isfahani[1], Farzad Khodamoradi[2]

[1] *West Health Center of Tehran, Iran University of Medical Sciences, Tehran, Iran*

[2] *Department of Social Medicine, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

Received: 11 Feb. 2022; Accepted: 18 Apr. 2023

Abstract- A systematic review and meta-analysis was conducted to determine the association between exposure to maternal diabetes and ADHD in the offspring. Major electronic databases, including Web of Science, PubMed, Scopus, Embase, and Proquest, were searched from inception until December 2018. The New Castle-Ottawa scale was used to assess the quality of the included studies. A fixed effects model was applied for analysis. Seven studies including a total of 5,658,871 individuals were retained. A significant association was found between maternal diabetes and ADHD [OR=1.23, 95% CI: 1.117, 1.345]. There was a significant heterogeneity (I^2=77.7, *P*<0.0001), while Egger's and Begg's test were not significant. This study showed a significant relationship between maternal diabetes and ADHD; however, more well-designed studies are needed to confirm the results.

Acta Med Iran 2023;61(6):315-322.

Keywords: Attention deficit disorder with hyperactivity; Diabetes mellitus; Systematic review

Introduction

Maternal diabetes includes either existing diabetes before the pregnancy, also known as pre-gestational Diabetes Mellitus (PGDM), or a first diagnosis of diabetes during pregnancy, known as Gestational Diabetes Mellitus (GDM) (1).

Diabetes is one of the most common complications of pregnancy. In fact, the number of pregnant women with diabetes is expected to rise due to increased sedentary habits and high-calorie diets (2). In the United States, about 9% of childbearing women have diabetes and 2-5% of pregnant women develop GDM. Similarly, the prevalence of GDM is 2-6% of all pregnancies in Europe (3).

Previous studies suggest that maternal diabetes (all types) is associated with an increased rate of neurocognitive and behavioral outcomes in the offspring, including autism, memory difficulties, deficit/ hyperactivity disorder (ADHD), and intelligence quotient (IQ) (4-7).

Attention-deficit hyperactivity disorder (ADHD) is a mental disease with a global prevalence of about 5 % (8) in children and 3% in adults (9). The etiology of ADHD is complex and influenced by the interaction of environmental and genetic factors (10). Previous studies demonstrated that some pregnancy-related factors could be effective in ADHD, including maternal obesity (11), alcohol consumption during pregnancy (12,13), and maternal smoking (14). Maternal metabolic complications increase the risk of behavioral disorders such as ADHD (15). Several studies found a significant association between maternal diabetes and ADHD (16-18). However, a prospective cohort study indicated that maternal diabetes was not related to ADHD (19). Since diabetes and ADHD are both common, ADHD and diabetic patients may represent a large proportion of the population needing care. Thus, it is worthy to obtain more data to assess the association between maternal diabetes and ADHD. Furthermore, it is important to recognize ADHD in children in the early stages because ADHD has some long-term adverse outcomes including learning difficulties, social and occupational problems, drug abuse, and criminal behaviors (20-24). Therefore,

Corresponding Author: F. Khodamoradi
Department of Social Medicine, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
Tel: +98 9122767039, E-mail address: f_khodamoradi@yahoo.com

this systematic review and meta-analysis was conducted to examine the association between maternal diabetes and ADHD.

Materials and Methods

A systematic search was conducted in Web of Science, PubMed (1990/01/01:2018/10/20), Scopus, Embase, and Proquest (January 1989 to December 2018).

A search strategy was created using MeSH terms "ADHD", "Attention Deficit Hyperactivity" "ADDH", "Minimal Brain Dysfunction", "hyperkinetic syndrome", "minimal brain disorders", "hyperactive child syndrome", "childhood hyperkinetic syndrome", "overactive child syndrome", "attention deficit hyperkinetic disorder", "hyperkinetic disorder", "attention deficit disorder hyperactivity", "child attention deficit disorder", "hyperkinetic syndrome childhood", "Attention Deficit Hyperactivity "Disorder", AND "Diabetes*", "Diabetes Mellitus", "IDDM" "GDM", "maternal diabetes", "T1DM", "Prediabetes" "Impaired Glucose Tolerance", (Intolerance AND Glucose), (Diabetes AND "Pregnancy Induced"), "Gestational Diabetes", "NIDDM", "MODY".

First, irrelevant articles were removed according to title and abstract screening. Two authors (BO and FKH) independently reviewed the full texts of the remaining articles based on the inclusion criteria of this meta-analysis. All observational studies investigating the relationship between maternal diabetes and ADHD in the offspring in which odds ratio (OR), relative risk (RR), or hazard ratio (HR) were reported or the data required for calculating the odds ratio was available, were included regardless of language, age, sex, and race limitations. When two articles reported the same data for the same cohort, the article that reported the data more comprehensively was included. Review and conference articles were excluded and any disagreement between reviewers was resolved by consensus. The inter-author reliability based on kappa coefficient was 91%.

Selection of studies, data extraction, and quality assessment were performed by BO and FKH.

The New Castle-Ottawa scale recommended by the Cochrane collaboration was used for assessing the quality of the studies. A "star system" was used to evaluate the quality of the studies in three categories: the selection (4 stars); the comparability (2 stars); and outcome for cohort studies or exposure for case-control studies (3 star). Studies with 7 to 9, 4 to 6, and 0 to 3 stars were classified as high, intermediate and low quality, respectively (25).

Data collection and validity assessment

Data were extracted by two authors (BO and FKH) independently. The extracted variables for data analysis included author's name, publication year, country, study design, type of diabetes, effect size with confidence interval, sex, and age.

Data synthesis

The Cochran's Q test was used to assess between-study inconsistency, and I^2 value was used to assess the heterogeneity of the effect size, which indicates the percentage of variation across studies due to heterogeneity rather than chance. An I^2 statistics less than 25%, 25-50%, and more than 50% represented low, intermediate, and high heterogeneity, respectively.

Publication bias was assessed by Egger's and Begg's tests. Trim and fill approach was used to calculate the unbiased effect size (26).

Sensitivity analysis was performed by removing each study to estimate the strength of association between maternal diabetes and ADHD in offspring.

A fixed effect method was used to check the heterogeneity of the studies and the analyses were performed using the "metan" command. The significance level was set at 0.2. The Stata13 was used to perform the meta-analysis. The Stata 13 was used for data analysis.

Results

Initially, 1537 records were identified through database search, of which 726 were excluded because of duplication and 24 were excluded due to grey literature. The remaining 787 studies were screened according to titles and abstracts. Then, 23 articles were selected for full-text review, of which 13 were excluded due to irrelevance to the objective of this study and 3 were excluded because of insufficient data. Finally, seven studies met the inclusion criteria for the meta-analysis (16-18,27-29).

Study characteristics

The characteristics of the included studies are summarized in Table 1. The sample size of the included studies ranged from 212 to 2,322,657 subjects, comprising a total of 5658871 participants. Among 7 articles, 4 were cohort and 3 were case-control studies.

The studies were performed in the US, Norway, Denmark, Sweden, and Germany. Therefore, the results of the present meta-analysis might be related to certain populations. Among the included studies, four assessed the effect of maternal type1 diabetes, two assessed the effect of GDM, and one assessed the effect of maternal type 2 diabetes on ADHD in the offspring.

Table 1. Characteristics of included studies

First author	Country	Year	Sample size	Study design	Kind of diabetes	Effect size (95% CI)	ADHD diagnosis	Diabetes diagnosis
Yoko nomura	US	2012	212	cohort	GDM	OR: 0.6(0.3,1.17)	ADHD RS–IV	face-to face interview
Johanne T	Norwegia	2015	2322657	Pop-nested case-control	Type2	OR: 0.6(0.4,0.9)	Individuals receiving ADHD medication during the years 2004–2012	Not specified
Johanne T	Norwegia	2015	2322657	Pop-nested case-control	Type1	OR: 1.1(0.9,1.3)	Individuals receiving ADHD medication during the years 2004–2012	Not specified
Philip rising nielsen	Denmark	2016	983680	cohort	Type1	IRR: 1.3(1.02,1.62)	ICD-10 code: F90.x + F98.8)	ICD-8-249
Jianguang ji	Sweden	2018	15615	retrospectiv e cohort	Type1	HR: 1.35(1.18,1.55)	ICD-9 code 314 and ICD-10 code F90	T1D patients were retrieved from these registries according to the ICD-8 (1970–1986, code 250), ICD-9 (1987–1996, code 250), and ICD-10 .(1997-, ICD code E10)
Jochen schmitt	German	2012	13488	Case-control	GDM	OR: 1.93(1.26,2.95)	ADHD is generally diagnosed according to the International Statistical Classification of ,Diseases	1-Average blood glucose levels and number of episodes of hypoglycemia (blood glucose levels <60 mg/dl) or hyperglycemia (160-199 or above 200 mg/dl) in relation to the week of pregnancy. 2-. The number of times urinary acetone was found on routine screening, tested several times each week. 3. The duration and complications of diabetes according to .White's classification
Birgitte bytoft	Denmark	2017	562	prospective cohort	Type1	OR: 14.48(0.812,258.28)	Conners CPT-II, version 5	oral glucose tolerance test (OGTT)

Meta-analysis results

The results of this meta-analysis demonstrated that gestational diabetes increased the risk of ADHD in the offspring by 23% [OR=1.23, 95% CI: 1.117, 1.345] (Table 2, Figure 1).

Subgroup analysis of ADHD by the type of diabetes, study design, and effect size is shown in Table 2 and Figures 2 to 4.

Meta-regression analysis showed that quality assessment did not significantly affect the pooled odds ratio [β= -0.06, 95% CI: -0.47, 0.35]

Heterogeneity was significant ($I^2 = 77.7, P < 0.0001$) while Egger's and Begg's tests were not significant. The bias score was -0.456 (P=0.826) according to Egger's test and 0.60 (P=0.548) according to Begg's test. The trim and fill approach showed no publication bias (Figure 6).

The results of sensitivity analysis based on one out remove method showed that the overall results did not change markedly when each study was removed. See Table 3 and Figure 5 for more details.

Table 2. Main results of the meta-analyses

	Number of study	Effect estimate (95% CI)	Heterogeneity χ^2	*P*	I^2(%)	Interaction *P*
Type of diabetes						
GDM	2	1.390(0.969, 1.994)	8.14	0.004	87	0.002
Type1	4	1.267(1.148, 1.399)	5.90	0.117	49.1	
Type2	1	0.6(0.4, 0.9)	-	-	0	
Type of estimate						
OR	5	1.061(0.912, 1.235)	21.20	<0.001	81.1	0.059
IRR	1	1.3(1.032, 1.638)	-	-	-	
HR	1	1.35(1.178, 1.547)	-	-	-	
Study design						
cohort	4	1.311(1.168, 1.472)	7.92	0.048	62.1	0.055
Case-control	3	1.085(0.928, 1.268)	15.26	<0.001	86.9	
Overall estimate	7	1.226(1.117, 1.345)	26.86	<001	77.7	

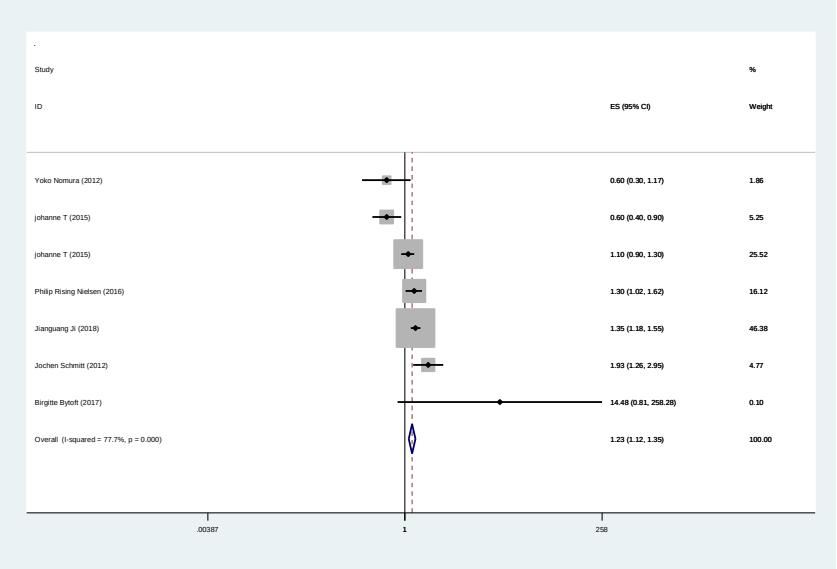

Figure 1. Forest plots of ADHD in offspring exposed to maternal diabetes

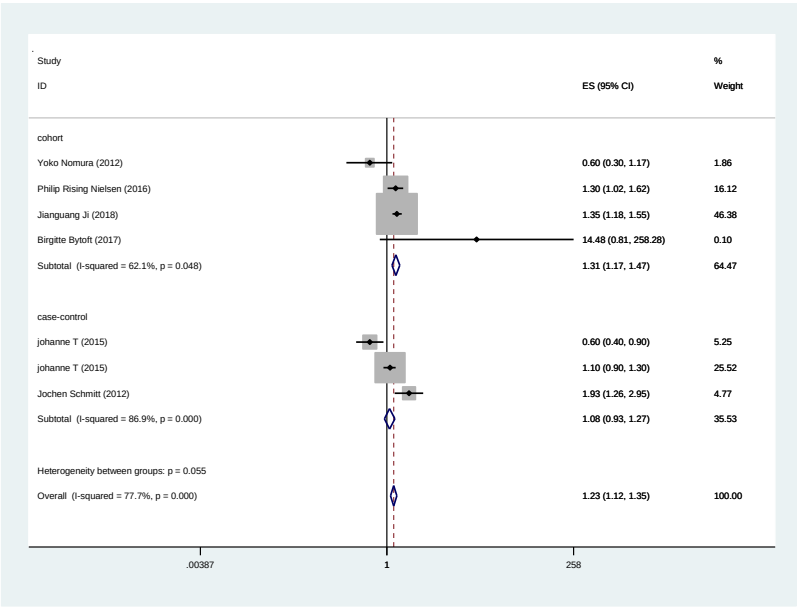

Figure 2. forest plot of ADHD in offspring exposed to maternal diabetes by study design

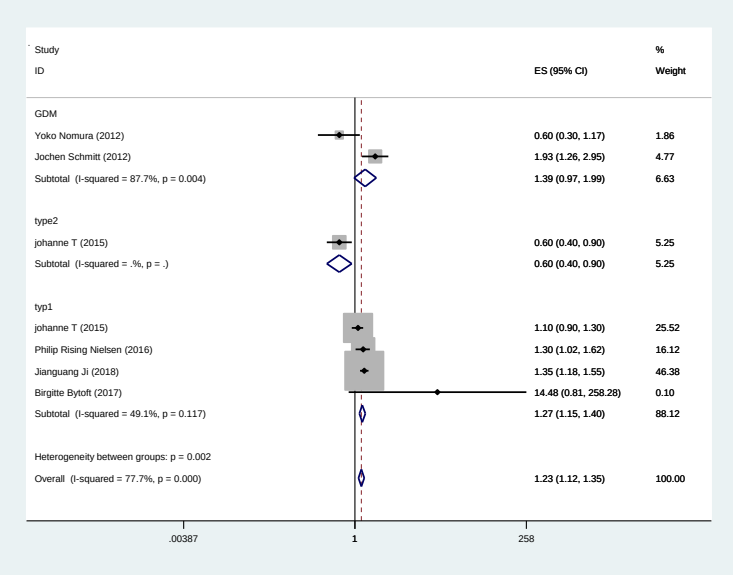

Figure 3. forest plot of ADHD in offspring exposed to maternal diabetes by type of diabetes

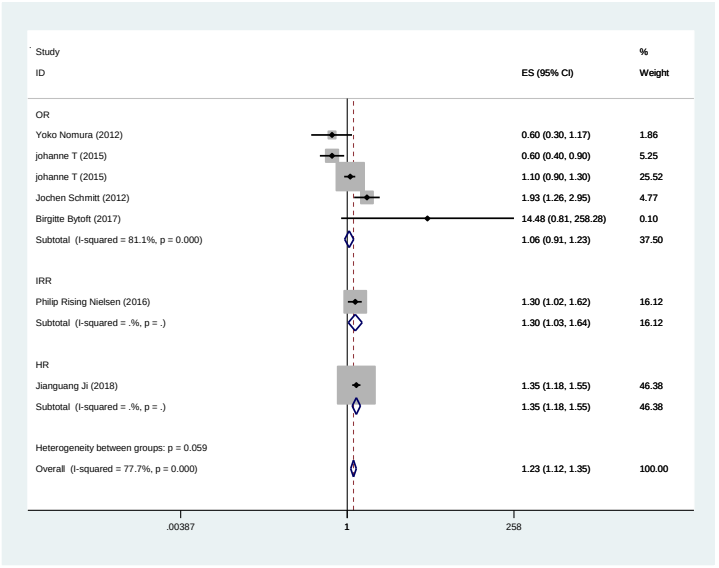

Figure 4. forest plot of ADHD in offspring exposed to maternal diabetes by effect size

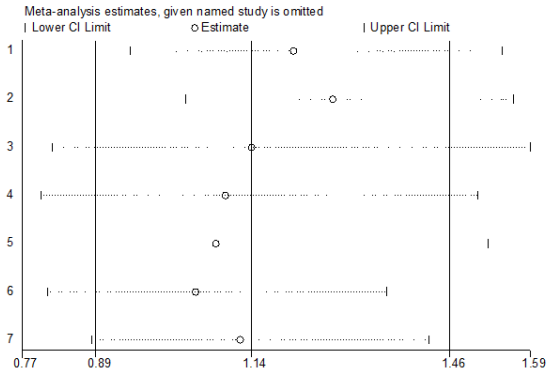

Figure 5. sensitivity analysis

Table 3. Sensitivity analysis

Study omitted	Estimate (95% CI)
Yoko nomura	1.21(0.94, 1.54)
Johanne T	1.27(1.03, 1.56)
Johanne T	1.14(0.82, 1.59)
Philip rising nielsen	1.098(0.8, 1.51)
Jianguang ji	1.08(0.77, 1.52)
Jochen schmitt	1.05(0.81, 1.36)
Birgitte bytoft	1.12(0.88, 1.43)
combined	1.14(0.89, 1.46)

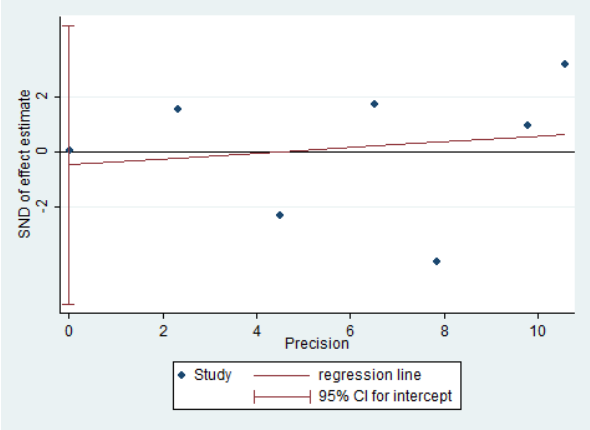

Figure 6. egger's gragh

Discussion

This systematic review and meta-analysis found that maternal diabetes was associated with an increased risk of ADHD in the offspring [OR: 1.23, 95% CI: 1.117, 1.345]. There was heterogeneity ($I^2 = 77.7$); therefore, subgroup analysis was conducted. Subgroup analysis based on type of diabetes, study design, and effect size did not change these results. The results of the present study are consistent with a previous meta-analysis (2019) of only two studies, which found that exposure to maternal diabetes in pregnancy was associated with an increased risk of ADHD in the offspring [HR: 1.36, 95% CI: 1.19, 1.55, $I^2 = 0\%$] (30). A cohort study found that maternal type1 diabetes was associated with ADHD in the offspring [IRR: 1.31, 95% CI: 1.03, 1.63] (16). In addition, in a study by Nomura *et al*., maternal GDM was associated with an increased risk of attention-deficit/hyperactivity disorder at age of 6 years [OR: 0.60, 95% CI:0.30, 1.17, *P*=0.13] (28). Another study also showed that maternal type1 diabetes was associated with the risk of ADHD in the offspring [HR: 1.35, 95%CI: 1.18, 1.55] (17).

By contrast, Vasiliki Daraki found no association between maternal diabetes and ADHD [β=1.75, 95% CI: -2.14, 5.66] in children aged 4 years adjusted for child sex and age (19). Another study showed that maternal diabetes was not associated with ADHD in the children (maternal type1 diabetes, [OR: 1.1, 95% CI: 0.9, 1.3]; maternal type 2 diabetes, [OR: 0.6, 95% CI: 0.4, 0.9]). However, after adjusted analysis, maternal type 1 diabetes was related to ADHD [adjusted OR: 1.6, 95% CI: 1.3, 2.0] (18). In addition, there was no correlation between maternal diabetes and ADHD in the study (31).

The present study had several strengths. First, we included studies with large sample sizes. Second, we performed subgroup analysis by design, effect size, and type of diabetes.

This study had several limitations. First, a small number of studies were included. Second, we tried to include unpublished studies by asking the authors to provide the relevant data, but it was not possible to contact all authors. This might have led to bias in effect size calculation. Third, the confounding factors were not adjusted in the included studies, some of which have a strong correlation with the risk of ADHD. For example, Kong et al showed that the risk of ADHD in the offspring was 88% higher in severely obese mothers without diabetes [HR: 1.88, 95% CI: 1.58, 2.33] compared to mothers with normal BMI (BMI<25). Moreover, maternal PGDM carries a sixfold-increased risk of ADHD in severely obese mothers with PGDM compared with

normal weight mothers without PGDM [HR: 6.03, 95% CI: 3.23, 11.24] (32). Hence, studies that adjusted potential confounders were more likely to report the true effect of maternal diabetes on ADHD. Therefore, more adjusted studies are recommended. Finally, although we performed subgroup analysis to reduce study heterogeneity, it was still significant in subgroup analysis.

In conclusion, this study found a significant relationship between maternal diabetes and ADHD in the offspring. However, because of the limited number of included studies in this meta-analysis, more well-designed studies are needed to confirm the results.

References

1. Camprubi Robles M, Campoy C, Garcia Fernandez L, Lopez-Pedrosa JM, Rueda R, Martin MJ. Maternal diabetes and cognitive performance in the offspring: a systematic review and meta-analysis. PLoS One 2015;10:e0142583.
2. Xiong X, Saunders LD, Wang FL, Demianczuk NN. Gestational diabetes mellitus: prevalence, risk factors, maternal and infant outcomes. Int J Gynaecol Obstet 2001;75:221-8.
3. Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005. Diabetes Care 2008;31:899-904.
4. Xiang AH, Wang X, Martinez MP, Page K, Buchanan TA, Feldman RK. Maternal type 1 diabetes and risk of autism in offspring. JAMA 2018;320:89-91.
5. Temple R, Hardiman M, Pellegrini M, Horrocks L, Martinez- Cengotitabengoa MT. Cognitive function in 6- to 12- year- old offspring of women with Type 1 diabetes. Diabet Med 2011;28:845-8.
6. Fraser A, Nelson SM, Macdonald-Wallis C, Lawlor DA. Associations of existing diabetes, gestational diabetes, and glycosuria with offspring IQ and educational attainment: the Avon Longitudinal Study of Parents and Children. Exp Diabetes Res 2012;2012:963735.
7. Clausen TD, Mortensen E, Schmidt L, Mathiesen E, Hansen T, Jensen D, et al. Cognitive function in adult offspring of women with Type 1 diabetes. Diabet Med 2011;28:838-44.
8. Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 2007;164:942-8.
9. Fayyad J, De Graaf R, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 2007;190:402-9.
10. Thapar A, Cooper M, Eyre O, Langley K. Practitioner review: what have we learnt about the causes of ADHD? J Child Psychol Psychiatry 2013;54:3-16.
11. Cortese S, Moreira-Maia CR, St. Fleur D, Morcillo-Peñalver C, Rohde LA, Faraone SV. Association between ADHD and obesity: a systematic review and meta-analysis. Am J Psychiatry 2016;173:34-43.
12. Schneider ML, Roughton EC, Lubach GR. Moderate alcohol consumption and psychological stress during pregnancy induce attention and neuromotor impairments in primate infants. Child Dev 1997;68:747-59.
13. Olson HC, Streissguth AP, Sampson PD, Barr HM, Bookstein FL, Thiede K. Association of prenatal alcohol exposure with behavioral and learning problems in early adolescence. J Am Acad Child Adolesc Psychiatry 1997;36:1187-94.
14. Zhu JL, Olsen J, Liew Z, Li J, Niclasen J, Obel C. Parental smoking during pregnancy and ADHD in children: the Danish national birth cohort. Pediatrics 2014;134:e382-e8.
15. Sullivan EL, Riper KM, Lockard R, Valleau JC. Maternal high-fat diet programming of the neuroendocrine system and behavior. Horm Behav 2015;76:153-61.
16. Nielsen PR, Benros ME, Dalsgaard S. Associations between autoimmune diseases and attention-deficit/hyperactivity disorder: a nationwide study. J Am Acad Child Adolesc Psychiatry 2017;56:234-40.e1.
17. Ji J, Chen T, Sundquist J, Sundquist K. Type 1 diabetes in parents and risk of attention deficit/hyperactivity disorder in offspring: a population-based study in Sweden. Diabetes Care 2018;41:770-4.
18. Instanes JT, Halmøy A, Engeland A, Haavik J, Furu K, Klungsøyr K. Attention-deficit/hyperactivity disorder in offspring of mothers with inflammatory and immune system diseases. Biol Psychiatry 2017;81:452-9.
19. Daraki V, Roumeliotaki T, Koutra K, Georgiou V, Kampouri M, Kyriklaki A, et al. Effect of parental obesity and gestational diabetes on child neuropsychological and behavioral development at 4 years of age: the Rhea mother-child cohort, Crete, Greece. Eur Child Adolesc Psychiatry 2017;26:703-14.
20. Tarver J, Daley D, Sayal K. Attention- deficit hyperactivity disorder (ADHD): an updated review of the essential facts. Child Care Health Dev 2014;40:762-74.
21. Lahey BB, Lee SS, Sibley MH, Applegate B, Molina BS, Pelham WE. Predictors of adolescent outcomes among 4–6-year-old children with attention-deficit/hyperactivity disorder. J Abnorm Psychol 2016;125:168-81.
22. Chan E, Fogler JM, Hammerness PG. Treatment of

attention-deficit/hyperactivity disorder in adolescents: a systematic review. JAMA 2016;315:1997-2008.

23. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult outcome of hyperactive children: adaptive functioning in major life activities. J Am Acad Child Adolesc Psychiatry 2006;45:192-202.
24. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult follow- up of hyperactive children: antisocial activities and drug use. J Child Psychol Psychiatry 2004;45:195-211.
25. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
26. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
27. Schmitt J, Romanos M. Prenatal and perinatal risk factors for attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 2012;166:1074-5.
28. Nomura Y, Marks DJ, Grossman B, Yoon M, Loudon H, Stone J, et al. Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring. Arch Pediatr Adolesc Med 2012;166:337-43.
29. Bytoft B, Knorr S, Vlachova Z, Jensen RB, Mathiesen ER, Beck-Nielsen H, et al. Assessment of attention deficits in adolescent offspring exposed to maternal type 1 diabetes. PloS One 2017;12:e0169308.
30. Yamamoto JM, Benham JL, Dewey D, Sanchez JJ, Murphy HR, Feig DS, et al. Neurocognitive and behavioural outcomes in offspring exposed to maternal pre-existing diabetes: a systematic review and meta-analysis. Diabetologia 2019;62:1561-74.
31. Ornoy A, Ratzon N, Greenbaum C, Wolf A, Dulitzky M. School-age children born to diabetic mothers and to mothers with gestational diabetes exhibit a high rate of inattention and fine and gross motor impairment. J Pediatr Endocrinol Metab 2001;14:681-90.
32. Kong L, Norstedt G, Schalling M, Gissler M, Lavebratt C. The risk of offspring psychiatric disorders in the setting of maternal obesity and diabetes. Pediatrics 2018;142:e20180776.