



The maternal prepregnancy body mass index and the risk of attention deficit hyperactivity disorder among children and adolescents: a systematic review and meta-analysis

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Background: Attention deficit hyperactivity disorder (ADHD) symptoms have a major impact on individuals, families, and society. Therefore identification risk factors of ADHD are a public health priority.

Purpose: This is meta-analysis evaluated the association between maternal prepregnancy body mass index and the risk of ADHD among the resulting offspring.

Methods: The search identified studies published through December 2018 in the PubMed, Web of Science, and Scopus databases. The odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CI) extracted from eligible studies were used as the common measure of association among studies.

Results: A significant association was found between overweight women and the risk of ADHD among children with the pooled HR and OR estimates (HR, 1.27 and 95% CI, 1.17–1.37; OR, 1.28 and 95% CI, 1.15–1.40, respectively). This association was significant between obese women and the risk of ADHD among children and adolescents with the pooled estimates of HR and OR (HR, 1.65 and 95% CI, 1.55–1.76; OR, 1.42 and 95% CI, 1.23–1.61).

Conclusion: The current epidemiological studies present sufficient evidence that prepregnancy overweight and obesity are significantly associated with an increased risk of ADHD among children and adolescents. These findings provide a new approach to preventing ADHD by controlling weight gain in the prenatal period, which should be considered by policymakers.

Key words: Attention deficit disorder with hyperactivity, Body mass index, Pregnancy

Key message

Question: Is there an association between maternal prepregnancy BMI and offspring ADHD?

Finding: The findings of this study showed a significant association between prepregnancy overweight and obesity and the risk of ADHD among children according to pooled estimates of HR and OR.

Meanings: These findings provide a new approach to preventing ADHD by controlling prenatal weight gain that should be considered by policymakers.

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Introduction

The Diagnostic and Statistical Manual of Mental Disorders 4th edition defines attention deficit hyperactivity disorder (ADHD) as a neurobehavioral disorder characterized by pervasive

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and impairing symptoms of inattention, hyperactivity, and impulsivity.¹⁾ ADHD is one of the most common mental health disorders in childhood, with an estimated global prevalence of 5.2%.²⁾

Although genetics plays a significant role in the development of ADHD, 10%–40% of the variance associated with ADHD is related to environmental factors.³⁾ Environmental factors may interact with genetic influences or participate in the casual pathway of ADHD and its symptoms.^{4,5)} Given that the symptoms of ADHD appear early in life, the prenatal environment might play an important role in its development. Previous studies identified numerous prenatal risk factors of ADHD, such as premature birth, low birth weight, number of pregnancies and deliveries, infancy complications, maternal substance use, and stress during pregnancy.^{6,7)}

Studies have shown that prepregnancy maternal overweight or obese status may be associated with central nervous system problems in the fetus and newborn, including ADHD.⁸⁻¹⁰⁾

Maternal conditions and care in the prepregnancy period play an important role in preventing adverse pregnancy outcomes.¹¹⁾ Given that ADHD symptoms have a major impact on individuals, families, and society and feature continuous complications through adulthood, the identification of its risk factors is a public health priority for health policymakers.

Although several studies have shown a significant association between maternal prepregnancy body mass index (BMI) and offspring ADHD, several other studies have not. Thus, the status of this association is uncertain. Accordingly, the current meta-analysis aimed to investigate the association between maternal prepregnancy BMI and offspring ADHD.

Methods

1. Data sources

To evaluate the association between maternal prepregnancy BMI and the risk of ADHD among children and adolescents, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement checklist was used to assess the retrieved studies and raise the study quality herein.¹²⁾

2. Search strategy

The search identified studies published until December 2018 in the PubMed, Web of Science, and Scopus databases. The search was performed using the following principal terms categorized in 2 groups: (1) ADHD, attention deficit disorder with hyperactivity, attention deficit disorder hyperactivity, attention deficit disorder hyperactivity, child attention deficit disorder; and (2) body size, obese, obesity, overweight, BMI, and prepregnancy (or prepregnancy).

3. Inclusion and exclusion criteria

Studies that systematically assessed the association between maternal prepregnancy BMI and the risk of ADHD among children and adolescents were included. Inclusion criteria were BMI divided according to World Health Organization category: underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), and obese (≥30 kg/m²). Reviews, letters to the editor, and case reports were excluded.¹³⁾

4. Data extraction

The study selection process was conducted by 2 investigators (EJ and SK). Any disagreements were decided by a third author. The datasheet used for the extraction included publication year, first author, country, study design, maternal prepregnancy BMI and ADHD, diagnostic criteria of ADHD, sample size, hazard ratio (HR) and rate ratio (RR) and their associated 95% confidence intervals (CI), adjustment, child's age, and study quality.

5. Quality assessment

The methodology quality assessment of the studies included in the present meta-analysis was performed using the Newcastle-Ottawa Scale.¹⁴⁾ Two investigators conducted the quality assessment independently and divided the studies into low quality (<7 points) and high quality (≥7 points).

6. Statistical analysis

The HRs or RRs with 95% CI from eligible studies were used as the common measure of the association among studies. Heterogeneity across studies was addressed using the *I*² statistic. Low, medium, and high heterogeneity were defined by *I*² statistic values of 25%, 50%, and 75%, respectively.

Publication bias was assessed using the Begg and Egger's regression model.¹⁵⁾ The statistical meta-analysis was performed using Stata ver. 13 (Stata Corp., College Station, TX, USA).

Results

1. Description of studies

In the primary search, 505 studies were identified. Of them, we excluded 166 duplicate papers. In the next stage, 322 papers were excluded after the title and abstract screening and 9 papers were excluded after the full-text screening. Finally, 10 papers^{9,10,16-23)} with a total of 1,464,097 participants were included in the analysis. All studies were of cohort design. A flowchart of the selection process is shown in Fig. 1.

In the present meta-analysis, the confounding variables of the association between maternal prepregnancy BMI and the risk of ADHD among children and adolescents included socioeconomic status, smoking during pregnancy, maternal psychiatric diagnoses,

year of birth, mother’s country of birth, parental age, gestational age, birth weight, child sex, maternal education, and maternal age at delivery (Table 1). All studies in this meta-analysis were adjusted for these confounding variables.

2. Main analysis

A forest plot of the association between maternal prepregnancy BMI and risk of ADHD among children and adolescents is shown in Figs. 2 and 3. Van der Burg et al.¹⁹ reported the association between maternal prepregnancy BMI and risk of ADHD based on separate teacher/parent ratings of ADHD symptoms.

A significant association was found between overweight women and risk of ADHD among children based on the pooled estimates of HR and OR, respectively (HR, 1.27 and 95% CI, 1.17–1.37; OR, 1.28 and 95% CI, 1.15–1.76) (Fig. 2). This association was significant

between obese women and risk of ADHD among children and adolescents based on the pooled estimates of HR and OR, respectively (HR, 1.65 and 95% CI, 1.55–1.76; OR, 1.42 and 95% CI, 1.23–1.61) (Fig. 3). There was medium and low heterogeneity among the studies reporting on the risk ADHD in children based on HR in overweight and obese women, respectively ($I^2=59.3\%$, $P=0.117$) ($I^2=17.2\%$, $P=0.299$). There was no heterogeneity in the studies reporting the risk of ADHD among children and adolescents based on OR in overweight women ($I^2=0.0\%$, $P=0.608$). The heterogeneity based on OR in obese women was low ($I^2=0.02\%$, $P=0.427$).

The *P* values for Begg and Egger’s regression were 0.600 and 0.068 in overweight and obese women were 0.697 and 0.954, respectively. Therefore, we did not observe publication bias among studies.

3. Study quality

All studies in this meta-analysis had high methodology quality according to the Newcastle-Ottawa Scale (Table 1).

4. Subgroup analysis

The subgroup analysis was conducted based on teacher/parent-identified ADHD symptoms among children and adolescents in European countries and the USA. The pooled results based on ORs of the teacher/parent-identified ADHD symptoms and overweight women studies were 1.33 (95% CI, 0.95–1.70) and 1.26 (95% CI, 1.12–1.41), while those in obese women were 1.42 (95% CI, 0.70–2.13) and 1.47 (95% CI, 1.25–1.68), respectively. There was no significant association in teacher-identified ADHD symptoms among children and adolescents and overweight and obese women (Table 2). There was no significant association in ADHD symptoms among children and adolescents and overweight women in European countries and the USA, but this association was significant in obese women in the USA (OR, 1.44; 95% CI, 1.23–1.66) (Table 2).

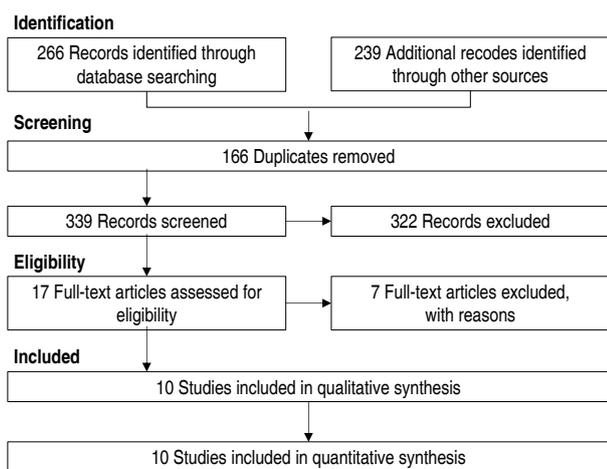


Fig. 1. Diagram of studies through the different phases of the meta-analysis.

Table 1. Results of the studies included in the present meta-analysis

Study	Country	Design	Sample size	Rated ADHD symptoms	Body mass index	Estimate	Adjustment	Child age in diagnose (yr)	Autism criteria	Quality
Chen et al. (2014) ¹⁶	Sweden	Cohort	673,632	Parents	Measured	Hazard ratio	Adjusted	9–17	DSM-V, ICD-10	High
van der Burg et al. (2007) ¹⁹	Netherland	Cohort	764	Parents/teacher	Self-reported	Odds ratio	Adjusted	10	DSM-V	High
Rodriguez et al. (2008) ⁹	Denmark, Finland, Sweden	Cohort	14,519	Teacher	Measured	Odds ratio	Adjusted	7–8	SDQ, RB2	High
Jo et al. (2015) ²¹	USA	Cohort	1,311	Parents	Self-reported	Odds ratio	Adjusted	6	By doctor or other health professional	High
Mikkelsen et al. (2017) ¹⁸	Denmark	Cohort	38,314	Parents	Self-reported	Odds ratio	Adjusted	7	SDQ	High
Kong et al. (2018) ¹⁷	Finland	Cohort	649,043	Parents	Measured	Hazard ratio	Adjusted	11	ICD-10	High
Rodriguez (2010) ¹⁰	Sweden	Cohort	1,714	Teacher	Measured	Odds ratio	Adjusted	5	DSM-V	High
Buss et al. (2012) ²²	USA	Cohort	174	Parents	Measured	Odds ratio	Crude	7.30	ICD-9	High
Li et al. (2016) ²³	USA	Cohort	2,734	Parents	Self-reported	Odds ratio	Crude	3.6–9	DSM-V	High

ADHD, attention deficit hyperactivity disorder; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; ICD-10, International Statistical Classification of Diseases, 10th revision; ICD-9, International Statistical Classification of Diseases, ninth revision; SDQ, Strengths and Difficulties Questionnaire.

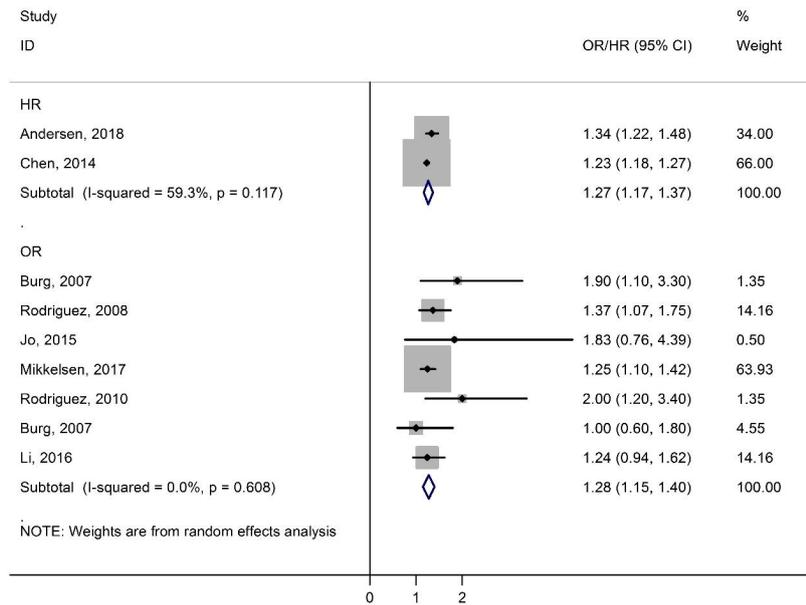


Fig. 2. Association between maternal prepregnancy overweight and risk of attention deficit disorder with hyperactivity among children. OR, odds ratio; HR, hazard ratio; CI, confidence interval.

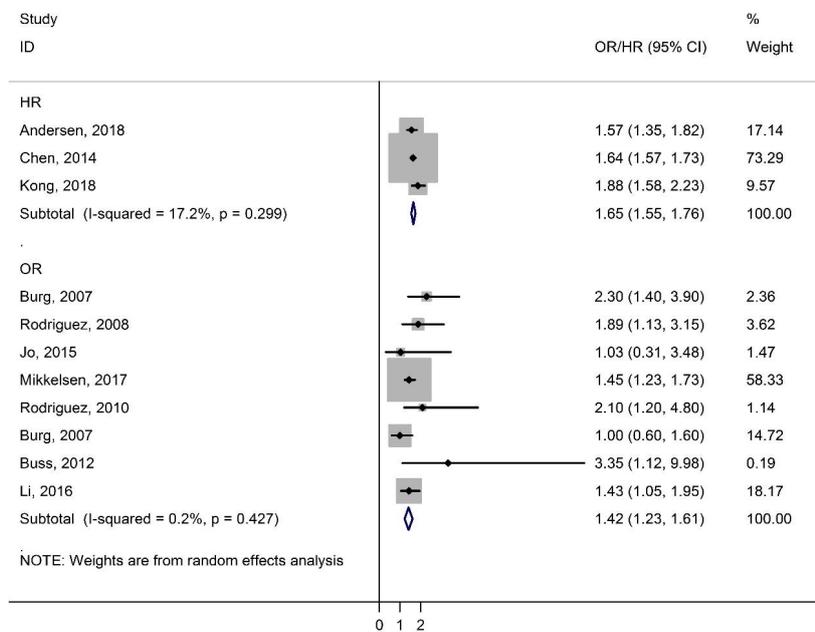


Fig. 3. Association between maternal prepregnancy obesity and the risk of attention deficit disorder with hyperactivity among children. OR, odds ratio; HR, hazard ratio; CI, confidence interval.

Discussion

This meta-analysis evaluated the association between maternal prepregnancy BMI and the risk of offspring ADHD in 8 individual studies. We found a statistically significant association between prepregnancy overweight and obesity and an increased risk of ADHD

among children based on the pooled estimates of both HR and OR. This study showed that the risk of offspring ADHD increased by about 30% in women with prepregnancy overweight status 42% and 65% in women with prepregnancy obesity according to OR and HR, respectively. In the subgroup analysis, there was no significant association in teacher-rated ADHD symptoms in the offsprings of

Table 2. Results of the subgroup analysis of the maternal prepregnancy BMI and ADHD based on teacher/parent-identified ADHD symptoms in the USA and European countries (studies based on OR)

Subgroups	Studies			
	No. of studies	BMI category	OR (95% CI)	<i>I</i> ²
By teacher/parents rated ADHD symptoms				
Parents	5	Overweight	1.26 (1.12–1.41)	0.0%
		Obese	1.47 (1.25–1.68)	0.0%
Teacher	3	Overweight	1.33 (0.95–1.70)	24.3%
		Obese	1.42 (0.70–2.13)	40.3%
By European/USA countries				
European countries	5	Overweight	1.38 (1.04–1.72)	16.9%
		Obese	1.25 (1.11–1.40)	0.0%
USA	3	Overweight	1.62 (0.91–2.34)	48.9%
		Obese	1.44 (1.23–1.66)	0.0%

BMI, body mass index; ADHD, attention deficit hyperactivity disorder; OR, odds ratio; CI, confidence interval.

overweight and obese women. This finding is important in terms of public health applications because it provides a new approach to preventing ADHD by controlling overweight and obesity in the prenatal period.

Some studies reported that maternal prepregnancy BMI is related to child ADHD and that it is not solely an artifact of effects that likely co-occur with maternal obesity.^{9,10} Other studies claim that the contribution of maternal overweight/obesity to adverse brain development is affected in part by inflammatory phenomena. Therefore, inflammation may play a role in the association between maternal overweight/obesity and ADHD in children and adolescents. Leptin, which is released in accordance with the amount of adipose tissue, has an inflammatory effect.²⁴ Obese pregnant women have higher levels of pro-inflammatory cytokines in the circulation than their normal-weight counterparts. Also, placental and intrauterine inflammation is related to an altered fetal cytokine situation, fetal neuronal damage, and changes in the neonatal brain gene expression. Furthermore, the normal developmental trajectory of the fetal brain can be disrupted by exposure to infection and high levels of pro-inflammatory cytokines, producing long-term or constant outcomes for gray matter volume and white matter integrity.^{25,26} This makes the fetus susceptible to psychiatric complications; therefore, ADHD is related to increased levels of inflammatory cytokines.^{27,28}

A meta-analysis conducted by Sanchez et al.²⁹ detailed the association of maternal obesity and diabetes with autism and other developmental disabilities. They reported that maternal overweight and obesity in prepregnancy were associated with ADHD in the offspring. However, they searched the PubMed and PsycINFO databases and found only 6 studies.

The present analysis revealed no significant association between teacher-identified ADHD symptoms among children and adolescents and prepregnancy overweight and obese status in women. The probable cause for this discrepancy between parent and teacher outcomes was differences in the settings for observing children

between them. The child is seen by teacher in the structured environment of the classroom while medicated, whereas the parent has seen the child in the unstructured home setting while not medicated.

In this study, to understand the role of ethnicity on findings, we divided the enrolled studies into 2 categories (conducted in the USA vs. European countries). The results showed consistent association in the 2 subgroups. Therefore, this hypothesis is strengthened that ethnic differences may not play a role in this association.

Regarding clinical implications, we know that meta-analysis studies provide a precise and less biased estimate of the effect size with increased statistical power on a specific topic, which is important when the power of the primary study is limited because of a small sample size. Understanding how to conduct meta-analysis aids clinicians in the process of making clinical decisions. The results of our meta-analysis should be interpreted with clear understanding of their strengths and limitations. Regarding strengths, we first performed a systematic search of the major international databases, placing no restrictions on language, publication date, and document type. Second, according to the Newcastle–Ottawa Scale, all of the included studies were of high quality. Finally, the included studies typically were longitudinal cohorts with large sample sizes and adequate statistical power. There are also a number of limitations that should be considered. First, this meta-analysis was based on observational studies, the design of which is associated with inherent biases. Second, BMI measured in 4 studies was based on self-reports; thus, their validity is questionable. Third, the studies included in this meta-analysis were conducted in the USA and European countries, which might introduce data bias to this meta-analysis assessing the relationship between ADHD and prepregnancy BMI. This knowledge about the association between maternal overweight/obesity and ADHD among children and adolescents can lead to an early assessment of children at risk and improve the methods of early diagnosis and intervention.

Epidemiological studies published to date provide sufficient

evidence that prepregnancy overweight and obesity are significantly associated with an increased risk of ADHD among children and adolescents. These findings provide a new approach to preventing ADHD by controlling overweight and obesity in the prenatal period, which should be considered by policymakers.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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