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Review article

Associations between maternal preconception and pregnancy adiposity and neuropsychiatric and behavioral outcomes in the offspring: A systematic review and meta-analysis

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ABSTRACT

Maternal adiposity (overweight or obesity) has been associated with adverse perinatal outcomes, although the potential risks of long-term neuropsychiatric and behavioral outcomes in the offspring remain unclear. Using the PRISMA guidelines, we searched PubMed, EMBASE, Scopus, and Web of Science to identify studies on maternal adiposity and offspring neuropsychiatric outcomes. Inverse variance-weighted random-effects meta-analyses were used to pool effect estimates with 95 % confidence intervals (95 % CIs) from adjusted odds ratios (OR) and hazard ratios (HR). Estimates were computed separately for preconception and pregnancy maternal overweight and obesity, with outcomes stratified by the type of neuropsychiatric outcome. In our meta-analyses of 42 epidemiological studies involving 3,680,937 mother-offspring pairs, we found increased risks of ADHD [OR=1.57, 95 % CI: 1.42-1.74], autism spectrum disorder [OR=1.42, 95 % CI: 1.22-1.65], conduct disorder [OR=1.16, 95 % CI: 1.00-1.35], Psychotic disorder [HR=1.61, 95 % CI: 1.41-1.83], externalizing behaviors [OR=1.30, 95 % CI: 1.07-1.56] and peer relationship problems [OR=1.25, 95 % CI: 1.04-1.27] in the offspring of preconception obese mothers. Similar increased risks were found in the offspring of preconception overweight mothers and those exposed to maternal adiposity during pregnancy. However, no association was found with offspring mood, anxiety, personality, eating, sleep disorders or prosocial problems. Preconception weight management may mitigate such adverse effects in the offspring.

1. Background

Over the past few decades, preconception and maternal obesity have emerged as a significant global epidemic among the reproductive age population, posing ongoing public health challenges (McIntyre et al., Cheney et al., 2018). This increase in adiposity is not limited to women alone but is also observed in the general population, where paternal adiposity may also serve as a risk factor. Epidemiologic studies consistently demonstrate a significant rise in the prevalence of obesity and excessive weight gain among women of childbearing age across diverse

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populations (Wang et al., 2021; Langley-Evans et al., 2022). This growing concern extends to intergenerational health, as maternal adiposity has been linked with adverse perinatal outcomes, including preterm birth, low birthweight (Cheney et al., 2018; Gete et al., 2020; Madzorera et al., 2020), small or large for gestational age and stillbirths (Cheney et al., 2018; Madzorera et al., 2020).

In addition to the associations of preconception and/or pregnancy obesity with adverse perinatal outcomes, recent evidence has also suggested positive associations with neuropsychiatric and behavioral outcomes in the offspring during childhood (Andersen et al., 2018; Casas et al., 2017; Chen et al., 2014; Grudzinski et al., 2019; Kong et al., 2018; Rodriguez, 2010; Rodriguez et al., 2008). Compared to offspring of mothers with a healthy preconception body weight, children born to overweight or obese mother have been found to be at higher risks of autism spectrum disorder (ASD) (Getz et al., 2016; Jo et al., 2015; Neuhaus et al., 2020), attention-deficit/hyperactivity disorder (ADHD) (Casas et al., 2017; Jo et al., 2015; Kong et al., 2020; Perea et al., 2022), mood disorders (Mina et al., 2017; Robinson, 2013), anxiety disorders (Kong et al., 2020; Mina et al., 2017) schizophrenia (Lahti-Pulkkinen et al., 2021), and a ranges of psycho-neurotic, mood, stress and somatization disorders (Grudzinski et al., 2019; Kong et al., 2018; Neuhaus et al., 2020). However, evidence is inconsistent, and additional observational studies have not found such associations between maternal adiposity and neuropsychiatric and behavioral outcomes in the offspring (Kong et al., 2020; Daraki et al., 2017; Fuemmeler et al., 2019; MacKay et al., 2017; Robinson et al., 2020; Lingineni et al., 2012).

These conflicting results could be due to differences in sample size or variations in covariate selection across studies. For instance, some studies have concluded that the association between maternal obesity and neuropsychiatric and behavioral outcomes in the offspring could be due to unmeasured socio-economic, familial, or maternal confounding rather than a direct causal effect of maternal adiposity (Chen et al., 2014; Grudzinski et al., 2019; Brion et al., 2011; Musser et al., 2017). This suggests that incomplete statistical control for such putative risk factors may lead to biased estimates. However, the association between maternal adiposity and neuropsychiatric and behavioral problems in the offspring has not been systematically and comprehensively reviewed or quantified to date. One of the existing reviews (Sanchez et al., 2018; Lei et al., 2019; Jenabi et al., 2019) has merely examined the association between preconception maternal obesity and a few offspring neurodevelopmental outcomes (Sanchez et al., 2018). Subsequent reviews in 2018 included a few studies to examine the association between pre-pregnancy obesity and ASD (Lei et al., 2019), and ADHD in the offspring (Jenabi et al., 2019). More importantly, over the past six years, there has been a considerable increase in the number of publications on similar topics, suggesting that an update of the existing evidence through a more comprehensive systematic review and meta-analysis is warranted. Moreover, a more detailed systematic review and meta-analysis that examines the specific period of adiposity, dose-related effects, and their impact on a wide range of offspring outcomes is imperative for mechanistic studies, clinical and policy implications. We, therefore, examined the association between maternal preconception and pregnancy adiposity and adverse neuropsychiatric and behavioral outcomes in the offspring.

2. Methods

2.1. Study design and search strategy

This systematic review and meta-analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2010). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42023414828. Two reviewers (BD and TSM) developed key search terms using the Population/participants, Interventions, Comparisons, Outcomes, and Study design (PICOS) framework (Methley et al., 2014) **(Supplementary table 1)**. We searched citations using key terms that encompass a wide range of conditions and symptoms related to neurodevelopmental and behavioral issues including "neurodevelopmental", "oppositional defiant disorder (ODD)", "conduct disorder (CD)", "attention deficit hyperactivity disorder (ADHD)", "antisocial behavior", "neuropsychiatric disorders", "anxiety or anxiety disorder", "depression or depressive disorder", "mood disorder", "posttraumatic stress disorder", "acute stress disorder", "panic attack", "conversion disorder", "bipolar disorder", "manic attack", "eating disorder", "anorexia nervosa or bulimia nervosa", "psychosis", "schizophrenia", "delusion" and "suicide". BD and TSM developed a search strategy combining key terms and medical subject heading [MeSH terms] with relevant filters. We used Boolean operators ("AND", "OR", "NOT") to combine key words or independent searches and truncations to capture words that could have multiple endings. We searched four databases including PubMed, EMBASE, Scopus and Web of Science from inception to April 2024. The full search strategy is included as a **Supplementary file 2**. The electronic database search was updated in April 2024.

2.2. Study selection and exclusion criteria

Citations retrieved from all electronic databases were imported into EndNote 20 and duplicates were removed. After removing duplicates, two reviewers (BD and TSM) independently screened titles and abstracts using Covidence systematic review software. Discrepancies in screening were resolved through discussion by AB. Studies were included in the meta-analysis if they: (McIntyre et al.) examined the association between preconception or pregnancy overweight or obesity and offspring neuropsychiatric or behavioral problems; (Cheney et al., 2018) were conducted on human populations and published in English language; and (Wang et al., 2021) used observational study designs (cohort studies, case-control, nested case-control, and cross-sectional studies). Studies on animals, reviews, case series/reports, conference papers, conference proceedings, editorials, letters to the editors and commentaries were excluded.

2.3. Data extraction and quality appraisal

TSM and BD extracted data on authors, year of publication, country, study design, study participants, study sample, study design/method, key findings and conclusion using a pre-prepared data extraction sheet. The extracted data was further checked consistency by AB. The methodological quality of the included studies was assessed by two independent reviewers (BD and TSM) using the Newcastle–Ottawa Scale (NOS) (Wells et al., 2009). This tool consists of three domains: selection of study participants, comparability of study groups, and reporting and ascertainment of outcomes. Each primary study was graded out of nine points as per the NOS coding manual (McPheeters et al., 2012) and summarized in three categories as good (if total score >7), fair (if total score 5–6) or poor (if total score <5). Studies were deemed to be at high risk of bias if the NOS score was < 6. Disagreements in the assessment of methodological quality ratings were resolved through discussion.

2.4. Study outcome

The outcomes of interest of this systematic review and meta-analysis are any neuropsychiatric and behavioral outcomes in the offspring (excluding addictive behaviors), ADHD, ASD, mood disorders, anxiety disorders, conduct disorder, psychotic disorders, personality disorders, eating disorders, sleep problems, peer relationship and prosocial problems, and internalizing and externalizing behaviors at any age.

2.5. Statistical analysis

We performed inverse-variance-weighted random-effects meta-

analysis to address heterogeneity among studies included in the review using a STATA version 18. All primary studies that reported effect size using odds ratios/ relative risks (OR/RR), hazard ratio (HR) or provided data to calculate these were included in the final meta-analysis. Otherwise, we tabulated the results and presented a narrative review of the studies. For the studies that reported multiple effect estimates, the estimate with the most extensive adjustment were used for meta-analyses. For the studies that reported multiple outcomes, each outcome was reported separately in this review. Inverse variance weighted random effects meta-analysis models were used to combine studies to estimate the association between maternal preconception and pregnancy adiposity and offspring neuropsychiatric and behavioral adverse outcomes and to account for heterogeneity across the studies included in the review. To explore which offspring outcomes were specifically associated with maternal preconception and pregnancy overweight or obesity, we stratified meta-analyses by classifying outcomes to ADHD, ASD, mood disorders, anxiety disorders, conduct disorder, psychotic disorders, personality disorder, eating disorders, sleep related, peer relationship and prosocial problems, and internalizing and externalizing symptoms. Further, the estimates for maternal preconception and pregnancy adiposity were computed separately to check whether the effect estimates were sensitive to the specified time of exposure, i.e., preconception and pregnancy. Sub-group analyses were also performed according to the maternal adiposity, determined based on their body mass index (BMI) and classified according to the WHO criteria as overweight (25.0–29.9 kg/m^2) and obesity (30.0–34.9kg/m^2) (WHO 2022). Tau-and I^2-test were used to detect the magnitude of statistical heterogeneity between studies. I^2-test scores 75 % was considered to high heterogeneity between studies. We checked potential publication bias by inspection of the funnel plot and Egger's test for regression asymmetry. As a sensitivity analysis, we calculated the statistical power of each study included in the meta-analysis to determine if they had sufficient power to detect the effect of exposure on outcomes **(Supplementary File 3).**

3. Results

3.1. Study selection and characteristics

The initial literature search returned 5421 eligible studies. After removing duplicates ($n = 1764$), and non-relevant studies that are not meeting the inclusion criteria ($n = 3598$), we proceeded with full-text review of 59 studies. Ultimately, 42 studies, consisting of 3,680,937 mothers and offspring pairs, were eligible for final inclusion (Fig. 1). Although there are fluctuations in the number of publications of similar observational studies every year, the trendline suggests a slight increase in the number of publications annually (**Supplementary file 4**). The characteristics and key findings of the included studies are summarized in Table 1, which provides a summary of the overweight/obesity classification, measured outcomes, and key results as effect estimates. Of the 42 studies, 15 were conducted in the USA (Robinson et al., 2020; Fuemmeler et al., 2019; Getz et al., 2016; Jo et al., 2015; Parker et al., 2022; Marmorstein and Iacono, 2016; Musser et al., 2017; van der Burg et al., 2017; Hendrix, 2011; Connolly et al., 2016; Buss et al., 2012; Krakowiak et al., 2012; Lyall et al., 2011; Li et al., 2016; Moss and Chugani, 2014; Reynolds et al., 2014), five in Sweden (Chen et al., 2014; Rodriguez, 2010; MacKay et al., 2017; Razaz and Cnattingius, 2018; Gardner et al., 2015), three in the UK (Mina et al., 2017; Lahti-Pulkkinen et al., 2021; Micali et al., 2018), two each in Australia (Robinson, 2013; Van Lieshout et al., 2013), Denmark (Andersen et al., 2018; Mikkelsen et al., 2017), Finland (Kong et al., 2018, 2020), Spain (Casas et al., 2017; Perea et al., 2022), and one study each in Brazil (Quinte et al., 2022), Canada(10), China (Zhang et al., 2023), France (Dow et al., 2022), Greece (Daraki et al., 2017), Israel (Neuhaus et al., 2020), the Netherlands (Menting et al., 2018), and Norway (Suren et al., 2014). Three studies were multi-national: one study in the UK and Netherlands (Brion et al., 2011), one in Sweden, Denmark, and Finland (Rodriguez et al., 2008) and one in the USA and Canada (Parker et al., 2022). Of the 42 included studies, 39 were cohort studies and three were case control studies. The sample sizes for the included studies are ranging from the smallest with 62 participants to the largest cohort with 673,632 participants (Table 1). All the studies included in this review scored ≥ 7 in the Newcastle Ottawa scale, suggesting good methodological quality (**Supplementary file 5**).

3.2. Meta-analysis: effect of preconception and pregnancy adiposity on offspring neuropsychiatric and behavioral outcomes

Of the 42 studies included in this review, 16 reported on ADHD, seven on ASD, 11 on mood and anxiety-related disorders, 10 on internalizing behaviors, seven on externalizing behaviors, and six on peer relationship problems. The remaining studies reported on prosocial behavior, eating disorders, psychotic disorders, personality disorders, and other eating disorders. Most studies included in this review reported fully adjusted effect estimates, whereas one study presented an unadjusted effect estimate (Fuemmeler et al., 2019) (Table 1).

Our meta-analyses demonstrated that offspring exposed to preconception overweight [pooled OR = 1.18, 95 % CI: 1.11-1.27] and obesity [pooled OR = 1.57, 95 % CI: 1.42-1.74] were at 18 % and 57 % increased risk of ADHD, respectively, when compared with non-exposed offspring (Fig. 2). Similarly, offspring exposed to maternal overweight [pooled OR=1.19, 95 % CI: 1.02-1.39] and obesity during pregnancy [pooled OR = 1.32, 95 % CI:1.04-1.66] were at 19 % and 32 % increased risk of ADHD, respectively, when compared with their non-exposed counterparts (Fig. 3).

Offspring exposed to maternal adiposity both during preconception period and pregnancy were at increased risk of ASD. We found that offspring exposed to maternal preconception overweight [pooled OR=1.09, 95 % CI:1.02-1.16] and obesity [pooled OR= 1.42, 95 % CI:1.22-1.65] were at 9 % and 42 % increased risk of ASD, respectively, when compared with non-exposed offspring (Fig. 4). We also observed a two-fold higher risk of ASD in offspring exposed to maternal obesity during pregnancy [pooled OR = 2.23, 95 % CI: 1.23-4.05] (Fig. 5).

Offspring born to mothers who were obese prior to conception had a 16 % higher likelihood of experiencing CD [pooled OR = 1.16, 95 % CI: 1.00-1.35]. However, maternal preconception overweight status was not associated with CD in offspring (Fig. 6). Similarly, our meta-analysis suggested insufficient statistical evidence to support associations between offspring mood disorders and internalizing behaviors with maternal preconception adiposity (Fig. 7). The meta-analysis of studies on externalizing behaviors found maternal preconception obesity associated with an increased risk [pooled OR = 1.30, 95 % CI: 1.07-1.56]. Conversely, maternal preconception overweight was not associated with an increased risk of offspring externalizing behaviors [pooled OR = 1.15, 95 % CI: 0.92-1.44], suggesting a dose-response association (Fig. 8). Similarly, unlike maternal preconception overweight, maternal preconception obesity was associated with an increased risk of offspring peer relationship problems [pooled OR = 1.47, 95 % CI: 1.09-1.97] (Fig. 9).

However, we were unable to examine the association between maternal preconception and pregnancy adiposity and certain offspring outcomes, such as anxiety disorder, sleep disorder, schizophrenia, and eating disorders, including anorexia nervosa, as only one study each examined those specific outcomes. Based on our narrative review of those studies, maternal preconception obesity was associated with an increased risk of anxiety disorder, while maternal pregnancy adiposity was associated with an increased risk of offspring peer relationship problems. All other offspring outcomes were not associated with maternal preconception and pregnancy adiposity **(Supplementary file 6).** Similarly, maternal pregnancy adiposity was not associated with offspring psychotic disorder and prosocial behaviors **(Supplementary file 7-8).**

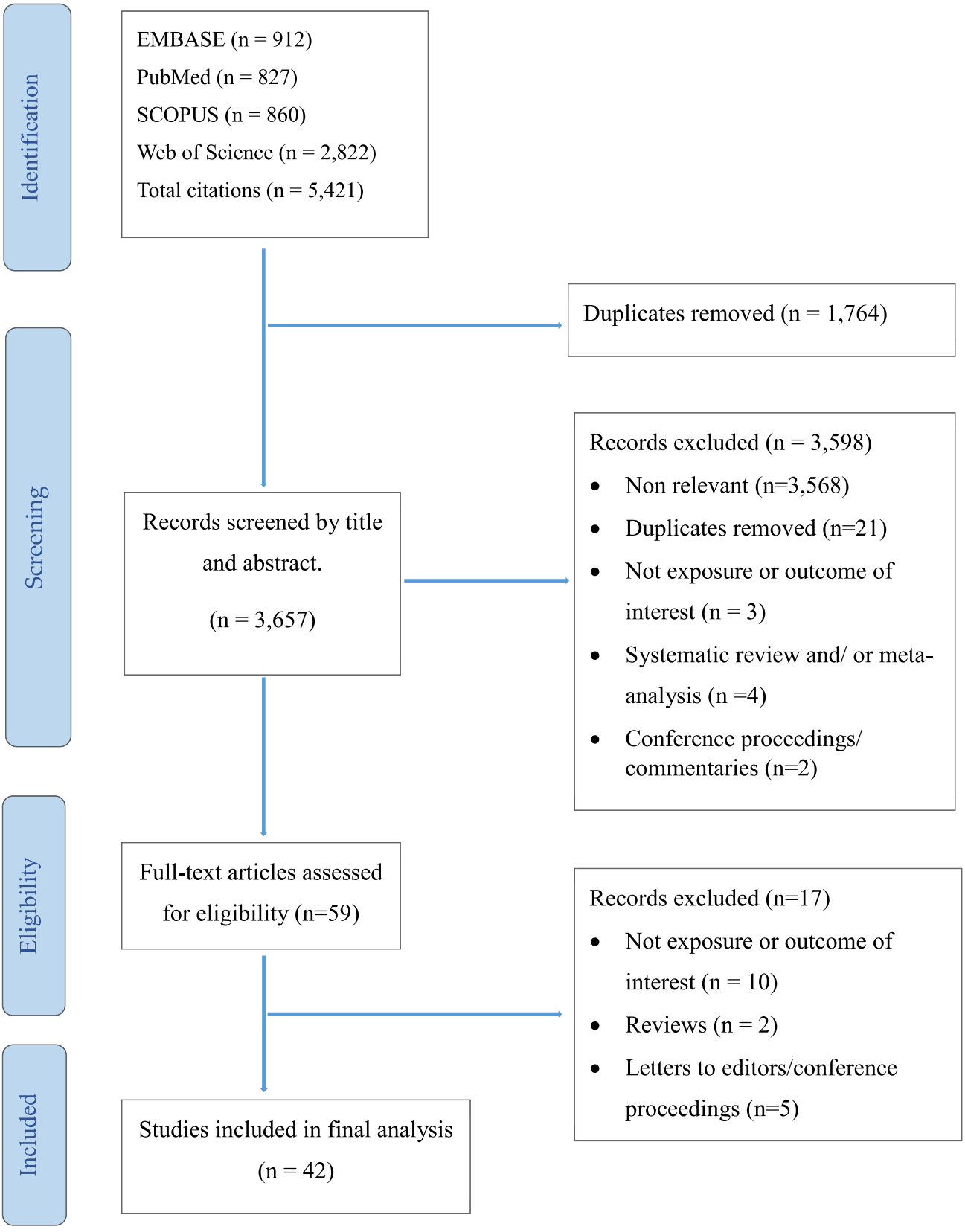

Fig. 1. PRISMA flow diagram of screening and selection process.

Table 1
Characteristics and key findings of studies included in the systematic review and meta-analysis ($n = 42$).

Author (year)	Country	Study design	Sample size	Time BMI measured	Offspring outcome	Number of cases from total sample	Offspring outcome ascertained by	Maternal BMI classifications (kg/m^2)	Adjusted effect estimates (OR/RR/HR/ Beta coef.)
Preconception period									
Andersen et al., 2018	Denmark	Longitudinal cohort	81,892	Any time before pregnancy	ADHD	2417	ICD-10	25.0–29.9	1.28 (1.15-1.41)
								30.0–34.9	1.47 (1.26-1.71)
								≥ 35.0	1.95 (1.58-2.40
					ASD	1118		25.0–29.9	1.09 (0.94-1.27)
								30.0–34.9	1.39 (1.11-1.75
								≥ 35.0	1.38 (0.97-1.97)
Brion et al., 2011	UK and Netherlands	Geographic based prospective cohort	6919	Any time before pregnancy	Attention/ Hyperactivity Problems	2349	Strengths and Difficulties Questionnaire	≥ 25.0	0.93 (0.82-1.05)
					Emotional / Internalizing Problems, Quintiles				1.00 (0.88-1.13)
					Conduct / Externalizing Problems, Quintiles	2358			1.00 (0.88-1.13)
					Attention/ Hyperactivity Problems				1.06 (0.89-1.27)
					Emotional / Internalizing Problems, Quintiles	2355			1.12 (0.93-1.36)
					Conduct / Externalizing Problems, Quintiles				1.21 (1.00-1.47)
Casas et al., 2017	Spain	Cohort study	1827	Self-reported at first antenatal visit	ADHD	486	DSM-IV	25.0–29.9	1.05 (0.55-1.99)
								≥30.0	1.40 (0.44-4.53)
					Autism spectrum disorder symptoms	486	Childhood Asperger Syndrome Test	25.0–29.9	1.02 (0.93-1.11)
								≥30.0	1.06 (0.91-1.23)
Chen et al., 2014	Sweden	Population-based cohort study	673,632	Self-reported at first antenatal visit	ADHD	17,380	ICD-9/ ICD-10	25.0–29.9	1.23 (1.18-1.27)
								≥30.0	1.64 (1.57-1.73)
Daraki et al., 2017	Greece	Prospective cohort	772	Self-reported at first antenatal visit	ADHD	581	Strengths and Difficulties Questionnaire	25.0–29.9	−0.69 (−3.03-1.64)
								≥30.0	4.28 (1.20-7.36)
Dow et al., 2022	France	Cohort study	1428	Self-reported at first third trimester	ADHD	247	Strengths and Difficulties Questionnaire	25.0–29.9	1.32 (0.87-2.01)
								≥ 30	1.87 (1.12-3.12)
Fuemmeler et al., 2019	USA	Cohort study	331	Self-reported at the last menstrual period prior to the first prenatal visit	ADHD symptoms	171	Behavior Assessment System for Children	25.0–29.9	Not reported
								30.0–34.9	Not reported
								≥35.0	Not reported
Getz et al., 2016	USA	Case control study	4419	Within the two years before and closest to the last	ASD	395	Clinically by GPs	25.0–29.9	1.20 (1.00-1.44)
								≥ 30	1.52 (1.23-1.86)

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Country	Study design	Sample size	Time BMI measured	Offspring outcome	Number of cases from total sample	Offspring outcome ascertained by	Maternal BMI classifications (kg/m^2)	Adjusted effect estimates (OR/RR/HR/ Beta coef.)
				menstrual period					
Grudzinski et al., 2019	Canada	Population-based retrospective cohort study	38,211	Self-reported at first antenatal visit	Any mental health disorder	716	ICD-9	25.0–29.9	1.03 (0.97–1.09)
								≥ 30	1.26 (1.19–1.34)
					Mood, anxiety, and adjustment disorders	246		25.0–29.9	1.02 (0.96–1.09)
								≥ 30	1.16 (1.07–1.25)
					Conduct disorder	57		25.0–29.9	0.99 (0.88–1.10)
								≥ 30	1.25 (1.08–1.45)
					ADHD	283		25.0–29.9	1.09 (0.95-1.26)
								≥ 30	1.45 (1.24–1.69)
Jo et al., 2015	USA	Longitudinal cohort study	1311	Not reported	Emotional symptoms	Not reported	Strengths and Difficulties Questionnaire	25.0–29.9	1.21 (0.72–2.03)
								30.0–34.9	1.45 (0.79–2.69)
								≥ 35.0	2.24 (1.27–3.98)
					Conduct problems			25.0–29.9	1.08 (0.71–1.66)
								30.0–34.9	1.47 (0.89–2.42)
								≥ 35.0	1.47 (0.88–2.45)
					Hyperactivity symptoms			25.0–29.9	1.06 (0.72–1.55)
								30.0–34.9	1.14 (0.71–1.84)
								≥ 35.0	1.31 (0.81–2.12)
					Peer problems			25.0–29.9	1.17 (0.76–1.80)
								30.0–34.9	1.04 (0.60–1.82)
								≥ 35.0	2.07 (1.26–3.40)
					Prosocial behavior			25.0–29.9	1.11 (0.64–1.93)
								30.0–34.9	0.47 (0.18–1.22)
								≥ 35.0	1.33 (0.66–2.67)
					ADHD		Clinical diagnoses	25.0–29.9	2.04 (0.88–4.75)
								30.0–34.9	1.18 (0.36–3.87)
								≥ 35.0	4.55 (1.80–11.46)
					Autism			25.0–29.9	1.08 (0.38–3.08)
								30.0–34.9	Not available
								≥ 35.0	3.13 (1.10–8.94)
					Depression or anxiety disorder		Strengths and Difficulties Questionnaire	25.0–29.9	0.81 (0.20–3.24)
								30.0–34.9	0.60 (0.07–4.96)
								≥ 35.0	3.08 (0.89–10.58)
Kong et al., 2020	Finland	Population based cohort study	649,043	Recorded at first prenatal visit	Mood disorder	1999	ICD-10	25.0–29.9	0.85 (074-0.98)
								30.0–34.9	0.91 0.72-1.15)
								≥ 35.0	1.26 (0.91-1.74)

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Table 1 (*continued*)

Author (year)	Country	Study design	Sample size	Time BMI measured	Offspring outcome	Number of cases from total sample	Offspring outcome ascertained by	Maternal BMI classifications (kg/m^2)	Adjusted effect estimates (OR/RR/HR/ Beta coef.)
					Anxiety disorder	4713		25.0–29.9	0.96 (0.88-1.05)
								30.0–34.9	1.31 (1.16-1.49)
								≥ 35.0	1.41 (1.15-1.72)
					Eating disorder	279		25.0–29.9	1.00 (0.71-1.41)
								30.0–34.9	0.81 (0.43-1.53)
								≥ 35.0	0.89 (0.33-2.40)
					Sleeping disorder	2219		25.0–29.9	1.07 (0.96-1.21)
								30.0–34.9	1.00 (0.82-1.22)
								≥ 35.0	1.04 (0.75-1.42)
					ADHD	5263		25.0–29.9	1.15 (1.06-1.24)
								30.0–34.9	1.43 (1.26-1.61)
								≥ 35.0	1.87 (1.58-2.23)
Kong et al., 2018	Finland	Population based cohort study	649 043	Recorded at first prenatal visit	ASD	2346	ICD-10	25.0–29.9	1.15 (1.03 – 1.29)
								30.0–34.9	1.28 (1.06 – 1.55)
								≥ 35.0	1.25 (0.92 – 1.70)
					ADHD	5263		25.0–29.9	1.15 (1.06 – 1.24)
								30.0–34.9	1.44 (1.28 – 1.63)
								≥ 35.0	1.88 (1.58 – 2.23)
					Conduct disorders	5301		25.0–29.9	0.85 (0.78 – 0.93)
								30.0–34.9	0.98 (0.86 – 1.12)
								≥ 35.0	1.15 (0.94 – 1.41)
					Behavioral and emotional disorders	8506		25.0–29.9	1.01 (0.95–1.07)
								30.0–34.9	1.14 (1.03–1.26)
								≥ 35.0	1.17 (0.99–1.37)
					Psycho-neurotic, mood, stress, and somatization disorders	2928		25.0–29.9	1.19 (1.07–1.32)
								30.0–34.9	1.58 (1.36–1.85)
								≥ 35.0	1.67 (1.31–2.13)
					Eating disorders	279		25.0–29.9	1.00 (0.71–1.41)
								30.0–34.9	0.08 (0.43–1.54)
								≥ 35.0	0.89 (0.33–2.41)
					Sleep disorders (nonorganic)	2219		25.0–29.9	1.08 (0.96–1.21)
								30.0–34.9	1.04 (0.85–1.26)
								≥ 35.0	1.04 (0.76–1.43)
Marmorstein & Iacono, 2016	USA	Longitudinal cohort study	863	Not reported	Major depressive disorder	589	Structured Clinical Interview for DSM-III-R	≥ 30	1.41 (1.09–1.81)
Menting et al., 2018	Netherlands	Population based	4094	Self-reported height	Emotional problems	44	Strengths and Difficulties Questionnaire	25.0–29.9	1.06 (0.81-1.38)

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Table 1 (*continued*)

Author (year)	Country	Study design	Sample size	Time BMI measured	Offspring outcome	Number of cases from total sample	Offspring outcome ascertained by	Maternal BMI classifications (kg/m^2)	Adjusted effect estimates (OR/RR/HR/ Beta coef.)
		prospective cohort study		and weight before pregnancy	Conduct problems	90			1.21 (0.90-1.63)
					Hyperactivity/ inattention symptoms	70			1.08 (0.87-1.34)
					Peer relationship problems	186			0.93 (0.71-1.21)
					Emotional problems	86			0.93 (0.73-1.18)
					Conduct problems	119			1.40 (1.06-1.84)
					Hyperactivity/ inattention symptoms	90			1.66 (0.99-2.81)
					Emotional problems	20		≥ 30	1.39 (0.96-2.03)
					Conduct problems	44			1.54 (1.00-2.36)
					Hyperactivity/ inattention symptoms	32			1.09 (0.79-1.52)
					Peer relationship problems	77			0.98 (0.64-1.49)
					Emotional problems	31			1.11 (0.77-1.60)
					Conduct problems	50			0.99 (0.62-1.59)
					Hyperactivity/ inattention symptoms	25			1.77 (1.18-2.64)
					Peer relationship problems	39			1.06 (0.81-1.38)
Micali et al., 2018	UK	Population-based cohort study	3,529	Self-reported height and weight at enrolment during pregnancy	Eating disorder behaviors	188	Developmental and Well-being Assessment	Overweight/ Obese	0.25 (0.18-0.32)
Musser et al., 2017	USA	Population based study	4682	Within one year prior to pregnancy	ADHD	187	Clinical diagnosis	≥ 30	0.04 (0.02 - 0.06)
Parker et al., 2022	USA/ Canada	Longitudinal study	469	Self-reported within 12 months of delivery	Externalizing	13	Child Behavior Checklist	25.0–29.9	1.40 (0.80-2.60)
					Internalizing	12			0.80 (0.40-1.50)
					Externalizing	11		≥ 30	1.60 (0.80-3.20)
					Internalizing	9			1.00 (0.50-2.10)
					Externalizing	16		25.0–29.9	1.50 (0.80-2.80)
					Internalizing	11			1.10 (0.60-2.20)
					Externalizing	9		≥ 30	1.70 (0.80-3.50)
					Internalizing	15			2.60 (1.50-4.60)
Perea et al., 2022	Spain	Prospective cohort study	1036	Self-reported at antenatal visit	ADHD	72	ICD-10	25.0–29.9	1.33 (0.88-2.00)
								≥ 30	1.66 (1.10-2.67)
								Excessive GWG	1.22 (0.75-1.99)
Quinte et al., 2022	Brazil	Population-based cohort study	4231	First trimester (from antenatal record)	Emotional symptoms	194	Strengths and Difficulties Questionnaire	25.0–29.9	1.01 (0.82-1.23)
					Conduct problems	136			1.32 (1.03-1.68)
					Hyperactivity/ inattention symptoms	129			0.79 (0.63-0.99)

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Table 1 (*continued*)

Author (year)	Country	Study design	Sample size	Time BMI measured	Offspring outcome	Number of cases from total sample	Offspring outcome ascertained by	Maternal BMI classifications (kg/m^2)	Adjusted effect estimates (OR/RR/HR/ Beta coef.)
					Peer relationship problems	130			1.05 (0.83-1.34)
					Emotional symptoms	105		≥ 30	1.14 (0.88-1.47)
					Conduct problems	71			1.42 (1.04-1.93)
					Hyperactivity/ inattention symptoms	82			1.09 (0.82-1.45)
					Peer relationship problems	64			1.01 (0.82-1.23)
Robinson et al, 2013	Australia	Prospective cohort study	2868	Self-reported at 18 weeks gestation	Affective disorder	Not reported	Child Behavior Checklist	25.0–29.9	1.51 (1.08-2.12)
								≥ 30	1.72 (1.11-2.67)
Robinson et al., 2020	USA	Population-based cohort study	1386	Self-reported at enrolment	ADHD	183	Vanderbilt ADHD Diagnostic Parent Rating Scale	25.0–29.9	1.14 (0.78-1.69)
								30.0–34.9	1.96 (1.29-2.98)
								≥ 35.0	1.82 (1.21-2.74)
					Anxiety	150	Strengths and Difficulties Questionnaire	25.0–29.9	1.28 (0.85-1.91)
								30.0–34.9	1.55 (0.95-2.54)
								≥ 35.0	1.29 (0.77-2.15)
					Emotional symptoms	193		25.0–29.9	0.92 (0.64-1.32)
								30.0–34.9	1.26 (0.84-1.89)
								≥ 35.0	1.30 (0.85-1.98)
					Peer relationship problems	211		25.0–29.9	0.94 (0.67-1.32)
								30.0–34.9	0.92 (0.58-1.45)
								≥ 35.0	1.38 (0.95-2.02)
					Conduct problems	201		25.0–29.9	1.08 (0.78-1.51)
								30.0–34.9	1.10 (0.73-1.66)
								≥ 35.0	1.26 (0.86-1.84)
					Prosocial behaviors	214		25.0–29.9	0.68 (0.37-1.27)
								30.0–34.9	0.87 (0.41-1.86)
								≥ 35.0	1.55 (0.84-2.89)
Rodriguez, 2010	Sweden	Population-based prospective cohort study	1714	At first trimester (10 gestational weeks)	Hyperactivity and inattention symptoms	Not reported	Strengths and Difficulties Questionnaire	25.0–29.9	2.00 (1.20–3.35)
								≥30.0	2.09 (1.19–4.82)
Rodriguez et al., 2008	Sweden, Denmark, and Finland	Population-based prospective cohort study	12556	Not reported	ADHD	62	Strengths and Difficulties Questionnaire	25.0–29.9	1.37 (1.07-1.75)
								≥ 30	1.89 (1.13-3.15)
van der Burg et al., 2017	USA	Multi-Centre prospective observational study	764	Shortly before or after delivery	ADHD	115	Child Symptom Inventory-4 Parent and Teacher Checklists	25.0–29.9	1.26 (0.96–1.65)
Van Lieshout et al., 2013	Australian	Cohort study	2785	At time of enrolment (average 18 weeks pregnancy)	Internalizing	55	Child Behavior Checklist	Not specified	1.90 (1.10-3.30)
					Externalizing				2.3 (1.4-3.9)
Zhang et al., 2023	China	Prospective Cohort Study	1216	Self-reported	Internalizing	35	Strengths and Difficulties Questionnaire	≥30.0	0.73 (0.48-1.11)

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Table 1 (*continued*)

Author (year)	Country	Study design	Sample size	Time BMI measured	Offspring outcome	Number of cases from total sample	Offspring outcome ascertained by	Maternal BMI classifications (kg/m^2)	Adjusted effect estimates (OR/RR/HR/ Beta coef.)
				before delivery	Externalizing				0.76 (0.51-1.13)
Connolly et al., 2016	USA	Case-control study	39313	Self-reported before pregnancy	ASD	503	ICD-9	≥30.0	1.5 (1.21-1.86)
								25.0-29.9	1.10 (0.87-1.39)
Gardner., et al 2015	Sweden	Cohort study	182,393	Self-reported before pregnancy	ASD	3381	ICD-9, ICD-10, DSM IV		Not reported
Lyall., et al 2011	USA	Cohort study	61,596	At the age of 18 years	ASD	743	Previous diagnosis, parent report	≥30.0	2.03 (1.34, 3.08)
Buss et al 2012	USA	Cohort study	174		ADHD	17	ADHD Child Behavior Checklist	≥30.0	$X^2 = 5.15$, P = 0.03
Pregnancy period									
Lahti-Pulkkinen et al., 2021	UK	Longitudinal cohort study	68,571 (58,634 for the year 1975–1999)	At first antenatal booking (Average 15.1 gestational weeks)	Schizophrenia	201	ICD-10	25.0–29.9	1.47 (1.07–2.00)
								30.0–34.9	1.34 (0.76–2.37)
								≥ 35.0	2.80 (1.40–5.63)
					Mood disorder	324		25.0–29.9	1.07 (0.83–1.38)
								30.0–34.9	1.06 (0.67–1.66)
								≥ 35.0	1.46 (0.76–2.80)
					Anxiety disorder	126		25.0–29.9	1.03 (0.69–1.55)
								30.0–34.9	0.57 (0.23–1.43)
								≥ 35.0	0.72 (0.17–2.99)
					Personality disorder	91		25.0–29.9	1.01 (0.61–1.66)
								30.0–34.9	1.76 (0.90–3.44)
								≥ 35.0	1.03 (0.24–4.31)
MacKay et al., 2017	Sweden	Population-based cohort	526042	First antenatal visit	Nonaffective psychosis	453	ICD-9/10	25.0–29.9	1.03 (0.91-1.15)
								≥ 30	1.16 (0.93-1.44)
					Schizophrenia	105		25.0–29.9	1.02 (0.81-1.27)
								≥ 30	0.91 (0.55-1.50)
Mikkelsen et al., 2017	Denmark	Cohort study	38,314	At 15 weeks of gestation	Emotional problems	Not reported	Strengths and Difficulties Questionnaire	25.0–29.9	1.15 (1.03-1.28)
					Conduct problems				1.18 (1.04-1.34)
					Hyperactivity symptoms				1.25 (1.10-1.42)
					Peer problems				1.31 (1.14-1.50)
					Emotional problems			≥ 30	1.46 (1.26-1.69)
					Conduct problems				1.55 (1.31-1.83)
					Hyperactivity symptoms				1.45 (1.23-1.73)
					Peer problems				1.73 (1.45-2.07)
Mina et al., 2017	UK	Longitudinal study	112	At first antenatal booking	ADHD	Not reported	DSM-oriented scales	⩾40	0.61 (0.12-1.09)
					Conduct problem		Child Behavior Checklist		0.49 (0.01-0.98)
					Peer-problem scale		Strengths and Difficulties Questionnaire		0.17 (-0.32-0.67)

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Table 1 (*continued*)

Author (year)	Country	Study design	Sample size	Time BMI measured	Offspring outcome	Number of cases from total sample	Offspring outcome ascertained by	Maternal BMI classifications (kg/m^2)	Adjusted effect estimates (OR/RR/HR/ Beta coef.)
					Aggressive behavior				0.63 (0.13-1.13)
					Anxiety		Child Behavior Checklist		0.63 (0.14-1.13)
					Pervasive developmental disorder		DSM-oriented scales		0.50 (-0.03-1.03)
					Oppositional defiant				0.12 (-0.40-0.63)
					Internalizing problems		Child Behavior Checklist		0.42 (-0.08-0.92)
					Externalizing problems				0.61 (0.12-1.10)
					Sleep problem		Child's Sleep Habits Questionnaire		0.52 (0.04-0.99)
Neuhaus et al., 2020	Israel	Population-based retrospective cohort study	242,342	Measured at first antenatal visit	ASD	3	ICD-9	≥ 30	Not reported
					Eating disorders	7			
					Sleep disorders	1			
					ADHD	4			
					Long-term neuropsychiatric morbidity	130			1.24 (1.04–1.47)
Razaz & Cnattingius, 2018	Sweden	Population based cohort study	486,688	At first trimester	Anorexia nervosa	426	ICD-9/10	25.0–29.9	0.74 (0.65–0.84)
								30.0–34.9	0.61 (0.47–0.78)
								≥ 35.0	0.82 (0.55–1.21)
Suren et al., 2014	Norway	Population-based prospective cohort study	92909	18 weeks pregnancy	ASD	115	Clinical diagnosis	25.0–29.9	1.26 (0.96–1.65)
								≥30.0	1.09 (0.74–1.59)
Gardner., et al 2015	Sweden	Cohort study	10,481	1st trimester	ASD	375	ICD-9, ICD-10, DSM IV	≥30.0	1.94 (1.72–2.17
			37,227			864		25.0–29.9	1.31 (1.21–1.41)
Hendrix., et al 2011	USA	Case-control study	140	Third trimester	ASD	2/14	Previous diagnosis, parent report	≥30.0	1.19 (0.53–2.66)
						2/14		25.0–29.9	0.60 (0.26–1.36)
Krakowiak., et al 2012	USA	Case-control study	1004	Third trimester	ASD	111/517	Autism Diagnostic Interview, Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS)	≥30.0	2.08 (1.20–3.61)
Li., et al 2016	USA	Cohort study	2734	First trimester	ASD	102	ICD-9	≥30.0	1.92 (1.20–3.07)
					ADHD	301		≥30.0	1.26 (0.88–1.80)
Moss and Chugani, 2014	USA	Cohort study	4800	9 months of pregnancy	Autism	743	Self-report	≥30.0	1.0 (0.97–1.10)
Reynolds 2014	USA	Cohort study	62		Autism		Modified checklist for autism in toddlers	≥30.0	9.8 (7.4–11.56)

To further explore whether the estimated effects of maternal adiposity on offspring neuropsychiatric and behavioral outcomes were influenced by level of statistical adjustments in each study, we conducted additional sensitivity analyses. For instance, the effect estimates for ADHD in the offspring exposed to maternal preconception overweight [pooled OR=1.51, 95 % CI:1.45-1.58, $I^2 = 97.90$ %; P-value = 0.001] appeared to be elevated in the studies that did not adjust for maternal mental health problems compared to those that did adjust for this risk factor [pooled OR=1.18, 95 % CI:1.12-1.24, $I^2 = 9.1$ %; P-value = 0.001]. Similarly, elevated effect estimates for ADHD were seen for offspring exposed to maternal preconception obesity in studies that did not control for maternal mental health problems [pooled OR=1.61, 95 % CI:1.54-1.69, $I^2 = 25.8$; P-value = 0.001] when compared to those adjusted for this risk factor [pooled OR=1.28, 95 % CI:1.21-1.36, $I^2 = 76.4$ %; P-value = 0.001]. We did not conduct additional sensitivity analysis based on the level of statistical adjustment for other risk factors due to a lack of sufficient data in the included studies.

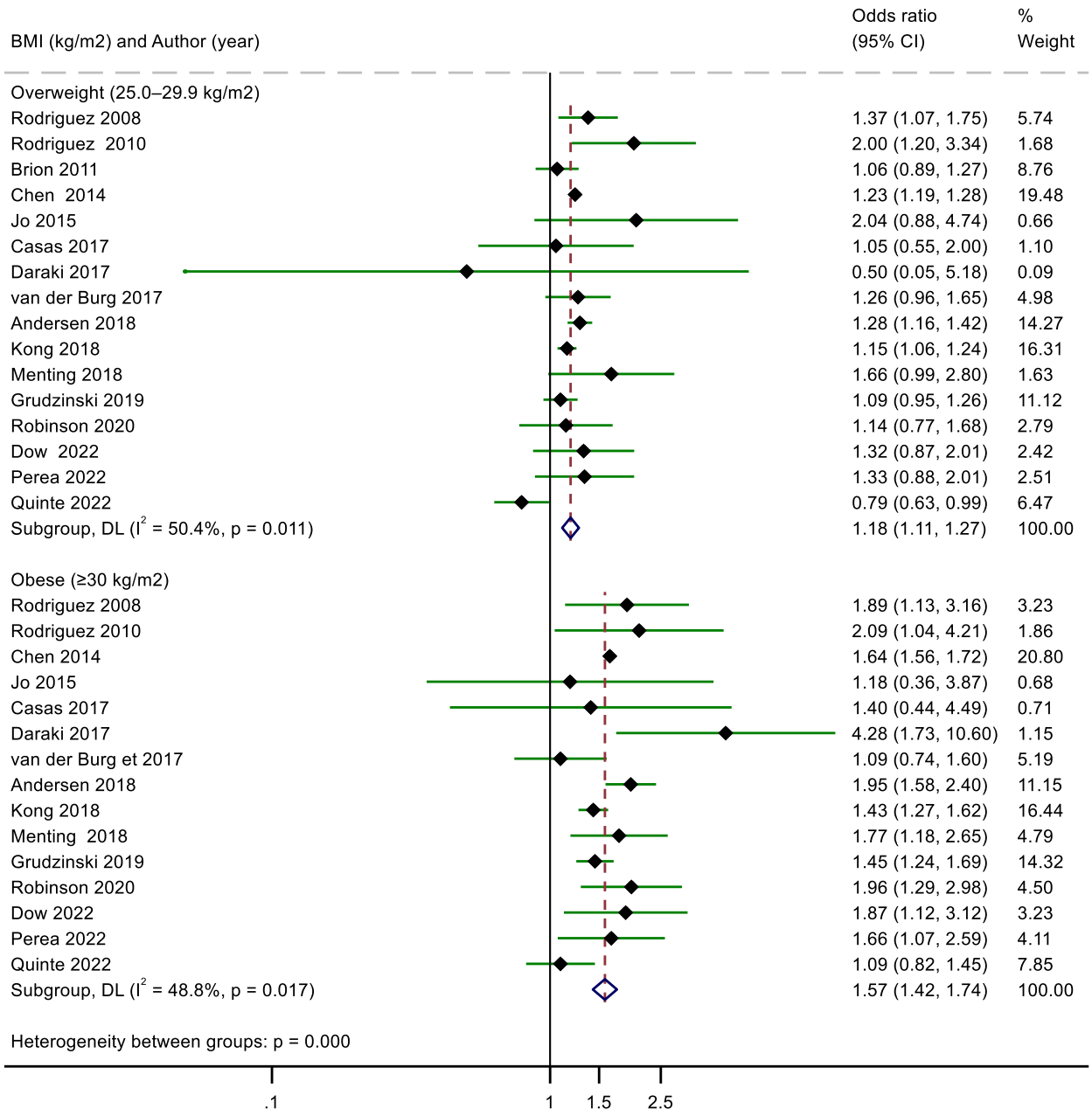


Fig. 2. The effects of maternal preconception overweight and obesity on offspring ADHD.

3.3. Publication bias

Based on visual inspection of the funnel plot and egger's test for small-study effects, with a p-value of 0.514, indicates no significant evidence of publication bias in the meta-analysis of 42 studies **(Supplementary file 9).**

3.4. Confounding variables

Confounders may influence or modify the association between maternal preconception and pregnancy adiposity and adverse neurodevelopmental and psychiatric outcomes in the offspring. The studies included in this systematic review and meta-analysis partially or fully adjusted for various potential confounders. Maternal education and age were commonly adjusted for in most studies, while other covariates were inconsistently included in the final statistical models of the included studies. For instance, 33 studies included maternal age as a covariate, 25 studies adjusted for maternal mental health problems, and 18 studies controlled for maternal tobacco smoking (Table 2).

4. Discussion

This systematic review and meta-analysis aimed to examine prospective associations between maternal preconception and pregnancy adiposity and a range of offspring neuropsychiatric disorders and behavioral outcomes. We retrieved 42 observational epidemiological studies, covering a range of disorders, including ADHD, ASD, CD, psychotic, mood, anxiety, personality and eating disorders, prosocial behavior, sleep and peer relationship problems, and internalizing and externalizing behaviors. Our meta-analyses found evidence supporting prospective positive associations between maternal preconception and pregnancy adiposity and the majority of offspring outcomes examined. Although the number of studies included in our meta-analyses and the magnitude of prospective associations varied, our findings are in line

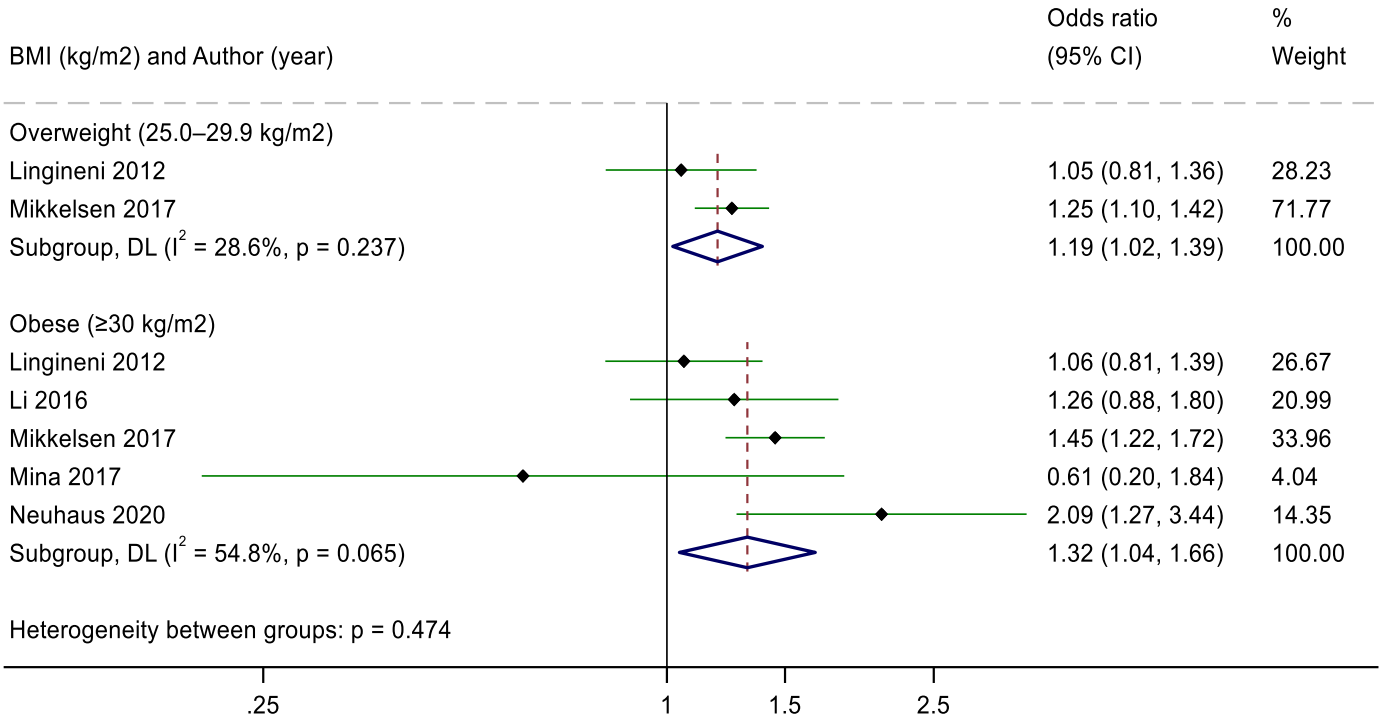


Fig. 3. The effects of maternal pregnancy overweight and obesity on offspring ADHD.

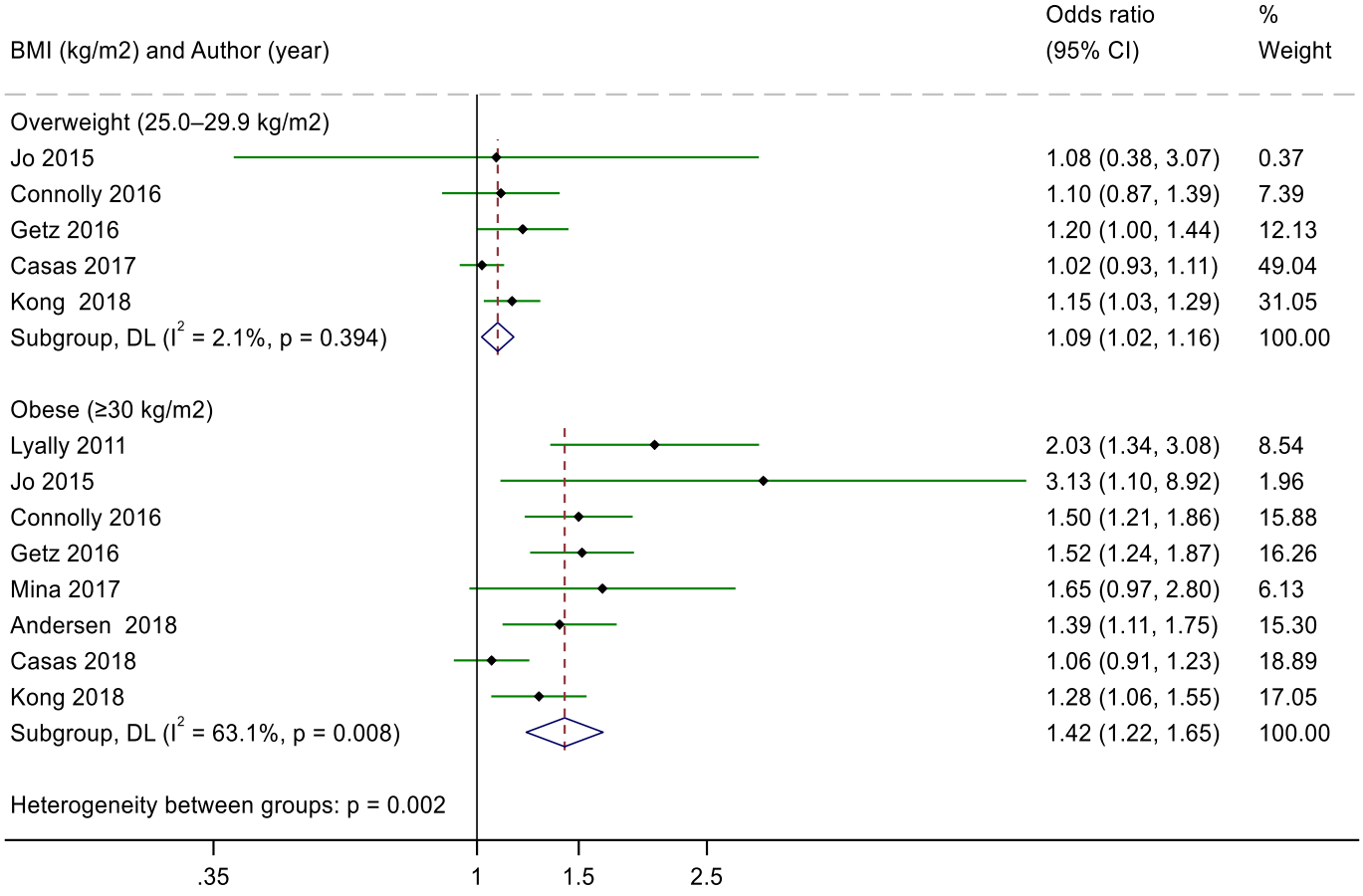


Fig. 4. The effects of maternal preconception overweight and obesity on offspring ASD.

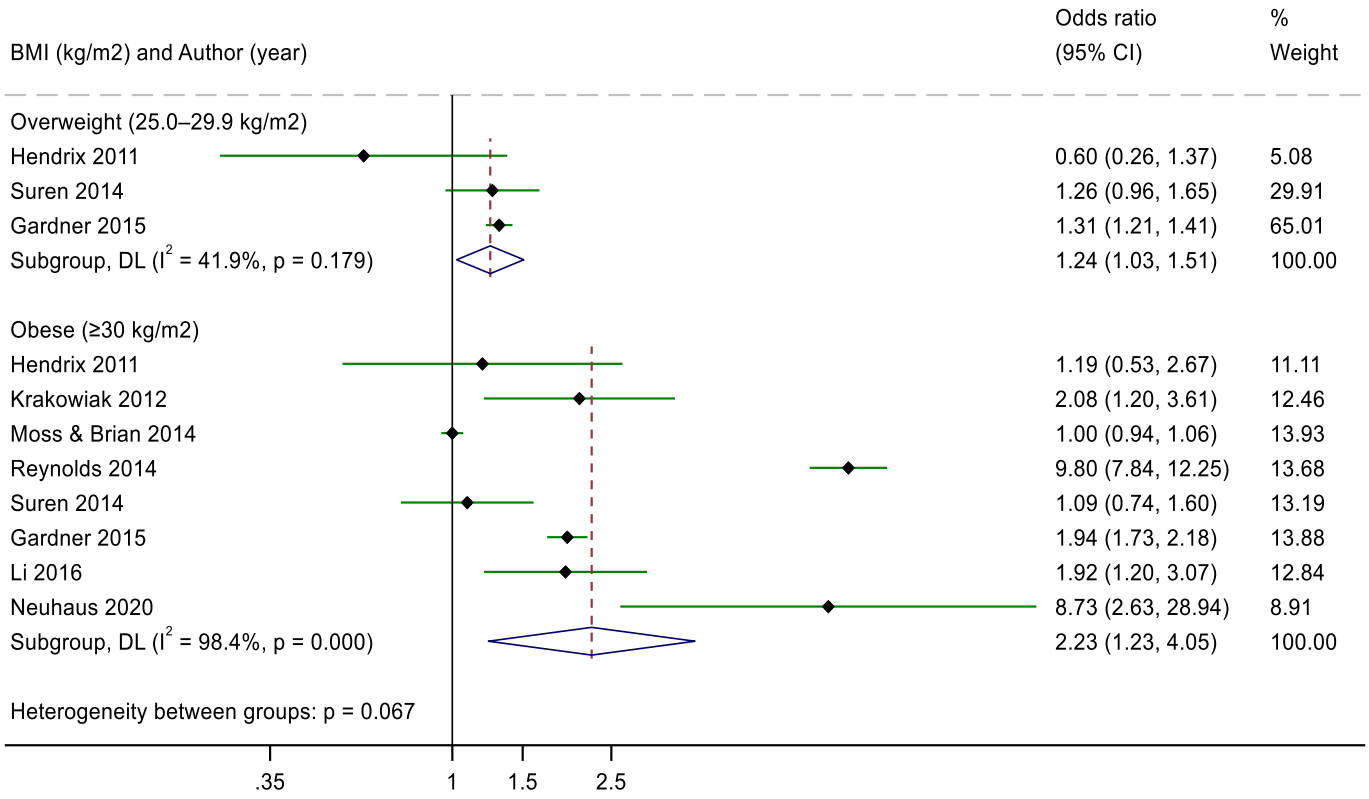


Fig. 5. The effects of maternal pregnancy overweight and obesity on offspring ASD.

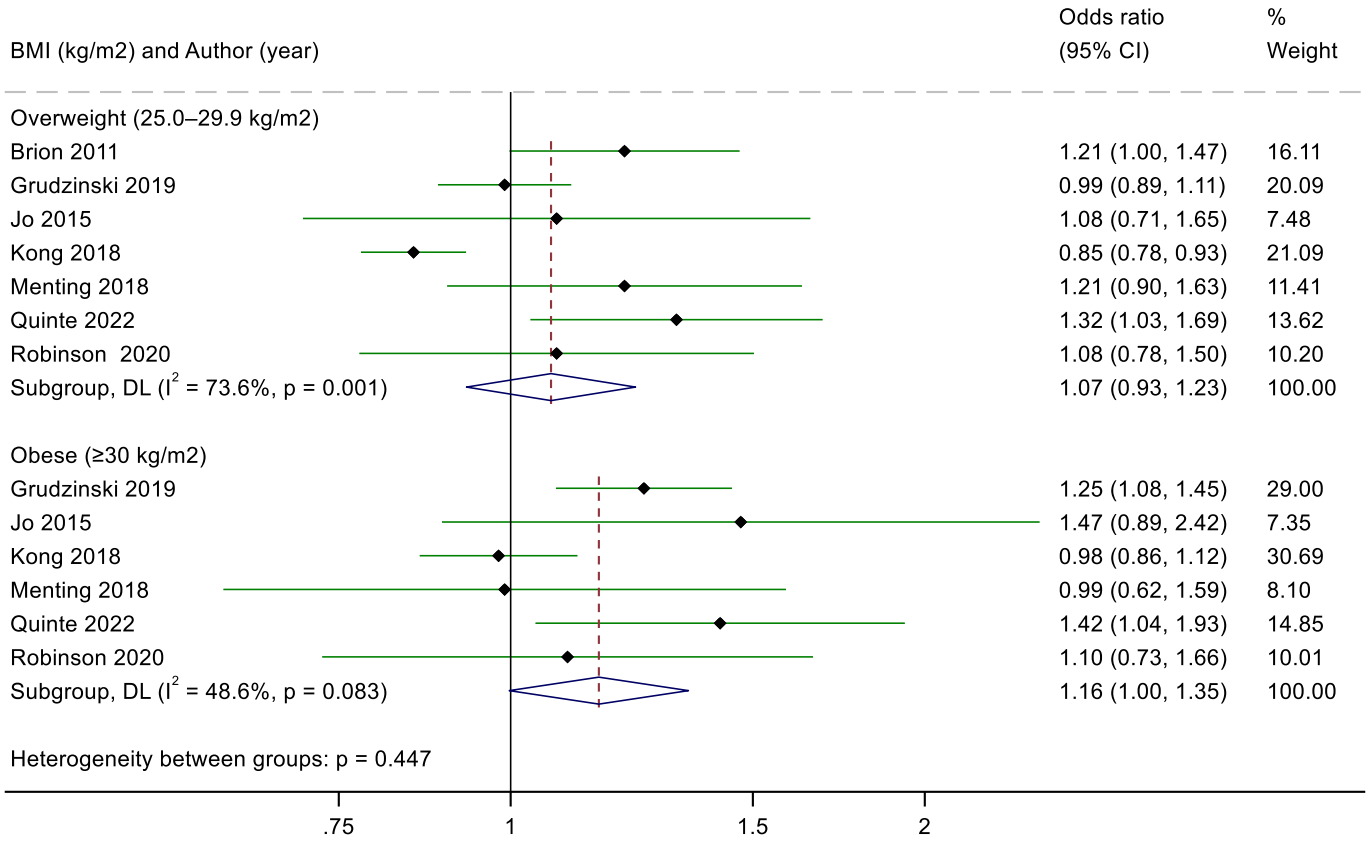
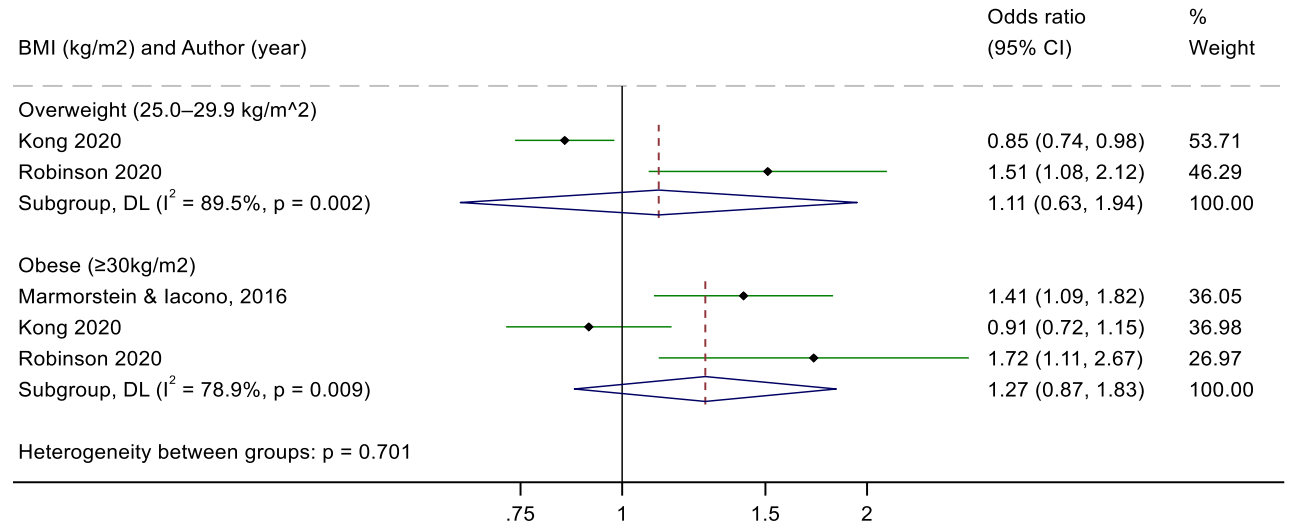
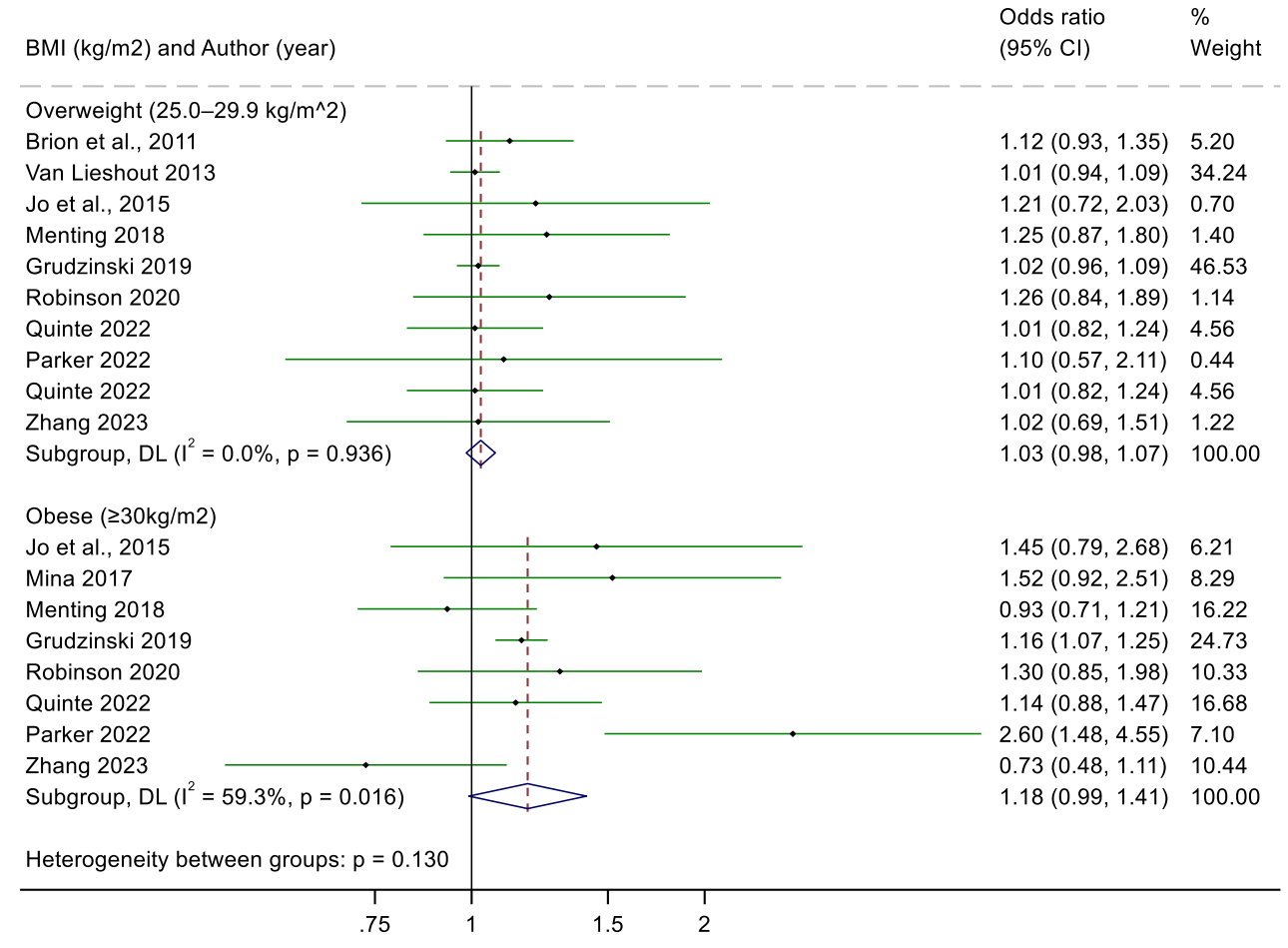


Fig. 6. The effects of maternal preconception overweight and obesity on offspring conduct disorder.



Offspring outcome - Mood disorders (a)



Offspring outcome – internalizing behaviours (b)

Fig. 7. The effects of maternal preconception overweight and obesity on offspring mood disorders (a) and internalizing behaviors (b).

with existing reviews (Sanchez et al., 2018; Lei et al., 2019; Jenabi et al., 2019).

The rising global prevalence of obesity among women of reproductive age highlights the relevance of examining the mechanistic relationship between preconception and maternal adiposity and the development of neuropsychiatric and behavioral outcomes in the offspring (63). Yet, the exact mechanisms are not fully understood despite several plausible suggestions proposed to elucidate such associations (Davis and Mire, 2021). Some of the plausible potential mechanisms linking neuropsychiatric and behavioral outcomes in offspring of preconception or pregnancy overweight or obese mothers include chronic low-grade inflammation, oxidative stress, dysregulated fatty acid metabolism, and hormonal imbalances, which can affect the intrauterine environment and disrupt fetal brain development (Rivera et al., 2015; Rodriguez, 2011).

Indirect mechanistic and causal associations are also conceivable, as

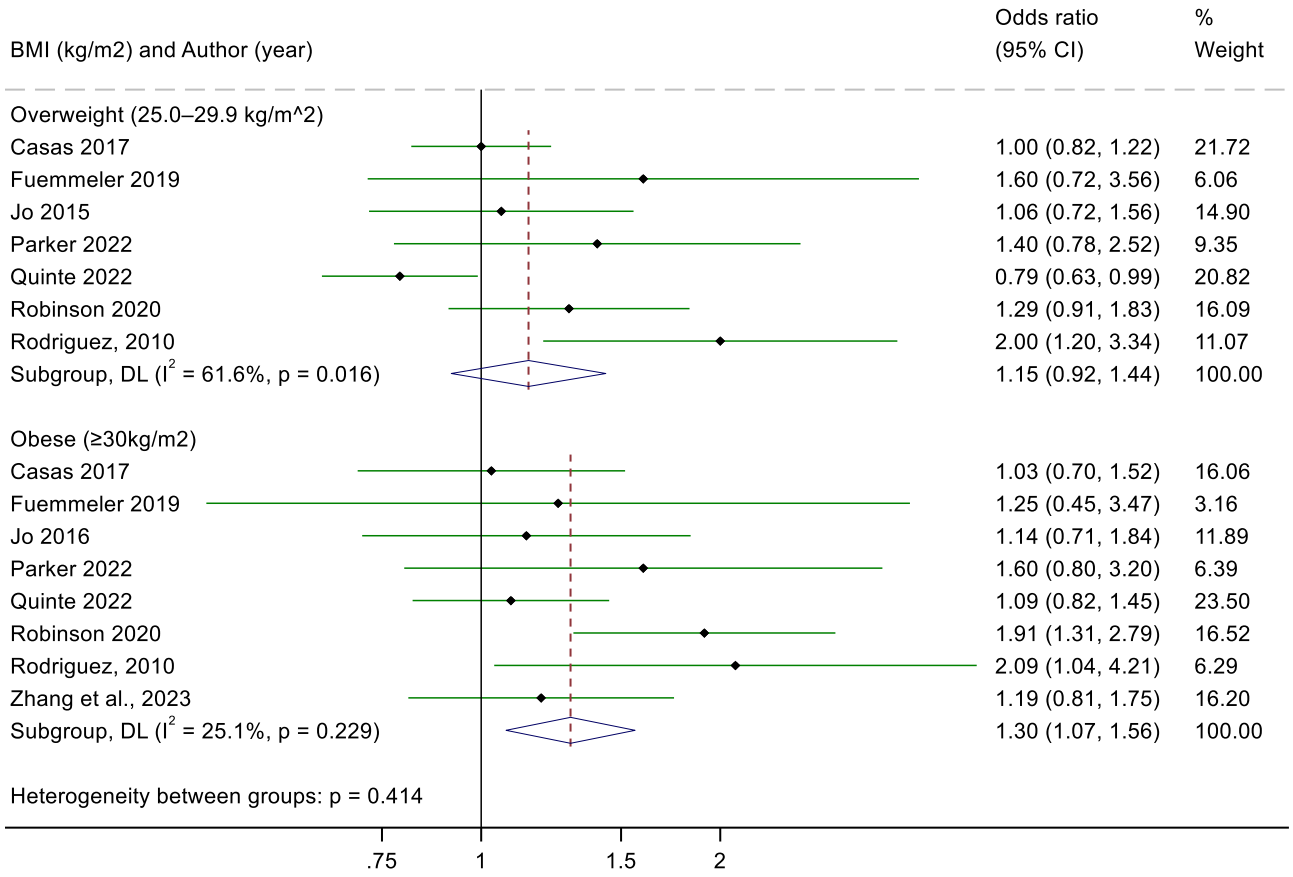


Fig. 8. The effects of maternal preconception overweight and obesity on offspring externalizing behaviors.

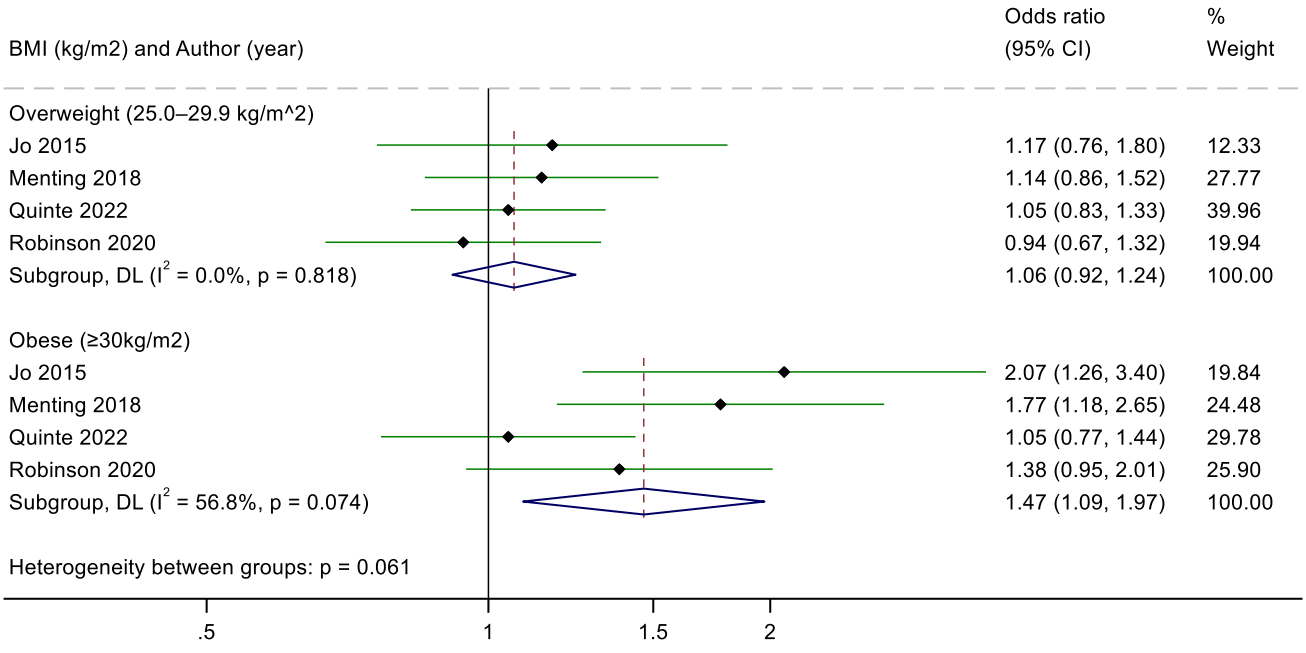


Fig. 9. The effects of preconception maternal overweight on offspring peer relationship problems.

maternal preconception and pregnancy adiposity are known to increase the risk of various acute and chronic maternal mental health conditions. These mental health conditions may potentially mediate the observed association between maternal adiposity and offspring behavior and mental health, making it challenging to disentangle the specific effect of maternal overweight/obesity on the offspring (Rodriguez, 2011). In support of this explanation, we also noted attenuation in the strength of associations in the studies that adjusted for maternal mental health conditions, suggesting a predisposition to maternal or paternal mental health problems may partly explain some part of the association

Table 2
Confounder matrix showing variables adjusted for in studies included in this systematic review ($n = 42$ studies). (References (Andersen 2018; Brion 2011; Buss 2012; Casas 2017; Chen 2014; Connolly 2016; Daraki 2017; Dow 2022; Fuemmeler 2019; Gardner 2015; Getz 2016; Grudzinski 2019; Hendrix. 2011; Kong 2020; Kong 2018; Krakowiak 2012; Lahti-Pulkkinen 2021; Li et al., 2016; Lyall 2011; MacKay 2017; Marmorstein and Iacono, 2016; Menting 2018; Micali 2018; Mikkelsen 2017; Mina 2017; Moss and Chugani, 2014; Musser 2017; Neuhaus 2020; Parker 2022; Perea 2022; Quinte 2022; Razaz 2018; Reynolds 2014; Robinson 2013; Robinson 2020; Rodrigue 2010; Rodriguez 2008; Suren 2014; Van der Burg 2017; Van Lieshout 2013; Zhang 2023) is cited in Table body part).

Study name	Maternal and sociodemographic factors												Paternal factors			Pregnancy complications and child related factors														Lifestyle factors						Clinical factors		
	Education	Age	Ethnicity	Marital status	Income	Birth year	Employment	Social class	Country of birth	Skin color	Area of residence	Maternal IQ	Paternal BMI	Paternal age	Paternal mental health	Parity	Gestational diabetes/any diabetes	Hypertensive disorders in pregnancy	Preterm labor/ prematurity	Any pregnancy complication	Gestational age	Caesarean delivery	Delivery mode	Birthweight	Birth order	Child sex	Breast feeding duration	Child age	Child's BMI	Child day-care attendance	Maternal smoking	Maternal alcohol drinking	Drug abuse	Maternal physical activity	Maternal prenatal diet	Maternal mental health	Maternal prenatal psychotropic medication	Maternal systemic inflammatory disease
Andersen 2018	-	-	-	-	√	-	-	-	-	-	-	-	-	√	-	-	-	-	-	-	√	-	-	√	-	-	-	-	-	-	√	-	-	-	-	√	-	-
Brion 2011	√	-	-	-	√	-	-	√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	√	-	-	-	-	-	-	-
Buss 2012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Casas 2017	√	√	-	-	-	-	√	-	√	-	-	√	√	-	-	-	-	-	-	-	-	-	-	-	√	√	-	√	-	√	-	-	-	-	-	-	-	-
Chen 2014	√	√	-	-	-	√	-	-	√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	√	√	-	-	-	-	√	-	-	-	-	-	-	-
Connolly 2016	-	√	√	-	-	√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Daraki 2017	√	√	√	-	-	-	-	-	-	-	-	-	√	-	-	√	-	-	-	-	-	-	-	-	-	√	-	√	-	-	√	-	-	-	-	-	-	-
Dow 2022	√	√	-	-	-	-	-	-	-	-	-	-	-	-	-	√	-	-	-	-	√	-	-	-	-	√	√	-	-	√	√	√	-	√	√	√	-	-
Fuemmeler 2019	√	√	√	-	-	-	-	-	-	-	-	-	-	-	-	√	√	-	-	-	√	-	-	√	-	√	-	√	-	-	√	-	-	-	√	-	-	-
Getz 2016	√	-	-	-	-	√	-	-	-	-	-	-	-	-	√	-	√	-	-	-	-	-	-	-	-	√	-	-	-	-	√	√	√	-	-	-	-	-
Grudzinski 2019	-	√	-	√	√	-	-	-	-	-	√	-	-	-	-	√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	√	-	-	-	√	-	-	-
Gardner 2015	√	√	-	-	√	√	-	-	√	-	-	-	√	√	√	√	-	-	-	-	-	-	-	-	-	√	-	-	-	-	-	-	-	-	-	-	-	-
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reported in our study.

Maternal obesity is frequently accompanied by comorbid conditions such as gestational diabetes and hypertensive disorders of pregnancy, which have been independently linked to an increased risk of neuropsychiatric and behavioral disorders in the offspring. Alternatively, pleiotropy may be driving some of this comorbidity. Most notably, fatty acids such as arachidonic acid have been shown to play a vital role in fetal brain development and may also be a potential risk factor in gestational diabetes (Szczuko et al., 2020). Therefore, it is imperative to consider and investigate the potential mediating roles of these comorbid conditions in order to gain a comprehensive understanding of the complex interplay between maternal obesity and offspring neuropsychiatric and behavioral outcomes (Kong et al., 2018; Kong et al., 2020).

Maternal obesity, diabetes and fatty acids share similar metabolic pathways, highlighting their intertwined roles in influencing offspring's behavioral and mental health outcomes (Kong et al., 2020; Tallima and El Ridi, 2018). For instance, arachidonic acid, an omega-6 fatty acid that forms a key component of phospholipids, is known to play a critical role in early brain development (Tallima and El Ridi, 2018). Further, arachidonic acid, along with its metabolites, modulates various brain processes, including neurotransmission and neuroinflammation (Hibbeln et al., 1989). Corresponding neuroinflammation has been associated with a number of neuropsychiatric and behavioral problem in the offspring (Dunn et al., 2020). Some studies have also suggested that maternal obesity may result in adverse neuropsychiatric and behavioral outcomes in the offspring through indirect pathways. A meta-analysis synthesizing the results of 22 observational epidemiological studies has suggested that maternal overweight and obesity increase the odds of child obesity by 264 % and 89 %, respectively (Heslehurst et al., 2019). This, in turn, was associated with some form of discrimination, social isolation and bullying, which have an impact on their neuropsychiatric and behavioral well-being (Reitz et al., 2020; Sagar and Gupta, 2018).

In addition to the overall association between maternal adiposity and offspring neuropsychiatric and behavioral outcomes, some evidence highlights severe maternal obesity (BMI $\geq$35 kg/m^2) is linked with specific neuropsychiatric outcomes in offspring (Kong et al., 2018, 2020; Mina et al., 2017; Lahti-Pulkkinen et al., 2021). Notably, ADHD co-morbid with ASD (Andersen et al., 2018) and co-occurring psycho--neurotic, mood, stress, and somatization disorders (Kong et al., 2018) were observed in offspring born to mothers with severe obesity. his underscores the need for more mechanistic studies that consider the severity of maternal obesity as a contributing factor to the increased risk of adverse outcomes in offspring, addressing the unique risks associated with this population. Indeed, it is also essential to highlight the increased risk of behavioral and mental health outcomes in offspring associated with both the combined and independent effects of obesity and/or excessive gestational weight gain (Perea et al., 2022; Shen et al., 2018; Windham et al., 2019).

Epidemiological evidence suggests that maternal adiposity increases the risk of preterm birth, with significant associations to spontaneous preterm labor, membrane rupture, and medically indicated preterm birth (Smith et al., 2007; Liu et al., 2022; Cornish et al., 2024). For instance, the odds of having a spontaneous preterm birth and medically indicated preterm birth increased approximately two-fold in the offspring of obese mothers (Liu et al., 2022; Cornish et al., 2024). These are associated with increased risks of neurobehavioral and psychiatric outcomes later in life (Fitzallen et al., 2023; Crump et al., 2023; Duko et al., 2024). More specifically, individuals born preterm are 2-3 times more likely to be diagnosed with ADHD, ASD, anxiety, and other behavioral problems later in life (Agrawal et al., 2018; Franz et al., 2018). A few studies in our review that considered prematurity or being born preterm in their final statistical models observed an attenuation in the strength of the association, suggesting that being born preterm may play a role in the associations reported by our study.

This comprehensive systematic review and meta-analysis has several strengths. A robust search strategy was employed to identify relevant studies, and a rigorous methodological quality assessment was conducted by three authors, ensuring the reliability of the findings. Meta-analyses were stratified by offspring outcomes, and maternal BMI status was stratified by BMI status and period of exposure, allowing us to investigate whether the timing of maternal obesity during pregnancy or preconception has differential effects on offspring outcomes. However, it is important to acknowledge the limitation of the study that we were unable to provide pooled estimates of neuropsychiatric and behavioral outcomes of offspring across detailed categories of obesity due to inconsistent cutoff points for BMI categories reported in the original studies. Moreover, the majority of studies included in this review had no information about gestational weight gain – a well-known risk factor for a number of adverse outcomes in offspring (Rooney et al., 2011). Further, inclusion of studies reporting neuropsychiatric and behavioral outcomes as reported by both mothers and teachers may have introduced heterogeneity in measurement approaches, potentially affecting the overall effect estimates in the meta-analysis. While this potential impact is less likely due to the limited number of studies presenting this issue, it is important to consider these biases when interpreting the results and drawing conclusions from this review. It remains difficult to isolate whether maternal adiposity before and during pregnancy contributes as a cause of adverse neuropsychiatric and behavioral outcomes in the offspring. Furthermore, there were large variations in the sample sizes of the studies included in our review. Furthermore, there were large variations in the sample size of the studies included in our review. The meta-analysis accounts for the standard error (SE), which is a function of sample size, and gives more weight to larger studies, thus systematically accounting for large sampling errors due to small sample sizes. We also confirm that we did not observe notable differences in the findings of studies based on their sample size. However, we note that studies with small sample sizes are more susceptible to the winner's curse, thereby impacting the pooled effect estimates of our meta-analyses. Moreover, alternative methods, such as negative control analysis, may provide insights into whether maternal adiposity before conception and during pregnancy influences neuropsychiatric and behavioral outcomes in the offspring. This can be done by comparing the association between maternal and paternal adiposity with offspring neuropsychiatric and behavioral outcomes. Assessing the impact of paternal adiposity on adverse outcomes in offspring can help determine if the observed associations are a result of genetic predisposition to neurodevelopmental disorders or if they are likely causal. Although this review does not include a dedicated investigation into the effects of paternal adiposity on offspring outcomes, existing evidence generally suggests no significant association between parental adiposity and offspring neuropsychiatric adverse outcomes such as ASD (Lei et al., 2019). It is also plausible that the associations observed in this systematic review and meta-analysis could be due to confounders, such as maternal and familial socio-economic positions, prenatal substance use, and parental mental health problems, which are linked with maternal preconception and pregnancy adiposity and the outcomes studied in the offspring. Some of these confounders were not consistently adjusted in the studies included in this review, and this may have affected the associations reported in our study.

5. Conclusion

This systematic review and meta-analysis provides evidence of prospective positive associations between maternal preconception and pregnancy adiposity and neuropsychiatric and behavioral outcomes in the offspring. However, to elucidate causal pathways and validate these findings, further mechanistic studies, such as genetically sensitive studies and sibling-controlled analyses, are warranted. These studies are also necessary to inform targeted intervention programs focusing on the management of preconception and pregnancy adiposity. Importantly, future studies should comprehensively address potential confounding factors such as socio-demographic, familial, environmental, and

genetic/biological confounders that could influence outcomes. The findings of this comprehensive review contribute to the existing body of knowledge and have important clinical, policy, and research implications.

Ethics statement

Not required.

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CRediT authorship contribution statement

Bereket Duko: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Tesfaye S. Mengistu:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **David Stacey:** Methodology, Writing – review & editing. **Lisa J Moran:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Writing – review & editing. **Gizachew Tessema:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Gavin Pereira:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **Asres Bedaso:** Investigation, Methodology, Validation, Writing – review & editing. **Amanuel Tesfay Gebremedhin:** Methodology, Writing – review & editing. **Rosa Alati:** Methodology, Resources, Writing – review & editing. **Oyekoya T Ayonrinde:** Investigation, Methodology, Writing – review & editing. **Beben Benyamin:** Investigation, Methodology, Resources, Supervision, Writing – review & editing. **S. Hong Lee:** Investigation, Methodology, Resources, Supervision, Writing – review & editing. **Elina Hyppönen:** Investigation, Methodology, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116149.

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