# **Original Article**

# **Environmental risk/protective factors and peripheral biomarkers for attention-deficit/hyperactivity disorder: an umbrella review of the evidence**

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**Summary**

**Background** Numerous potential environmental risk/protective factors and peripheral biomarkers for attention-deficit/hyperactivity disorder (ADHD) have been investigated, but their consistency and magnitude are unclear.

**Methods** We conducted an umbrella review (registered in PROSPERO, registration: CRD42019145032) to systematically appraise the evidence of association between potential risk/protective factors or peripheral biomarkers and ADHD. We searched PubMed/MEDLINE, Embase, and the Cochrane Database of Systematic Reviews from inception to Oct 31st, 2019 and screened the references of relevant articles. We calculated the summary effect estimates (e.g. odds ratio [OR], relative risk [RR], and weighted mean difference [WMD]), 95% confidence interval (CI), heterogeneity *I*2 statistic, 95% prediction interval, small study effects and excess significance biases. Analyses under credibility ceilings were conducted. We assessed the quality of the meta-analyses with AMSTAR 2.

**Findings** The 35 eligible articles yielded 63 meta-analyses encompassing 40 environmental risk/protective factors (median cases=16 850, median population=91 954) and 23 peripheral biomarkers (median cases=175, median control=187). Evidence of association was convincing (class I) for maternal pre-pregnancy obesity (OR=1·63, 95% CI 1·49–1·77), childhood eczema (OR=1·31, 1·20–1‧44), hypertensive disorders during pregnancy (OR=1·29, 1·22–1·36), preeclampsia (OR=1·28, 1·21–1‧35), and maternal acetaminophen exposure during pregnancy (RR=1·25, 95% CI=1·17–1·34), and highly suggestive (class II) for maternal smoking during pregnancy (OR=1·6, 1·45–1·76), childhood asthma (OR=1·51, 1·4–1·63), maternal pre-pregnancy overweight (OR=1·28, 1·21–1·35), and serum vitamin D levels (WMD=−6·93, −9·34–−4·51).

**Interpretation** Features of maternal metabolic syndrome, maternal acetaminophen exposure or smoking during pregnancy, and childhood atopic diseases were strongly associated with ADHD. Caution in interpreting these findings is necessary because we assessed the robustness of the associations but not necessarily their causality. Previous familial studies suggested that pre-pregnancy obesity, overweight, and maternal smoking during pregnancy were confounded by familial or genetic factors. Further high-quality studies to confirm causality would be required.

**Funding** None.

**Introduction**

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood neurodevelopmental disorders characterized by inattention, hyperactivity, and impulsive behavior.1 The prevalence of ADHD, which was estimated to be 5–7%2,3 , is expected to increase4 as the classification of ADHD is advanced from DSM-IV to DSM-5, and years lived with disability per 100 000 global population among children younger than 5 years is estimated to be 2.0 in 2016.5

Numerous studies have been done to better understand and advance the diagnosis, prognosis, and treatment of the disorder across neurodevelopmental stages, with an emerging core focusing on early detection and prevention.5 The complex nature of ADHD pathophysiology has been reflected by multimodal research studies investigating both the association of a multitude of genetic and non-genetic (i.e. environmental) risk/protective factors with ADHD,6,7 and potential biomarkers which may reflect the effect of these factors on the disorder.7 While substantial advances have been made in understanding the genetic factors linked to ADHD,6,8 findings on environmental factors and peripheral biomarkers have been inconsistent with unclear magnitude of association with ADHD.7,9 Numerous meta-analyses and systematic reviews for environmental risk/protective factors and biomarkers have been published. However, these are usually restricted to a single topic and some of their results may be affected by several types of bias including excess significance bias and publication bias.10 Furthermore, they did not apply hierarchy of evidence among the various environmental factors and peripheral biomarkers to stratify their level of association with ADHD. Finally, with the lack of an established pathophysiology of the disorder, the boundaries between risk/protective factors and biomarkers may become blurred, and pragmatic evidence synthesis encompassing both domains are preferred.11

The current umbrella review —a systematic collection and evaluation of multiple systematic reviews and meta-analyses performed on a specific research topic12 —identifies and appraises for the first time the consistency and magnitude of evidence of environmental factors and peripheral biomarkers associated with diagnosis of ADHD, controlling for several biases.

**Methods**

We followed state-of-the-art methods of umbrella reviews.11,13,14 The study was registered in PROSPERO (registration: CRD42019145032). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (Appendix pp 2–3).15 The screening, data extraction and methodological appraisal of included studies were conducted by at least two independent investigators (JHK and JYK).

*Literature search strategy and eligibility criteria*

We systematically searched PubMed/MEDLINE, Embase, and the Cochrane Database of Systematic Reviews from inception to October 31st, 2019 to identify eligible articles, employing search keywords such as attention-deficit/hyperactivity disorder and meta-analysis (Appendixp 4). For identifying eligible articles, two investigators (JHK and JYK) independently screened titles, abstracts, and full texts (Figure 1). We also manually searched the references of relevant studies to identify further eligible articles. Any disagreement was solved by consultation between three authors (JYK, JHK, and JIS).

We only included systematic reviews providing meta-analyses of observational studies (e.g. cohort, case-control, and cross-sectional studies) examining associations of potential environmental risk/protective factors or peripheral biomarkers with diagnosis of ADHD. There was no language restriction. The definitions of risk/protective factor and biomarker followed those of the World Health Organization (Appendix p 5). We included meta-analyses using categorical ADHD diagnosis criteria according to DSM or hyperkinetic disorder according to ICD and accepted less rigorous criteria such as self-reports as well.

We excluded articles not examining environmental risk/protective factors or peripheral biomarkers of ADHD, not performing a meta-analysis, and not presenting sufficient data for re-analysis (i.e. individual study estimates or necessary data to calculate these). We excluded non-human studies, primary studies, genetic studies, and conference abstracts. When two or more meta-analyses studied an identical topic, we selected only one meta-analysis to avoid overlaps, employing the following procedure. First, we prioritized the meta-analysis with adjusted study estimates over those with crude estimates. Next, we scored the meta-analyses by their recency and quality, utilizing items from AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2), a critical meta-analysis appraisal tool16 and chose the one with the highest score (Appendix p 6). Finally, when two or more meta-analyses had the same score, we chose the one with the largest number of studies. For meta-analyses of risk/protective factors, some meta-analyses studied “later” risk/protective factors possibly measured after childhood and thus temporal causality with ADHD-onset is unclear (e.g. obesity, eczema, and asthma). In these instances, we included articles providing meta-analysis of childhood-only population or created new subsets by including individual studies only of which the mean age was 18 or below. We did not consider such temporal relationships in meta-analyses of biomarkers, as most biomarker studies used samples derived from those already diagnosed with ADHD. We excluded meta-analyses studying indices of cognitive function (e.g. verbal fluency, risky decision making, and emotion dysregulation), as these have recently been described in another umbrella review.17 We also excluded meta-analyses regarding behavioral outcomes of ADHD (oral health, suicidal attempts, dietary pattern, internet addiction, and unintentional physical injuries). The list of the meta-analyses excluded in the text-screening stage is provided in Appendix pp 7–9.

*Data extraction*

For each eligible article, two investigators (JHK and JYK) independently extracted the name of the first author, publication year, environmental risk/protective factor or peripheral biomarker of interest, the number of ADHD cases and study population, the maximally adjusted individual study estimate and corresponding 95% confidence interval (CI), and metrics used in the original analyses such as odds ratio (OR), relative risk (RR), hazard ratio (HR), weighted mean difference (WMD), Cohen’s d, and Hedges’ g. We also extracted the individual study designs of meta-analyses (e.g. cohort, case-control).

*Data analysis*

We adopted a series of statistical tests to assess the robustness and consistency of the identified association. While environmental risk/protective factors and peripheral biomarkers might be of different use in clinical situations, we used identical assessment method to test the robustness of the association itself regardless of causality or temporal relationships with ADHD, as in previous umbrella reviews.11,13 We re-analyzed each eligible meta-analysis using the extracted individual study estimates. Metrics followed those of the original meta-analyses. Moreover, we calculated the summary effect estimate and p-values of eligible meta-analyses under both fixed and random effects models. Statistical significance was claimed at p-value < 0‧05. Further, we also assessed p-values below 10−3 or 10−6 thresholds18,19 and performed Cochran’s Q test and calculated the *I*2 statistic for the evaluation of heterogeneity between studies (*I*2 > 50% is considered to indicate high heterogeneity).20 We estimated the 95% prediction interval, the range we expect the effect of the association will lie for 95% of future studies.21 We assessed the presence of small study effects (i.e. large studies have significantly more conservative results than smaller studies) with the regression asymmetry test proposed by Egger and colleagues.22 Small study effect was claimed when Egger p-value < 0‧1 with the effect of the largest study being more conservative than random effects estimate. For statistically significant meta-analyses, we assessed the presence of potential excess significance bias, a measure of literature bias that compares the expected versus the observed number of statistically significant (p-value < 0‧05) individual studies.23 Random-effects meta-analyses were performed after applying various levels (5/10/15/20%) of credibility ceilings to account for potential methodological limitations of observational studies which might result in spurious significant results.24,25 All statistical tests were two-tailed. The software used for the analysis was R version 3.5.1. and its packages.26,27 For each eligible article, two investigators (JHK and JYK) independently assessed the methodological quality of the meta-analyses using AMSTAR 2 and reached consensus through discussion in case of disagreement.16

*Determining the credibility of evidence*

In accordance with the previous umbrella reviews,11,13,14,28we classified the eligible meta-analyses according to the strength of the evidence of potential environmental risk/protective factors and peripheral biomarkers for ADHD into five levels: convincing (class Ⅰ), highly suggestive (class Ⅱ), suggestive (class Ⅲ), weak (class Ⅳ), and not significant (NS) (Figure 2). Criteria for the level of evidence were based on p-values a under random effects model, the number of ADHD cases, the statistical significance of the largest study, the *I²* statistic, small study effects, excess significance bias, random effects summary estimate under a 10% credibility ceiling, and the 95% prediction interval. For associations graded as convincing or highly suggestive evidence, we attempted further assessment for the robustness of the evidence by performing subset analyses of cohort studies (retrospective and prospective), prospective cohort studies, and study estimates adjusted for at least one covariate.

*Role of the funding source*

There was no funding source for this study. All authors had full access to all of the study data and the corresponding authors had the final responsibility for the decision to submit for publication.

**Results**

*Database*

From the three databases, we initially identified 1 839 articles, 35 of which were finally eligible (Figure 1).29-63 The 35 eligible articles provided 63 unique meta-analyses (40 potential environmental risk/protective factors and 23 peripheral biomarkers) (Table 1, 2, Appendix pp 10–12, 17–34). The 40 meta-analyses of environmental risk/protective factors were based on data of 649 669 total ADHD cases, 32 342 401 total population, the median number of 16 850 ADHD cases per meta-analysis (inter-quartile range [IQR] 1 490 to 37 086, range 79 to 92 426), and the median number of 83 884 total population per meta-analysis (IQR 14 095 to 1 276 239, range 1 072 to 9 244 291). Twenty-nine meta-analyses were based on cohort studies, 15 of which also included case-control or cross-sectional studies. The median number of study estimates of the meta-analyses was 6 (IQR=4 to 8, range 2 to 30). Effect metrics used were either RR, OR, or HR. A total of 31 (78%) associations were statistically significant under random effects model, of which 23 (58%) had a p-value < 10-3, and 12 (30%) a p-value < 10-6. Out of 31 statistically significant associations, 25 had more than 1 000 ADHD cases. Nineteen (48%) associations showed large heterogeneity (*I*2 > 50%). Fifteen (38%) statistically significant associations had neither small study effects nor excess significance bias. The 95% prediction interval excluded the null in only 14 (35%) associations, and 19 (48%) associations retained statistical significance under a 10% credibility ceiling.

The 23 meta-analyses of peripheral biomarkers were based on data of 13 807 total ADHD cases and 23 649 total controls, the median number of 175 ADHD cases per meta-analysis (IQR 136 to 798, range 53 to 2 557), and the median number of 187 control per meta-analysis (IQR 91 to 921, range 39 to 8 154). Meta-analyses were only based on a case-control or cross-sectional design. The median number of study estimates of the meta-analyses was 7 (IQR 5 to 9, range 3 to 19). Used effect metrics were either WMD, Cohen’s d, or Hedges’ g. A total of 14 (61%) associations were statistically significant under random effects model, 6 (26%) of which had p-value < 10−3, and only 2 (9%) p-value < 10−6. Out of 14 statistically significant associations, 5 had more than 1 000 ADHD cases. Fifteen associations (65%) showed large heterogeneity (*I*2 > 50%). Eleven (48%) statistically significant associations had neither small study effects nor excess significance bias. The 95% percent prediction interval excluded the null in only two (9%) associations, and 8 (35%) associations retained statistical significance under 10% credibility ceiling.

*Quality assessment*

AMSTAR 2 quality assessment was available for all but one (maternal cell phone use). For 25 meta-analyses articles of environmental risk/protective factors, 13 were graded as high quality, one moderate, and 11 low or critically low, mainly because the article did not report the protocol for the systematic review (Table 1). When the quality assessment criterion for the protocol was ruled out, only three were graded as low or critically low. Out of nine meta-analysis articles of peripheral biomarkers, two were graded as high quality, and the rest as low or critically low (Table 2). When we ruled out the protocol criterion as well, five were graded as high or moderate.

*Hierarchical level of evidence: potential environmental risk/protective factors*

A total of five environmental risk factors were graded as convincing evidence (class I) (Table 1, Figure 3) —pre-pregnancy obesity (defined as body mass index [BMI] of 30 kg/m2 or higher)59 (OR=1·63, 95% CI 1·49–1·77), childhood eczema (OR=1·31, 1·2–1·44), hypertensive disorders during pregnancy (including chronic hypertension, gestational hypertension, and preeclampsia)50 (OR=1·29, 1·22–1·36), preeclampsia (de novo or superimposed on chronic hypertension)50 (OR=1·28, 1·21–1·35), and maternal acetaminophen exposure during pregnancy (RR=1·25, 1·17–1·34) —and three were graded as highly suggestive evidence (class Ⅱ) (Table 1, Figure 3) —maternal smoking during pregnancy (OR=1·6, 1·45–1·76), childhood asthma (OR=1·51, 1·4–1·63), and pre-pregnancy overweight (defined as BMI between 25 and 29·9 kg/m2)59 (OR=1·28, 1·21–1·35). Among eight environmental risk factors with high level of evidence (class Ⅰ or Ⅱ), four were maternal metabolic syndrome (pre-pregnancy obesity, overweight, preeclampsia, and hypertensive disorders during pregnancy) and two were childhood atopic diseases (childhood eczema and asthma).

Some markers of perinatal hypoxic conditions (5-min Apgar score < 7 and breech/transverse presentation) and preterm birth were graded as suggestive evidence (class ⅠⅠⅠ). Factors related to the parenting environment were at best graded as class IV evidence (parental education level and singly parent family). Meanwhile, only one factor, breastfeeding, showed statistically significant protective effects against ADHD (class IV). Only four associations had effect sizes larger than 2 (eating disorder, preterm birth/low birth weight, low education level of father, and head trauma), which were all class Ⅳ evidence.

Meta-analyses included studies ascertaining ADHD with parental or physician report, medical records of diagnosis or ADHD medication, or self-report, and only four class IV meta-analyses included studies using self-report (childhood/adolescent obesity, head trauma, preterm or low birth weight, and maternal gestational diabetes).31,34,45,57 The subset analyses excluding the self-report studies are provided in Appendix p 13.

*Hierarchical level of evidence: potential peripheral biomarkers*

Only one biomarker was graded as high level of evidence, which was serum vitamin D level in ADHD patients (WMD=−6·93, −9·34–−4·51, class II) (Table 2, Figure 3). Two were graded as suggestive evidence (higher blood lead and lower blood magnesium in ADHD, class III).

*Sensitivity subset analyses*

Subset analyses for class I and II were available for the eight meta-analyses of environmental risk factors (Appendix p 14). In the cohort subset analyses, four maternal factors (pre-pregnancy obesity, overweight, maternal acetaminophen exposure during pregnancy, and maternal smoking during pregnancy) retained their level of evidence, while the rest were downgraded to class III or IV or the subset analysis was not available since there were less than two cohort studies. The same four maternal factors were also graded as class I or II in the prospective cohort subset analyses. In the subset analyses of study estimates adjusted for at least one covariate, all eight retained their level of evidence.

**Discussion**

This study is the first umbrella review to systematically and quantitatively collect and assess the hierarchy of evidence for potential environmental risk/protective factors and peripheral biomarkers of ADHD. Only nine associations showed evidence of high credibility: Maternal acetaminophen exposure during pregnancy, childhood eczema, hypertensive disorder during pregnancy, preeclampsia, and maternal pre-pregnancy obesity were graded as convincing evidence (class I), and maternal smoking during pregnancy, childhood asthma, maternal pre-pregnancy overweight, and serum vitamin D level were graded as highly suggestive evidence (class II).

There was convincing evidence that maternal acetaminophen exposure during pregnancy was associated with a higher risk of ADHD in offspring, retaining the level of evidence in all three subset analyses. Various potential mechanisms have been suggested such as excess toxic *N*-acetyl-*p*-benzoquinoneimine formation, oxidative stress due to inflammation-induced immune activation, brain-derived neurotropic factor alteration, endocannabinoid dysfunction, Cox-2 inhibition, and endocrine disruption.56,64 Although the exact biological mechanism has not yet been identified, one hypothesis is that prenatal acetaminophen exposure affects normal neurodevelopment and it is consistent with the evidence that 1) acetaminophen readily crosses the placenta65 and blood-brain barrier66 and 2) prenatal acetaminophen exposure during the third trimester of pregnancy, the period the fetal brain grows rapidly and is thereby highly sensitive to stimulation,67 is associated with a higher risk of ADHD than in earlier trimesters.56,68,69 The association is supported by a sibling-controlled study which reports that children exposed to prenatal acetaminophen for more than 28 days had substantially poorer neurodevelopment than those exposed less than 28 days.67 Moreover, one prospective cohort study reported positive dose-responsive associations with offspring ADHD diagnosis for maternal acetaminophen biomarkers.70 However, this association must be interpreted in light of possible confounding by indication since the same result can postulate that use of the medication may imply presence of maternal comorbidities (such as inflammation and infections), which may themselves increase the risk of ADHD in offspring.56,71 Meanwhile, some studies reported the retained association with statistical significance even after adjusting for indications of acetaminophen.56,68,69 In interpreting the current acetaminophen results, prudent caution is required as our evidence grading did not consider the biological plausibility of the association, nor considered all the potential confounders; the association itself does not necessarily indicate causality.

Components of maternal metabolic syndrome were associated with an increased risk of ADHD in offspring with convincing evidence for pre-pregnancy obesity, preeclampsia, and hypertensive disorders during pregnancy, and highly suggestive for pre-pregnancy overweight, two of which survived all three subset analyses. One possible underlying mechanism involves a changed in utero environment created by metabolic syndrome. Potential causative bases include reduced placental blood flow, maternal oxidative stress, and maternal inflammatory pathways.72 As inflammatory agents induce the increased permeability of the blood-brain barrier of the immature fetus, they can reach the fetal brain,73 possibly involving in neuroanatomical alteration.72,74 Altered fetal developmental trajectories, especially in the brain, may increase the risk of long-term vascular, cognitive and psychiatric sequelae in the offspring,75-77 which may subsequently lead to higher risk of ADHD as well as other neurodevelopmental disorders including autism spectrum disorder.78 The causal relationship between preeclampsia and offspring ADHD is further supported by a sibling-matched study reporting similar effect sizes between sibling-matched and unmatched population model (sibling-matched: HR 1·13, 1·05–1·22; unmatched population: HR 1·15, 1·12–1·19),79 which implies that the association is possibly independent of genetic or familial confounding. On the other hand, the association of pre-pregnancy obesity or overweight with ADHD seems to be confounded by genetic or familial factors, as studies have reported attenuated, non-significant associations in sibling-matched models (obesity: HR 1·15, 0·85–1·56; overweight: HR 0·98, 0·83–1·16; pre-pregnancy BMI: regression coefficient −0·08, −0·23–0·06).80,81

In accordance with the evidence that ADHD is one of the common co-occurring conditions in autism spectrum disorder,82 it is notable that some components of metabolic syndrome (preeclampsia, hypertensive disorders during pregnancy, and maternal pre-pregnancy overweight) and acetaminophen exposure during pregnancy had robust associations with both autism spectrum disorder with a high level of evidence (Appendix p 15).11 This findings may support the pathological similarity between the two psychiatric disorders, previously characterized by reports of similarity of brain structural alterations in ADHD and autism,74 and shared genetic influences, which suggest similar biological pathways.83 One possible hypothesis is that shared environmental risk factors of ADHD and autism spectrum disorder may have a transdiagnostic feature.84,85 Further studies regarding the possible linkage between the disorders with the consideration of abovementioned findings would be worthwhile.

Childhood atopic diseases were associated with an increased risk of ADHD with convincing evidence for childhood eczema and highly suggestive evidence for childhood asthma. Neuroimmunological pathways and psychological mechanisms have been broadly accepted in terms of etiology,38,51 which respectively account for the disruptive effect of allergic inflammatory cytokines86 and elevated psychological stress levels,87 damaging ADHD-relevant brain circuits during early-life on which the brain is particularly sensitive to stimulation.88 However, the causality of the comorbidity of atopic diseases and ADHD is still a matter of debate. Indeed, previous studies suggested that early ADHD is a predictor of subsequent asthma.51,88 Some twin studies have been conducted to control for genetic or familial factors one of which suggested genetic influences underlying the association between asthma and subsequent ADHD symptoms by reporting a significant correlation between them (correlation coefficient 0·23, 0·04–0·37).89 However, another study reported conflicting findings that cross-twin cross-trait correlation between ADHD and asthma is higher between dizygotic twins than monozygotic twins (correlation coefficient: monozygotic 0·05, −0·08–0·17; dizygotic same sex 0·13, 0·03–0·23), contradicting the notion of a shared genetic component in asthma and ADHD,90 and this result was also supported by other familial studies.91,92 Our findings should also be addressed in light of the large between-study heterogeneity in the asthma meta-analysis. The large heterogeneity may be attributed to heterogeneous nature of asthma such as diverse clinical presentation, multiple causes, and variable developmental courses93,94 and the fact that most individual studies were case-control or cross-sectional. Meanwhile, one suggested confounder of the association between eczema and subsequent ADHD symptoms is sleeping problems caused by eczema. Eczema was reported to be positively associated with impaired sleep quality,95 and childhood sleep problems were found to be associated with subsequent hyperactivity in a twin-matched study.96

Maternal smoking during pregnancy showed highly suggestive evidence for the increased risk of ADHD, retaining the level of evidence in all three subset analyses. Potential mechanisms have been suggested proposing the harmful effect of cigarettes on child neurodevelopment.46 Meanwhile, three separate sibling studies97-99 controlled for familial or genetic confounding consistently reported non-significant, attenuated effect estimates, and a meta-analysis of these three studies reported an effect close to the null (OR 1·04, 0·95–1·15).46 Another sibling study reported effect estimates gradually being attenuated towards the null when adjusting for unmeasured confounders (unmatched population: HR 1·62, 1·56–1·69; cousin comparison: HR 1·45, 1·24–1·68; sibling comparison: HR 0·88, 0·73–1·06).100 These findings suggest that the association is confounded by familial or genetic factors, which supports the hypothesis that shared genetic components between mother and child are causes of ADHD rather than adverse effect of cigarettes.101,102 Maternal psychiatric conditions including ADHD may be another possible confounding factor in that they were associated with both smoking during pregnancy103 and offspring ADHD.

We identified 23 potential peripheral biomarkers for ADHD. The evidence of association between ADHD and serum vitamin D was highly suggestive with large heterogeneity and 95% prediction interval including the null value. However, most peripheral biomarkers identified in our study were graded as low level partly owing to the low number of ADHD cases, probably attributable to the dearth of research in this field. Quality of meta-analyses were poorer than that of environmental factors, as many were lacking in protocol registration and risk of bias assessment. These findings are consistent with current consensus that biomarkers are not yet reliable enough to be used clinically. Consensus studies published in 2012 concluded that no single biomarker reliably predicts ADHD,104 while concurrent guidelines do not mention or recommend the use of any for the management of ADHD (Appendix p 16).105,106

The current study has some limitations. First, due to the nature of observational studies, the identified associations do not necessarily imply causality. While we identified robust associations consistently found across the multiple studies, the possibility of confounding such as genetic linkage cannot be ruled out. The associations of maternal smoking, obesity, and overweight supported by high level of evidence were not replicated in familial studies, suggesting significant familial or genetic confounding underlying the association. Second, we could not consider changes in classification for ADHD and its varieties and could not distinguish between specific ADHD symptoms (i.e. inattention, hyperactivity, or co-occurrence of them) for diagnosing ADHD. Third, we could not assess potential environmental risk/protective factors or biomarkers of ADHD according to important factors such as sex, intellectual disability, and comorbid psychiatric disorders. Fourth, we assessed peripheral biomarkers but did not assess neurocognitive markers, which may act as biomarkers for ADHD.17 Fifth, there is no assumption that the identified factors are independent. Furthermore, we could only address associations in the published meta-analyses and therefor might have missed those that had not been evaluated in preceding meta-analyses or underestimated some genuine environmental factors or biomarkers owing to the nature of the systematic review. For example, other reviews have argued that preterm birth is strongly associated with a higher risk of ADHD compared to other potential risk factors45,107 since the association was supported by sibling studies108 and dose-response relationship.109 However, in our review, preterm birth42 was graded as suggestive evidence (class Ⅲ), not meeting the criteria for highly suggestive (class Ⅱ) because random effects p-value was larger than 10−6 and the largest study was not statistically significant. This is partly because we did not reward high-quality study designs, such as familial studies or dose-response relationships, or further attempt to control for confounders in our evidence grading, which is another limitation of our review.

Acknowledging these limitations, this umbrella review mapped and established the hierarchy of evidence among 63 potential environmental risk/protective factors and peripheral biomarkers of ADHD. Among them, only pre-pregnancy obesity, overweight, maternal acetaminophen exposure during pregnancy and maternal smoking during pregnancy retained high level of evidence in all subset analyses. These associations, however, are not necessarily causative and therefor further high-quality primary studies to confirm these findings would be valuable.

**Contributors**

JHK, JYK, and JIS designed the study. JHK, JYK, and JIS did the literature search and screening, extracted, analysed, and interpreted the data, and made the figures and tables. All authors drafted and critically revised the manuscript. All authors gave approval to the final version of the manuscript for publication. PFP provided overall supervision on the conduct of the study. All authors approved the final version of the manuscript for publication. The corresponding author (JIS) attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. JHK and JYK contributed equally to the manuscript as joint first authors.

**Declaration of interests**

We declare no competing interests in relation to the current manuscript.

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None.

**Figure legends**

Figure 1. Flow chart of literature search

Figure 2. Level of evidence grading methods

Figure 3. Summary estimates of meta-analyses of potential environmental risk/protective factors and peripheral biomarkers for ADHD

**References**

1. Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet* 2016; **387**(10024): 1240–50.

2. 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**(6): 942–8.

3. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics* 2015; **135**(4): e994–e1001.

4. Tannock R. Rethinking ADHD and LD in DSM-5: proposed changes in diagnostic criteria. *J Learn Disabil* 2013; **46**(1): 5–25.

5. Global Research on Developmental Disabilities Collaborators. Developmental disabilities among children younger than 5 years in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Glob Health* 2018; **6**(10): e1100–e21.

6. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet* 2019; **51**(1): 63–75.

7. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal Risk Factors and the Etiology of ADHD-Review of Existing Evidence. *Curr Psychiatry Rep* 2017; **19**(1): 1.

8. Lichtenstein P, Carlstrom E, Rastam M, Gillberg C, Anckarsater H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am J Psychiatry* 2010; **167**(11): 1357–63.

9. Froehlich TE, Anixt JS, Loe IM, Chirdkiatgumchai V, Kuan L, Gilman RC. Update on environmental risk factors for attention-deficit/hyperactivity disorder. *Curr Psychiatry Rep* 2011; **13**(5): 333–44.

10. Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005; **2**(8): e124.

11. Kim JY, Son MJ, Son CY, et al. Environmental risk factors and biomarkers for autism spectrum disorder: an umbrella review of the evidence. *Lancet Psychiatry* 2019; **6**(7): 590–600.

12. Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ* 2009; **181**(8): 488–93.

13. Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *Lancet Neurol* 2015; **14**(3): 263–73.

14. Bellou V, Belbasis L, Tzoulaki I, Middleton LT, Ioannidis JPA, Evangelou E. Systematic evaluation of the associations between environmental risk factors and dementia: An umbrella review of systematic reviews and meta-analyses. *Alzheimers Dement* 2017; **13**(4): 406–18.

15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**(7): e1000097.

16. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; **358**: j4008.

17. Pievsky MA, McGrath RE. The Neurocognitive Profile of Attention-Deficit/Hyperactivity Disorder: A Review of Meta-Analyses. *Arch Clin Neuropsychol* 2018; **33**(2): 143–57.

18. Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? *BMJ* 2001; **322**(7280): 226–31.

19. Ioannidis JP, Tarone R, McLaughlin JK. The false-positive to false-negative ratio in epidemiologic studies. *Epidemiology* 2011; **22**(4): 450–6.

20. Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954; **10**(1): 101–29.

21. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc A Stat* 2009; **172**(1): 137–59.

22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**(7109): 629–34.

23. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials* 2007; **4**(3): 245–53.

24. Salanti G, Ioannidis JP. Synthesis of observational studies should consider credibility ceilings. *J Clin Epidemiol* 2009; **62**(2): 115–22.

25. Papatheodorou SI, Tsilidis KK, Evangelou E, Ioannidis JP. Application of credibility ceilings probes the robustness of meta-analyses of biomarkers and cancer risk. *J Clin Epidemiol* 2015; **68**(2): 163–74.

26. Champely S, Ekstrom C, Dalgaard P, et al. pwr: basic functions for power analysis. R package version 1.2-2. March 3, 2018. https://cran.r-project.org/package=pwr (accessed Oct 30, 2019).

27. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; **36**(1–48).

28. Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. *Evid Based Ment Health* 2018; **21**(3): 95–100.

29. Scassellati C, Bonvicini C, Faraone SV, Gennarelli M. Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses. *J Am Acad Child Adolesc Psychiatry* 2012; **51**(10): 1003-19.e20.

30. Yoshimasu K, Kiyohara C, Takemura S, Nakai K. A meta-analysis of the evidence on the impact of prenatal and early infancy exposures to mercury on autism and attention deficit/hyperactivity disorder in the childhood. *Neurotoxicology* 2014; **44**: 121–31.

31. Adeyemo BO, Biederman J, Zafonte R, et al. Mild traumatic brain injury and ADHD: a systematic review of the literature and meta-analysis. *J Atten Disord* 2014; **18**(7): 576–84.

32. Hawkey E, Nigg JT. Omega-3 fatty acid and ADHD: blood level analysis and meta-analytic extension of supplementation trials. *Clin Psychol Rev* 2014; **34**(6): 496–505.

33. Russell AE, Ford T, Williams R, Russell G. The Association Between Socioeconomic Disadvantage and Attention Deficit/Hyperactivity Disorder (ADHD): A Systematic Review. *Child Psychiatry Hum Dev* 2016; **47**(3): 440–58.

34. 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**(1): 34–43.

35. Sun GX, Wang BH, Zhang YF. [Relationship between serum zinc levels and attention deficit hyperactivity disorder in children]. *Zhongguo Dang Dai Er Ke Za Zhi* 2015; **17**(9): 980–3.

36. Zhu T, Gan J, Huang J, Li Y, Qu Y, Mu D. Association Between Perinatal Hypoxic-Ischemic Conditions and Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis. *J Child Neurol* 2016; **31**(10): 1235–44.

37. Nazar BP, Bernardes C, Peachey G, Sergeant J, Mattos P, Treasure J. The risk of eating disorders comorbid with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *Int J Eat Disord* 2016; **49**(12): 1045–57.

38. Schans JV, Çiçek R, de Vries TW, Hak E, Hoekstra PJ. Association of atopic diseases and attention-deficit/hyperactivity disorder: A systematic review and meta-analyses. *Neurosci Biobehav Rev* 2017; **74**(Pt A): 139–48.

39. Miyazaki C, Koyama M, Ota E, et al. Allergic diseases in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis. *BMC Psychiatry* 2017; **17**(1): 120.

40. Birks L, Guxens M, Papadopoulou E, et al. Maternal cell phone use during pregnancy and child behavioral problems in five birth cohorts. *Environ Int* 2017; **104**: 122–31.

41. He J, Ning H, Huang R. Low blood lead levels and attention-deficit hyperactivity disorder in children: a systematic review and meta-analysis. *Environ Sci Pollut Res Int* 2019; **26**(18): 17875–84.

42. Allotey J, Zamora J, Cheong-See F, et al. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. *BJOG* 2018; **125**(1): 16–25.

43. Zhang J, Luo W, Li Q, Xu R, Wang Q, Huang Q. Peripheral brain-derived neurotrophic factor in attention-deficit/hyperactivity disorder: A comprehensive systematic review and meta-analysis. *J Affect Disord* 2018; **227**: 298–304.

44. Jiang HY, Peng CT, Zhang X, Ruan B. Antidepressant use during pregnancy and the risk of attention-deficit/hyperactivity disorder in the children: a meta-analysis of cohort studies. *BJOG* 2018; **125**(9): 1077–84.

45. Franz AP, Bolat GU, Bolat H, et al. Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis. *Pediatrics* 2018; **141**(1).

46. Huang L, Wang Y, Zhang L, et al. Maternal Smoking and Attention-Deficit/Hyperactivity Disorder in Offspring: A Meta-analysis. *Pediatrics* 2018; **141**(1).

47. Thompson W, Russell G, Baragwanath G, Matthews J, Vaidya B, Thompson-Coon J. Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2018; **88**(4): 575–84.

48. Tseng PT, Cheng YS, Yen CF, et al. Peripheral iron levels in children with attention-deficit hyperactivity disorder: a systematic review and meta-analysis. *Sci Rep* 2018; **8**(1): 788.

49. Khoshbakht Y, Bidaki R, Salehi-Abargouei A. Vitamin D Status and Attention Deficit Hyperactivity Disorder: A Systematic Review and Meta-Analysis of Observational Studies. *Adv Nutr* 2018; **9**(1): 9–20.

50. Maher GM, O'Keeffe GW, Kearney PM, et al. Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-analysis. *JAMA Psychiatry* 2018; **75**(8): 809–19.

51. Cortese S, Sun S, Zhang J, et al. Association between attention deficit hyperactivity disorder and asthma: a systematic review and meta-analysis and a Swedish population-based study. *Lancet Psychiatry* 2018; **5**(9): 717–26.

52. Shih JH, Zeng BY, Lin PY, et al. Association between peripheral manganese levels and attention-deficit/hyperactivity disorder: a preliminary meta-analysis. *Neuropsychiatr Dis Treat* 2018; **14**: 1831–42.

53. Lønfeldt NN, Verhulst FC, Strandberg-Larsen K, Plessen KJ, Lebowitz ER. Assessing risk of neurodevelopmental disorders after birth with oxytocin: a systematic review and meta-analysis. *Psychol Med* 2019; **49**(6): 881–90.

54. Huang YH, Zeng BY, Li DJ, et al. Significantly lower serum and hair magnesium levels in children with attention deficit hyperactivity disorder than controls: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **90**: 134–41.

55. Zeng Y, Tang Y, Tang J, et al. Association between the different duration of breastfeeding and attention deficit/hyperactivity disorder in children: a systematic review and meta-analysis. *Nutr Neurosci* 2018: 1–13.

56. Gou X, Wang Y, Tang Y, et al. Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis. *Aust N Z J Psychiatry* 2019; **53**(3): 195–206.

57. Zhao L, Li X, Liu G, Han B, Wang J, Jiang X. The association of maternal diabetes with attention deficit and hyperactivity disorder in offspring: a meta-analysis. *Neuropsychiatr Dis Treat* 2019; **15**: 675–84.

58. San Martin Porter M, Maravilla JC, Betts KS, Alati R. Low-moderate prenatal alcohol exposure and offspring attention-deficit hyperactivity disorder (ADHD): systematic review and meta-analysis. *Arch Gynecol Obstet* 2019; **300**(2): 269–77.

59. Jenabi E, Bashirian S, Khazaei S, Basiri Z. The maternal prepregnancy body mass index and the risk of attention deficit hyperactivity disorder among children and adolescents: a systematic review and meta-analysis. *Korean J Pediatr* 2019; **62**(10): 374–9.

60. Yamamoto JM, Benham JL, Dewey D, et al. Neurocognitive and behavioural outcomes in offspring exposed to maternal pre-existing diabetes: a systematic review and meta-analysis. *Diabetologia* 2019; **62**(9): 1561–74.

61. Manzari N, Matvienko-Sikar K, Baldoni F, O'Keeffe GW, Khashan AS. Prenatal maternal stress and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis. *Soc Psychiatry Psychiatr Epidemiol* 2019; **54**(11): 1299–309.

62. Caye A, Petresco S, de Barros AJD, et al. Relative Age and Attention-Deficit/Hyperactivity Disorder: Data From Three Epidemiological Cohorts and a Meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2019.

63. Zhang T, Sidorchuk A, Sevilla-Cermeño L, et al. Association of Cesarean Delivery With Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2019; **2**(8): e1910236.

64. Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH. Prenatal paracetamol exposure and child neurodevelopment: A review. *Horm Behav* 2018; **101**: 125–47.

65. Nitsche JF, Patil AS, Langman LJ, et al. Transplacental Passage of Acetaminophen in Term Pregnancy. *Am J Perinatol* 2017; **34**(6): 541–3.

66. Kumpulainen E, Kokki H, Halonen T, Heikkinen M, Savolainen J, Laisalmi M. Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. *Pediatrics* 2007; **119**(4): 766–71.

67. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol* 2013; **42**(6): 1702–13.

68. Stergiakouli E, Thapar A, Davey Smith G. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. *JAMA Pediatr* 2016; **170**(10): 964–70.

69. Ystrom E, Gustavson K, Brandlistuen RE, et al. Prenatal Exposure to Acetaminophen and Risk of ADHD. *Pediatrics* 2017; **140**(5).

70. Ji Y, Riley AW, Lee LC, et al. Maternal Biomarkers of Acetaminophen Use and Offspring Attention Deficit Hyperactivity Disorder. *Brain Sci* 2018; **8**(7).

71. Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I. Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies. *Am J Epidemiol* 2018; **187**(8): 1817–27.

72. Bohm S, Curran EA, Kenny LC, O'Keeffe GW, Murray D, Khashan AS. The Effect of Hypertensive Disorders of Pregnancy on the Risk of ADHD in the Offspring. *J Atten Disord* 2019; **23**(7): 692–701.

73. Rees S, Harding R. Brain development during fetal life: influences of the intra-uterine environment. *Neurosci Lett* 2004; **361**(1-3): 111–4.

74. Ratsep MT, Paolozza A, Hickman AF, et al. Brain Structural and Vascular Anatomy Is Altered in Offspring of Pre-Eclamptic Pregnancies: A Pilot Study. *AJNR Am J Neuroradiol* 2016; **37**(5): 939–45.

75. Davis EF, Lazdam M, Lewandowski AJ, et al. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. *Pediatrics* 2012; **129**(6): e1552–61.

76. Pinheiro TV, Brunetto S, Ramos JG, Bernardi JR, Goldani MZ. Hypertensive disorders during pregnancy and health outcomes in the offspring: a systematic review. *J Dev Orig Health Dis* 2016; **7**(4): 391–407.

77. Nomura Y, John RM, Janssen AB, et al. Neurodevelopmental consequences in offspring of mothers with preeclampsia during pregnancy: underlying biological mechanism via imprinting genes. *Arch Gynecol Obstet* 2017; **295**(6): 1319–29.

78. Maher GM, O'Keeffe GW, Kenny LC, Kearney PM, Dinan TG, Khashan AS. Hypertensive disorders of pregnancy and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis protocol. *BMJ Open* 2017; **7**(10): e018313.

79. Maher GM, Dalman C, O'Keeffe GW, et al. Association between preeclampsia and attention-deficit hyperactivity disorder: a population-based and sibling-matched cohort study. *Acta Psychiatr Scand* 2020.

80. Chen Q, Sjölander A, Långström N, et al. Maternal pre-pregnancy body mass index and offspring attention deficit hyperactivity disorder: a population-based cohort study using a sibling-comparison design. *Int J Epidemiol* 2014; **43**(1): 83–90.

81. Musser ED, Willoughby MT, Wright S, et al. Maternal prepregnancy body mass index and offspring attention-deficit/hyperactivity disorder: a quasi-experimental sibling-comparison, population-based design. *J Child Psychol Psychiatry* 2017; **58**(3): 240–7.

82. Lai MC, Lombardo MV, Baron-Cohen S. Autism. *Lancet* 2014; **383**(9920): 896–910.

83. Stergiakouli E, Davey Smith G, Martin J, et al. Shared genetic influences between dimensional ASD and ADHD symptoms during child and adolescent development. *Mol Autism* 2017; **8**: 18.

84. Fusar-Poli P, Solmi M, Brondino N, et al. Transdiagnostic psychiatry: a systematic review. *World Psychiatry* 2019; **18**(2): 192–207.

85. Fusar-Poli P. TRANSD recommendations: improving transdiagnostic research in psychiatry. *World Psychiatry* 2019; **18**(3): 361–2.

86. Verlaet AAJ, Noriega DB, Hermans N, Savelkoul HFJ. Nutrition, immunological mechanisms and dietary immunomodulation in ADHD. *Eur Child Adolesc Psychiatry* 2014; **23**(7): 519–29.

87. Paus R, Theoharides TC, Arck PC. Neuroimmunoendocrine circuitry of the 'brain-skin connection'. *Trends Immunol* 2006; **27**(1): 32–9.

88. Buske-Kirschbaum A, Schmitt J, Plessow F, Romanos M, Weidinger S, Roessner V. Psychoendocrine and psychoneuroimmunological mechanisms in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder. *Psychoneuroendocrinology* 2013; **38**(1): 12–23.

89. Mogensen N, Larsson H, Lundholm C, Almqvist C. Association between childhood asthma and ADHD symptoms in adolescence--a prospective population-based twin study. *Allergy* 2011; **66**(9): 1224–30.

90. Holmberg K, Lundholm C, Anckarsäter H, Larsson H, Almqvist C. Impact of asthma medication and familial factors on the association between childhood asthma and attention-deficit/hyperactivity disorder: a combined twin- and register-based study: Epidemiology of Allergic Disease. *Clin Exp Allergy* 2015; **45**(5): 964–73.

91. Biederman J, Milberger S, Faraone SV, Guite J, Warburton R. Associations between childhood asthma and ADHD: issues of psychiatric comorbidity and familiality. *J Am Acad Child Adolesc Psychiatry* 1994; **33**(6): 842–8.

92. Hammerness P, Monuteaux MC, Faraone SV, Gallo L, Murphy H, Biederman J. Reexamining the familial association between asthma and ADHD in girls. *J Atten Disord* 2005; **8**(3): 136–43.

93. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2018; **391**(10122): 783–800.

94. Agnew-Blais J. Intriguing findings regarding the association between asthma and ADHD. *Lancet Psychiatry* 2018; **5**(9): 689–90.

95. Ramirez FD, Chen S, Langan SM, et al. Association of Atopic Dermatitis With Sleep Quality in Children. *JAMA Pediatr* 2019; **173**(5): e190025.

96. Gregory AM, Eley TC, O'Connor TG, Plomin R. Etiologies of associations between childhood sleep and behavioral problems in a large twin sample. *J Am Acad Child Adolesc Psychiatry* 2004; **43**(6): 744–51.

97. Obel C, Olsen J, Henriksen TB, et al. Is maternal smoking during pregnancy a risk factor for hyperkinetic disorder?--Findings from a sibling design. *Int J Epidemiol* 2011; **40**(2): 338–45.

98. Obel C, Zhu JL, Olsen J, et al. The risk of attention deficit hyperactivity disorder in children exposed to maternal smoking during pregnancy - a re-examination using a sibling design. *J Child Psychol Psychiatry* 2016; **57**(4): 532–7.

99. Gustavson K, Ystrom E, Stoltenberg C, et al. Smoking in Pregnancy and Child ADHD. *Pediatrics* 2017; **139**(2).

100. Skoglund C, Chen Q, D'Onofrio BM, Lichtenstein P, Larsson H. Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. *J Child Psychol Psychiatry* 2014; **55**(1): 61–8.

101. Rice F, Langley K, Woodford C, Davey Smith G, Thapar A. Identifying the contribution of prenatal risk factors to offspring development and psychopathology: What designs to use and a critique of literature on maternal smoking and stress in pregnancy. *Dev Psychopathol* 2018; **30**(3): 1107–28.

102. Thapar A, Rice F. Family-Based Designs that Disentangle Inherited Factors from Pre- and Postnatal Environmental Exposures: In Vitro Fertilization, Discordant Sibling Pairs, Maternal versus Paternal Comparisons, and Adoption Designs. *Cold Spring Harb Perspect Med* 2020.

103. Talati A, Wickramaratne PJ, Keyes KM, Hasin DS, Levin FR, Weissman MM. Smoking and psychopathology increasingly associated in recent birth cohorts. *Drug Alcohol Depend* 2013; **133**(2): 724–32.

104. Thome J, Ehlis AC, Fallgatter AJ, et al. Biomarkers for attention-deficit/hyperactivity disorder (ADHD). A consensus report of the WFSBP task force on biological markers and the World Federation of ADHD. *World J Biol Psychiatry* 2012; **13**(5): 379–400.

105. Wolraich ML, Hagan JF, Jr., Allan C, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics* 2019; **144**(4).

106. National Guideline Centre. National Institute for Health and Care Excellence: Clinical Guidelines. Attention deficit hyperactivity disorder: diagnosis and management. London: National Institute for Health and Care Excellence (UK) Copyright © NICE 2018.; 2018.

107. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 2002; **288**(6): 728–37.

108. Ask H, Gustavson K, Ystrom E, et al. Association of Gestational Age at Birth With Symptoms of Attention-Deficit/Hyperactivity Disorder in Children. *JAMA Pediatr* 2018; **172**(8): 749–56.

109. D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA Psychiatry* 2013; **70**(11): 1231–40.

**Panel: Environmental risk/protective factors and peripheral biomarkers for attention-deficit/hyperactivity disorder: an umbrella review of the evidence**

<Evidence before this study>

We searched PubMed/MEDLINE, Embase, and Cochrane Database of Systematic Reviews from inception to Oct 31st, 2019, for meta-analyses of observational studies regarding any environmental risk/protective factors and peripheral biomarkers of attention deficit/hyperactivity disorder, employing search terms such as attention-deficit/hyperactivity disorder and meta-analysis without any language restrictions. Our research identified numerous potential environmental risk/protective factors and peripheral biomarkers associated with attention deficit/hyperactivity disorder in systematic reviews and meta-analyses. However, some results have been inconsistent across studies, and it is unclear whether the claimed associations are prone to biases in literature such as excess significance bias and publication bias.

<Added value of this study>

To overcome the limitations of previous studies, we performed an umbrella review of meta-analyses. We conducted various bias assessment tests and applied criteria for determining the level of credibility of the associations. We identified and analyzed 63 unique associations of potential environmental risk/protective factors or peripheral biomarkers of attention deficit/hyperactivity disorder. Among these, eight environmental risk factors and one peripheral biomarker were identified as factors which were associated with the risk of attention deficit/hyperactivity disorder with high level of evidence (class I or II). Maternal pre-pregnancy obesity, childhood eczema, hypertensive disorders during pregnancy, preeclampsia, and maternal acetaminophen exposure during pregnancy were graded as convincing evidence (class I) and maternal smoking during pregnancy, childhood asthma, and maternal pre-pregnancy overweight as highly suggestive evidence (class II). Considering peripheral biomarkers, evidence was scarce with few ADHD cases and p-values close to the significance threshold, and only serum vitamin D level was graded as highly suggestive evidence (class II). In subset analyses of prospective cohort studies, only maternal smoking during pregnancy, maternal acetaminophen exposure during pregnancy, and maternal pre-pregnancy obesity and overweight retained their level of evidence.

<Implications of all the available evidence>

We identified factors strongly associated with ADHD, which will help clinicians to identify children with high risks of ADHD and possibly lead to earlier diagnosis and treatment. We found that maternal metabolic syndromes, acetaminophen exposure during pregnancy, and childhood atopic diseases were strongly associated with ADHD, suggesting that immunologic pathways may play an important role in ADHD. Maternal metabolic syndromes and acetaminophen use during pregnancy were found to be robust environmental risk factors for both ADHD and autism spectrum disorder, suggesting their potential role as transdiagnostic risk factors. It should be noted that the identified associations are not necessarily causative, and high-quality studies are required to confirm their causality and assess the interaction between the factors and genetic components, sex, intellectual disability, and comorbid psychiatric disorders.

**Table 1. Potential environmental risk/protective factors of ADHD**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Potential environmental risk/protective factor** | **Author, year** | **Number of cases / total population** | **Number of study estimates** | **Study design** | **Effect metrics** | **Random effects summary estimate (95% CI)** | **Random effects p-value** | **I2** | **95% prediction interval** | **Egger p-value** | **Large heterogeneity, small study effect, excess significance bias, or loss of significance under 10% credibility ceiling** | **AMSTAR 2 quality / AMSTAR 2 quality when protocol assessment is ruled out** |
| **Convincing (class I)** |
| Maternal pre-pregnancy obesity | Jenabi, et al. 2019 | 40880 / 1464097 | 11 | Cohort | OR | 1·63 (1·49 to 1·77) | 1·6E-29 | 30% | 1·35 to 1·95 | 0·92 | None | Critically Low / Low |
| Childhood eczema | Schans, et al. 2017 | 10636 / 54429 | 6 | Cohort, case-control | OR | 1·31 (1·2 to 1·44) | 1·5E-08 | 0% | 1·15 to 1·5 | 0·94 | None | Low / High |
| Hypertensive disorders during pregnancy | Maher, et al. 2018 | 37128 / 1395605 | 8 | Cohort, case-control | OR | 1·29 (1·22 to 1·36) | 1·2E-19 | 0% | 1·2 to 1·38 | 0·73 | None | High / High |
| Preeclampsia | Maher, et al. 2018 | >1000 / NR | 6 | Cohort, case-control | OR | 1·28 (1·21 to 1·35) | 7·2E-19 | 0% | 1·19 to 1·39 | 0·76 | None | High / High |
| Maternal acetaminophen exposure during pregnancy | Gou, et al. 2019 | >1000 / 244940 | 8 | Cohort | RR | 1·25 (1·17 to 1·34) | 9·3E-11 | 26% | 1·08 to 1·44 | 0·42 | None | Low / High |
| **Highly suggestive (class II)** |
| Maternal smoking during pregnancy | Huang, et al. 2018 | 50044 / 3011050 | 20 | Cohort, case-control | OR | 1·6 (1·45 to 1·76) | 3·8E-21 | 79% | 1·15 to 2·22 | 0·004 | Large heterogeneity \* | High / High |
| Childhood asthma | Cortese, et al. 2018 | 32539 / 355686 | 11 | Cross-sectional | OR | 1·51 (1·4 to 1·63) | 1·9E-26 | 52% | 1·26 to 1·82 | 0·05 | Large heterogeneity; small study effect | High / High |
| Maternal pre-pregnancy overweight | Jenabi, et al. 2019 | 23525 / 814880 | 9 | Cohort | OR | 1·28 (1·21 to 1·35) | 1·4E-16 | 20% | 1·14 to 1·43 | 0·068 | Small study effect | Critically Low / Low |
| **Suggestive (class III)** |
| Preterm birth | Allotey, et al. 2018 | 1542 / 45298 | 11 | NR | OR | 1·84 (1·36 to 2·49) | 0·000077 | 48% | 0·86 to 3·95 | 0·00037 | Small study effect \* | High / High |
| Maternal stress during pregnancy | Manzari, et al. 2019 | 25547 / 1758906 | 8 | Cohort, case-control | OR | 1·72 (1·27 to 2·34) | 0·00047 | 85% | 0·71 to 4·21 | 3·2e-05 | Large heterogeneity; small study effect; loss of significance under 10% credibility ceiling \* | High / High |
| Maternal SSRI exposure during pre-pregnancy period | Jiang, et al. 2018 | 39097 / 1836001 | 3 | Cohort | RR | 1·59 (1·23 to 2·06) | 0·00044 | 45% | 0·12 to 20·62 | 0·76 | Loss of significance under 10% credibility ceiling \* | Low / High |
| Maternal non-SSRI exposure during pregnancy | Jiang, et al. 2018 | 23064 / 1212802 | 6 | Cohort | RR | 1·5 (1·24 to 1·82) | 0·000042 | 0% | 1·14 to 1·97 | 0·18 | None \* | Low / High |
| Maternal SSRI exposure during pregnancy | Jiang, et al. 2018 | 56502 / 2858185 | 5 | Cohort | RR | 1·37 (1·16 to 1·63) | 0·00025 | 67% | 0·79 to 2·39 | 0·16 | Large heterogeneity \* | Low / High |
| Maternal diabetes | Yamamoto, et al. 2019 | >1000 / NR | 2 | Cohort | HR | 1·36 (1·19 to 1·55) | 0·0000059 | 0% | NA | NA | Loss of significance under 10% credibility ceiling \* | High / High |
| Relatively younger age | Caye, et al. 2019 | >1000 / NR | 30 | Cohort, case-control | RR | 1·36 (1·25 to 1·47) | 7·4E-13 | 98% | 0·88 to 2·08 | 2·1e-05 | Large heterogeneity; small study effect \* | High / High |
| 5-minute Apgar score < 7 | Zhu, et al. 2016 | 37414 / 9244291 | 7 | Cohort, case-control | OR | 1·3 (1·11 to 1·52) | 0·00087 | 62% | 0·84 to 2·01 | 0·076 | Large heterogeneity; small study effect; excess significance bias | Low / High |
| High frequency cell phone use during pregnancy | Birks, et al. 2017 | 6922 / 83884 | 5 | Cohort | OR | 1·29 (1·12 to 1·48) | 0·00038 | 0% | 1·03 to 1·61 | 0·52 | None | NR |
| Cesarean delivery | Zhang, et al. 2019 | 92426 / 3711607 | 14 | Cohort, case-control | OR | 1·17 (1·08 to 1·26) | 0·0002 | 78% | 0·94 to 1·45 | 0·3 | Large heterogeneity; loss of significance under 10% credibility ceiling | High / High |
| Breech/transverse presentation | Zhu, et al. 2016 | 29051 / 1297384 | 5 | Case-control | OR | 1·14 (1·06 to 1·22) | 0·00039 | 0% | 1·01 to 1·28 | 1 | None | Low / High |
| **Weak (class IV)** |
| Childhood eating disorder | Nazar, et al. 2016 | 79 / 1072 | 2 | Case-control, cross-sectional | OR | 5·64 (3·08 to 10·33) | 2·2E-08 | 0% | NA | NA | Loss of significance under 10% credibility ceiling | Moderate / Moderate |
| Preterm birth/low birth weight | Franz, et al. 2018 | 592 / 6163 | 12 | Cohort, case-control | OR | 3·04 (2·19 to 4·21) | 2·7E-11 | 18% | 1·6 to 5·75 | 0·83 | None | High / High |
| Low education level of father | Russell, et al. 2016 | 513 / 12769 | 3 | Case-control, cross-sectional | OR | 2·1 (1·27 to 3·47) | 0·0037 | 86% | 0 to 973·93 | 0·22 | Large heterogeneity | High / High |
| Childhood/adolescent head trauma | Adeyemo, et al. 2014 | NR / 6255 | 6 | NR | RR | 2·09 (1·68 to 2·61) | 5·5E-11 | 0% | 1·53 to 2·86 | 0·69 | None | Critically Low / Critically Low |
| Gestational diabetes | Zhao, et al. 2019 | 648 / 2516 | 4 | Cohort | RR | 2 (1·42 to 2·81) | 0·000064 | 0% | 0·95 to 4·22 | 0·038 | Small study effect | Low / Moderate |
| Low education level of mother | Russell, et al. 2016 | 6960 / 108812 | 6 | Cohort, case control, cross-sectional | OR | 1·91 (1·2 to 3·03) | 0·0062 | 91% | 0·37 to 9·79 | 0·12 | Large heterogeneity; excess significance bias; loss of significance under 10% credibility ceiling | High / High |
| Childhood allergic conjunctivitis | Miyazaki, et al. 2017 | 6400 / 35508 | 3 | Case-control, cross-sectional | OR | 1·69 (1·04 to 2·75) | 0·035 | 92% | 0·01 to 462·51 | 0·66 | Large heterogeneity; loss of significance under 10% credibility ceiling | Low / High |
| Childhood allergic rhinitis | Miyazaki, et al. 2017 | 7937 / 51709 | 5 | Case-control, cross-sectional | OR | 1·59 (1·13 to 2·22) | 0·0072 | 93% | 0·46 to 5·44 | 0·22 | Large heterogeneity; loss of significance under 10% credibility ceiling | Low / High |
| Low perinatal vitamin D concentration | Khoshbakht, et al. 2018 | 202 / 4137 | 4 | Cohort, case-control | RR | 1·41 (1·09 to 1·82) | 0·0088 | 0% | 0·8 to 2·47 | 0·49 | Loss of significance under 10% credibility ceiling | High / High |
| Single parent family | Russell, et al. 2016 | 7838 / 99305 | 6 | Cohort, cross-sectional | OR | 1·28 (1·08 to 1·52) | 0·0044 | 0% | 1·01 to 1·63 | 0·068 | Loss of significance under 10% credibility ceiling | High / High |
| Childhood obesity | Cortese, et al. 2016 | 45183 / 649991 | 30 | NR | OR | 1·2 (1·05 to 1·37) | 0·0085 | 82% | 0·7 to 2·07 | 0·43 | Large heterogeneity; loss of significance under 10% credibility ceiling \* | High / High |
| Breastfeeding | Zeng, et al. 2018 | 1305 / 40053 | 7 | Cohort, case-control, cross-sectional | OR | 0·7 (0·53 to 0·93) | 0·015 | 74% | 0·33 to 1·49 | 0·014 | Large heterogeneity; small study effect; loss of significance under 10% credibility ceiling \* | High / High |
| **Not significant (NS)** |
| Maternal hypothyroidism during pregnancy | Thompson, et al. 2018 | NR / 5317 | 2 | Cohort | OR | 1·58 (0·5 to 5) | 0·44 | 85% | NA | NA | Large heterogeneity | High / High |
| Maternal subclinical hypothyroidism during pregnancy | Thompson, et al. 2018 | NR / 5190 | 2 | Cohort | OR | 1·34 (0·17 to 10·47) | 0·78 | 82% | NA | NA | Large heterogeneity | High / High |
| Perinatal synthetic oxytocin use | Lonfeldt, et al. 2019 | 532 / 1582 | 3 | Cohort, case-control | RR | 1·17 (0·77 to 1·78) | 0·46 | 86% | 0·01 to 184·42 | 0·76 | Large heterogeneity | Low / High |
| Childhood food allergy | Miyazaki, et al. 2017 | 1473 / 7140 | 3 | Case-control, cross-sectional | OR | 1·14 (0·88 to 1·47) | 0·33 | 0% | 0·21 to 6·08 | 0·93 | None | Low / High |
| Prenatal and early infancy thimerosal exposure | Yoshimasu, et al. 2014 | NR / 248134 | 7 | Cohort, case-control | OR | 1·09 (0·82 to 1·43) | 0·56 | 73% | 0·48 to 2·45 | 0·46 | Large heterogeneity | Low / High |
| Prolapsed/nuchal cord | Zhu, et al. 2016 | 26728 / 124988 | 4 | Case-control | OR | 1·08 (0·99 to 1·17) | 0·095 | 49% | 0·79 to 1·47 | 0·6 | None | Low / High |
| Prenatal alcohol exposure <= 20g per week | San Martin Porter, et al. 2019 | NR / 18072 | 2 | Cohort | OR | 1·01 (0·68 to 1·5) | 0·96 | 87% | NA | NA | Large heterogeneity | Critically Low / Low |
| Prenatal alcohol exposure <= 70g per week | San Martin Porter, et al. 2019 | NR / 74502 | 7 | Cohort | OR | 0·94 (0·86 to 1·02) | 0·14 | 41% | 0·76 to 1·16 | 0·57 | None | Critically Low / Low |
| Prenatal alcohol exposure <= 50g per week | San Martin Porter, et al. 2019 | NR / 68036 | 5 | Cohort | OR | 0·94 (0·85 to 1·04) | 0·2 | 58% | 0·69 to 1·28 | 0·71 | Large heterogeneity | Critically Low / Low |
| All statistical tests are two-tailed.\*Presence of excess significance bias could not be assessed since necessary data were not reported. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2; CI, confidence interval; HR, hazard ratio; NA, not available; NR, not reported; OR, odds ratio; RR, relative risk; SSRI, selective serotonin reuptake inhibitor |

**Table 2. Potential peripheral biomarkers of ADHD**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Potential peripheral biomarker** | **Author, year** | **Number of cases / total population** | **Number of study estimates** | **Study design** | **Effect metrics** | **Random effects summary estimate (95% CI)** | **Random effects p-value** | **I2** | **95% prediction interval** | **Egger p-value** | **Large heterogeneity, small study effect, excess significance bias, or loss of significance under 10% credibility ceiling** | **AMSTAR 2 quality / AMSTAR 2 quality when protocol assessment is ruled out** |
| **Highly suggestive (class II)** |
| Serum vitamin D | Khoshbakht, et al. 2018 | 2163 / 10317 | 9 | Case-control, cross-sectional | WMD | -6·93 (-9·34 to -4·51) | 1·9E-08 | 94% | -14·99 to 1·14 | 0·47 | Large heterogeneity | High / High |
| **Suggestive (class III)** |
| Blood magnesium | Huang, et al. 2019 | 2557 / 5059 | 8 | Cross-sectional | Hedges' g | -0·55 (-0·82 to -0·28) | 0·000078 | 92% | -1·43 to 0·34 | 0·42 | Large heterogeneity | High / High |
| Blood lead | He, et al. 2019 | 1160 / 2155 | 7 | Case-control | WMD | 1 (0·46 to 1·53) | 0·00025 | 97% | -0·89 to 2·89 | 0·36 | Large heterogeneity | Low / Moderate |
| **Weak (class IV)** |
| Serum zinc | Sun, et al. 2015 | 2177 / 5077 | 17 | NR | Cohen's d | -1·33 (-2·23 to -0·43) | 0·0038 | 99% | -5·47 to 2·81 | 0·17 | Large heterogeneity | Critically Low / Low |
| Platelet monoamine-oxidase | Scassellati, et al. 2012 | 273 / 460 | 5 | Case-control | Cohen's d | -1·05 (-1·55 to -0·55) | 0·000036 | 67% | -2·68 to 0·58 | 0·32 | Large heterogeneity | Critically Low / Critically Low |
| Hair magnesium | Huang, et al. 2019 | 155 / 331 | 4 | Cross-sectional | Hedges' g | -0·71 (-1·36 to -0·07) | 0·031 | 85% | -3·63 to 2·2 | 0·29 | Large heterogeneity; loss of significance under 10% credibility ceiling | High / High |
| Urine 3-methoxy-4-hydroxyphenylethylene glycol | Scassellati, et al. 2012 | 259 / 478 | 15 | Case-control | Cohen's d | -0·43 (-0·7 to -0·15) | 0·0025 | 53% | -1·31 to 0·45 | 0·87 | Large heterogeneity | Critically Low / Critically Low |
| Blood omega-3 | Hawkey, et al. 2014 | 311 / 586 | 9 | NR | Hedges' g | -0·42 (-0·59 to -0·26) | 4·5E-07 | 0% | -0·62 to -0·22 | 0·38 | None | Critically Low / Critically Low |
| Saliva cortisol | Scassellati, et al. 2012 | 323 / 673 | 8 | Case-control | Cohen's d | -0·31 (-0·47 to -0·15) | 0·00014 | 0% | -0·51 to -0·11 | 0·79 | None | Critically Low / Critically Low |
| Serum ferritin | Tseng, et al. 2018 | 1560 / 6251 | 19 | Case-control, cross-sectional | Hedges' g | -0·25 (-0·44 to -0·05) | 0·013 | 83% | -1·02 to 0·53 | 0·43 | Large heterogeneity; loss of significance under 10% credibility ceiling \* | Low / High |
| Peripheral manganese | Shih, et al. 2018 | 175 / 1209 | 5 | Case-control, cross-sectional | Hedges' g | 0·31 (0·03 to 0·58) | 0·032 | 52% | -0·54 to 1·15 | 0·0016 | Large heterogeneity; small study effect; excess significance bias; loss of significance under 10% credibility ceiling | Low / Moderate |
| Urine norepinephrine | Scassellati, et al. 2012 | 158 / 249 | 7 | Case-control | Cohen's d | 0·41 (0·11 to 0·71) | 0·0075 | 16% | -0·17 to 0·99 | 0·71 | Excess significance bias; loss of significance under 10% credibility ceiling | Critically Low / Critically Low |
| Urine metanephrine | Scassellati, et al. 2012 | 157 / 311 | 5 | Case-control | Cohen's d | 0·47 (0·1 to 0·84) | 0·013 | 14% | -0·32 to 1·27 | 0·31 | Loss of significance under 10% credibility ceiling | Critically Low / Critically Low |
| Urine normetanephrine | Scassellati, et al. 2012 | 131 / 222 | 6 | Case-control | Cohen's d | 0·51 (0·01 to 1·01) | 0·047 | 63% | -1·01 to 2·02 | 0·35 | Large heterogeneity; loss of significance under 10% credibility ceiling | Critically Low / Critically Low |
| **Not significant (NS)** |
| Plasma norepinephrine | Scassellati, et al. 2012 | 53 / 92 | 4 | Case-control | Cohen's d | -0·42 (-1·75 to 0·91) | 0·54 | 88% | -6·62 to 5·78 | 0·42 | Large heterogeneity | Critically Low / Critically Low |
| Serum transferrin | Tseng, et al. 2018 | 89 / 179 | 3 | Case-control | Hedges' g | -0·32 (-0·7 to 0·06) | 0·095 | 36% | -3·91 to 3·26 | 0·59 | None | Low / High |
| Urine homovanillic acid | Scassellati, et al. 2012 | 141 / 247 | 9 | Case-control | Cohen's d | -0·15 (-0·51 to 0·2) | 0·4 | 43% | -1·09 to 0·78 | 0·25 | None | Critically Low / Critically Low |
| Serum iron | Tseng, et al. 2018 | 941 / 1788 | 9 | Case-control, cross-sectional | Hedges' g | -0·06 (-0·27 to 0·15) | 0·57 | 67% | -0·67 to 0·55 | 0·14 | Large heterogeneity | Low / High |
| Urine dopamine | Scassellati, et al. 2012 | 99 / 152 | 4 | Case-control | Cohen's d | 0·13 (-0·22 to 0·49) | 0·47 | 4% | -0·71 to 0·97 | 0·078 | None | Critically Low / Critically Low |
| Plasma epinephrine | Scassellati, et al. 2012 | 53 / 92 | 4 | Case-control | Cohen's d | 0·19 (-0·59 to 0·98) | 0·63 | 69% | -3·14 to 3·53 | 0·63 | Large heterogeneity | Critically Low / Critically Low |
| Urine 5-hydroxyindoleacetic acid | Scassellati, et al. 2012 | 73 / 122 | 4 | Case-control | Cohen's d | 0·34 (-0·14 to 0·81) | 0·16 | 33% | -1·25 to 1·93 | 0·52 | None | Critically Low / Critically Low |
| Urine epinephrine | Scassellati, et al. 2012 | 145 / 223 | 6 | Case-control | Cohen's d | 0·41 (-0·15 to 0·97) | 0·16 | 71% | -1·39 to 2·2 | 0·39 | Large heterogeneity | Critically Low / Critically Low |
| Peripheral blood brain-derived neurotrophic factor | Zhang, et al. 2018 | 654 / 1183 | 10 | Case-control, cross-sectional | Cohen's d | 0·62 (-0·12 to 1·35) | 0·099 | 97% | -2·18 to 3·41 | 0·31 | Large heterogeneity | Critically Low / Low |
| All statistical tests are two-tailed.\*Presence of excess significance bias could not be assessed since necessary data were not reported. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AMSTAR 2, A Measurement Tool to Assess Systematic Reviews 2; CI, confidence interval; NR, not reported; WMD, weighted mean difference |

**Figure 1**



**Figure 2**



**Figure 3**

