Original Article

Environmental risk/protective factors and peripheral biomarkers for attention-deficit/hyperactivity disorder: an umbrella review

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Summary

Background Many potential environmental risk and protective factors, and peripheral biomarkers for ADHD have been investigated, but their consistency and magnitude are unclear. We aimed to systematically appraise the published evidence of association between potential risk factors, protective factors, or peripheral biomarkers, and ADHD.

Methods We did an umbrella review of meta-analyses. We searched PubMed, Embase, and the Cochrane Database of Systematic Reviews from inception to Oct 31, 2019, and screened the references of relevant articles. We included systematic reviews providing meta-analyses of observational studies that examined associations of potential environmental risk factors, protective factors, or peripheral biomarkers with diagnosis of ADHD. 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. We excluded articles that did not examine environmental risk factors, protective factors, or peripheral biomarkers of ADHD; articles that did not include a meta-analysis; and articles that did not present enough data for re-analysis. We excluded non-human studies, primary studies, genetic studies, and conference abstracts. We calculated the summary effect estimates (odds ratio [OR], relative risk [RR], and weighted mean difference [WMD]), 95% CI, heterogeneity *I*2 statistic, 95% prediction interval, small study effects, and excess significance biases. We did analyses under credibility ceilings, and assessed the quality of the meta- analyses with AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2). This study is registered with PROSPERO, number CRD42019145032.

Findings We identified 1839 articles, of which 35 were eligible for inclusion. These 35 articles yielded 63 meta-analyses encompassing 40 environmental risk factors and 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 (1·31, 1·20–1·44), hypertensive disorders during pregnancy (1·29, 1·22–1·36), preeclampsia (1·28, 1·21–1·35), and maternal acetaminophen exposure during pregnancy (RR 1·25, 95% CI 1·17–1·34). Evidence of association was highly suggestive (class II) for maternal smoking during pregnancy (OR 1·6, 95% CI 1·45–1·76), childhood asthma (1·51, 1·4–1·63), maternal pre- pregnancy overweight (1·28, 1·21–1·35), and serum vitamin D (WMD −6·93, 95% CI −9·34 to −4·51).

Interpretation Maternal obesity, overweight, preeclampsia, and hypertension; maternal acetaminophen exposure or smoking during pregnancy; and childhood atopic diseases were strongly associated with ADHD in offspring. Previous familial studies suggest that pre-pregnancy obesity, overweight, and maternal smoking during pregnancy are confounded by familial or genetic factors, and further high-quality studies are therefore required to establish causality.

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Introduction

ADHD is one of the most common childhood neuro-developmental disorders, characterised 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 DSMIV to DSM5. Years lived with disability per 100000 children younger than 5 years was

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 topic[12] —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 (Appendix p 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 tool[16] 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} thresholds[18,19] 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,[11,13,14,28] we 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 I^2 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/m^2 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/m^2)[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 Ⅰ Ⅰ Ⅰ). 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 placenta[65] and blood-brain barrier[66] 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 cytokines[86] 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 courses[93,94] 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 studies[97-99] 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 pregnancy[103] 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 factors[45,107] since the association was supported by sibling studies[108] and dose-response relationship.[109] However, in our review, preterm birth[42] 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

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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	I^2	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%	Low / High

											credibility ceiling	
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 /	4	Case-control	OR	1·08 (0·99 to 1·17)	0·095	49%	0·79 to 1·47	0·6	None	Low / High

		124988										
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	I^2	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

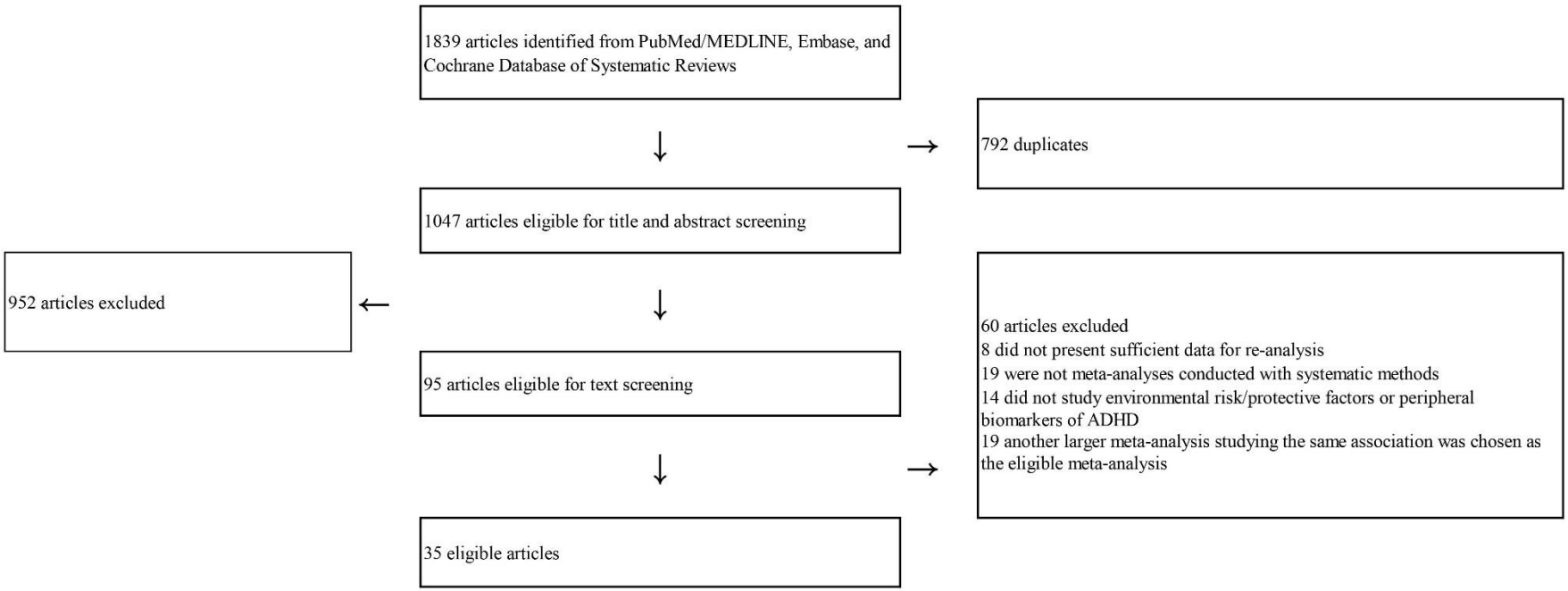
1839 articles identified from PubMed/MEDLINE, Embase, and Cochrane Database of Systematic Reviews
792 duplicates
1047 articles eligible for title and abstract screening
952 articles excluded
60 articles excluded
8 did not present sufficient data for re-analysis
19 were not meta-analyses conducted with systematic methods
14 did not study environmental risk/protective factors or peripheral biomarkers of ADHD
19 another larger meta-analysis studying the same association was chosen as the eligible meta-analysis
95 articles eligible for text screening
35 eligible articles

Figure 2

Main analysis					
Evidence level Statistical analysis	Convincing (class I)	Highly suggestive (class II)	Suggestive (class III)	Weak (class IV)	Not significant (NS)
Random effects p value	< 10^{-6}	< 10^{-6}	< 10^{-3}	< 0·05	> 0·05
Number of ADHD cases	> 1 000	> 1 000	> 1 000	x	x
P value of the largest study	< 0·05	< 0·05	x	x	x
Heterogeneity: I^2	< 50%	x	x	x	x
Small study effects	Not detected	x	x	x	x
Excess significance bias	Not detected	x	x	x	x
95% prediction interval	Excludes the null	x	x	x	x
P value under 10% credibility ceiling	< 0·05	x	x	x	x

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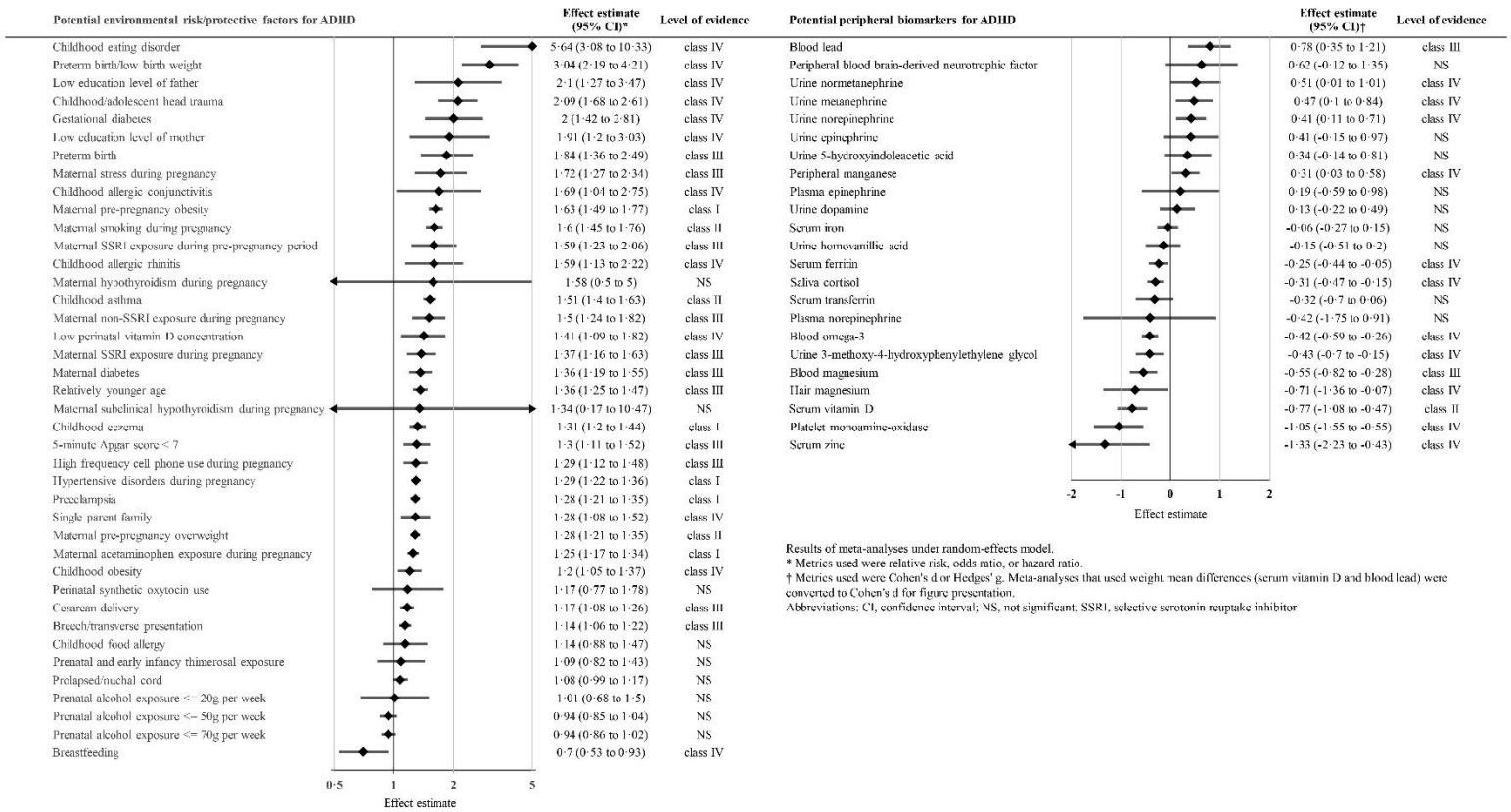
Further assessment
Subgroup analysis of cohort studies
Subgroup analysis of prospective cohort studies
Subgroup analysis of adjusted study estimates

Figure 3



Results of meta-analyses under random-effects model.
* Metrics used were relative risk, odds ratio, or hazard ratio.
† Metrics used were Cohen's d or Hedges' g. Meta-analyses that used weight mean differences (serum vitamin D and blood lead) were converted to Cohen's d for figure presentation.
Abbreviations: CI, confidence interval; NS, not significant; SSRI, selective serotonin reuptake inhibitor