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Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: an umbrella review

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Summary

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

Methods In this umbrella review of meta-analyses, we searched PubMed including MEDLINE, Embase, and the Cochrane Database of Systematic Reviews, from database inception to Oct 31, 2019, and screened the references of relevant articles. We included systematic reviews that provided meta-analyses of observational studies that examined associations of potential environmental risk factors, environmental protective factors, or peripheral biomarkers with diagnosis of ADHD. We included meta-analyses that used categorical ADHD diagnosis criteria according to DSM, hyperkinetic disorder according to ICD, or criteria that were less rigorous than DSM or ICD, such as self-report. We excluded articles that did not examine environmental risk factors, environmental 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 summary effect estimates (odds ratio [OR], relative risk [RR], weighted mean difference [WMD], Cohen's d, and Hedges' g), 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 environmental protective factors (median cases 16 850, median population 91 954) and 23 peripheral biomarkers (median cases 175, median controls 187). Evidence of association was convincing (class I) for maternal pre-pregnancy obesity (OR 1·63, 95% CI 1·49 to 1·77), childhood eczema (1·31, 1·20 to 1·44), hypertensive disorders during pregnancy (1·29, 1·22 to 1·36), pre-eclampsia (1·28, 1·21 to 1·35), and maternal acetaminophen exposure during pregnancy (RR 1·25, 95% CI 1·17 to 1·34). Evidence of association was highly suggestive (class II) for maternal smoking during pregnancy (OR 1·6, 95% CI 1·45 to 1·76), childhood asthma (1·51, 1·4 to 1·63), maternal pre-pregnancy overweight (1·28, 1·21 to 1·35), and serum vitamin D (WMD −6·93, 95% CI −9·34 to −4·51).

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

Funding None.

Introduction

ADHD is one of the most common childhood neurodevelopmental disorders, characterised by inattention, hyperactivity, and impulsive behaviour.[1] The prevalence of ADHD, which was estimated to be 5–7% in 2015,[2,3] is expected to increase[4] as the classification of ADHD has changed from DSM-IV to DSM-5. Years lived with disability per 100 000 children younger than 5 years was 2·0 in 2016.[5]

Many studies have been done to understand and improve the diagnosis, prognosis, and treatment of ADHD across neurodevelopmental stages, with an emerging core focusing on early detection and prevention.[5] The complex nature of ADHD pathophysiology is

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Research in context

Evidence before this study

We searched PubMed including MEDLINE, Embase, and the Cochrane Database of Systematic Reviews from inception to Oct 31, 2019, for meta-analyses of observational studies regarding any environmental risk factors, environmental protective factors, or peripheral biomarkers of ADHD, without any language restrictions. Search terms are included in the appendix (p 4).

Added value of this study

We identified and analysed 63 unique associations of potential environmental risk factors, environmental protective factors, and peripheral biomarkers with ADHD. Among these, eight environmental risk factors and one peripheral biomarker were associated with risk of ADHD 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). Evidence was scarce for peripheral biomarkers, with few ADHD cases and p values close to the significance threshold. Only the association between ADHD and low concentration of serum vitamin D 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 that could help clinicians to identify children with high risk of ADHD and possibly lead to earlier diagnosis and treatment. The association of maternal metabolic syndrome, acetaminophen exposure during pregnancy, and childhood atopic diseases with ADHD suggests that immunological pathways could play an important role in ADHD. Maternal metabolic syndrome and acetaminophen use during pregnancy were robust environmental risk factors for both ADHD and autism spectrum disorder, suggesting their potential role as transdiagnostic risk factors. The identified associations are not necessarily causative, and high-quality studies are required to confirm causality and assess the interaction between these factors and genetic components, sex, intellectual disability, and comorbid psychiatric disorders.

reflected by multimodal research studies investigating the association of many genetic and environmental factors with ADHD,[6,7] and biomarkers that might reflect the effect of these factors.[7] Although 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] Many meta-analyses and systematic reviews have assessed environmental risk factors, environmental protective factors, and biomarkers. However, these reviews are usually restricted to a single topic and their results could be affected by biases, including excess significance bias and publication bias.[10] Furthermore, these studies do not apply hierarchy of evidence among the various environmental factors and peripheral biomarkers to stratify association with ADHD. Finally, with no established pathophysiology of the disorder, the boundaries between risk factors, protective factors, and biomarkers can become blurred. Pragmatic evidence synthesis that encompasses all of these contributing factors is preferred.[11]

In this umbrella review—a systematic collection and evaluation of systematic reviews and meta-analyses done on a specific research topic[12]—we identify and appraise the consistency and magnitude of evidence of environmental factors and peripheral biomarkers associated with diagnosis of ADHD, controlling for several biases.

Methods

We followed the PRISMA reporting guideline (appendix pp 2–3).[13] Screening, data extraction, and methodological appraisal of included studies were done by at least two independent investigators (JHK and JYK).

Search strategy and selection criteria

We systematically searched PubMed including MEDLINE, Embase, and the Cochrane Database of Systematic Reviews from database inception to Oct 31, 2019. Full details of the search strategy, including search terms used, are included in the appendix (p 4). To identify 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 that provided meta-analyses of observational studies (eg, cohort, case-control, and cross-sectional studies), that examined associations of potential environmental risk factors, environmental protective factors, or peripheral biomarkers with diagnosis of ADHD. There was no language restriction. The definitions of risk factor, protective factor, and biomarker followed those of WHO (appendix p 5). We included meta-analyses that used categorical ADHD diagnosis criteria according to DSM, hyperkinetic disorder according to ICD, or less rigorous criteria than these, such as self-reports.

We excluded articles that did not examine environmental risk factors, environmental protective factors, or peripheral biomarkers of ADHD; articles that did not include a meta-analysis; and articles that did not present sufficient data for re-analysis (ie, 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. First, we prioritised the meta-analysis with adjusted study estimates over those with crude estimates. Next, we scored the meta-analyses by their recency and quality, using items from AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2),[14] and chose the one with the highest score (appendix p 6). When two or more meta-analyses had the same score, we chose the one that included more studies. Some meta-analyses studied risk factors and protective factors that might have been measured after childhood (eg, obesity, eczema, and asthma), and temporal causality with onset of ADHD is therefore unclear. In these instances, we included articles that provided meta-analysis of childhood-only populations, or created new subsets by including individual studies in which the mean patient age was 18 years or less. 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 that studied indices of cognitive function (eg, verbal fluency, risky decision making, and emotion dysregulation), as these have been described elsewhere.[15] We also excluded meta-analyses about behavioural 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 the appendix (pp 7–9).

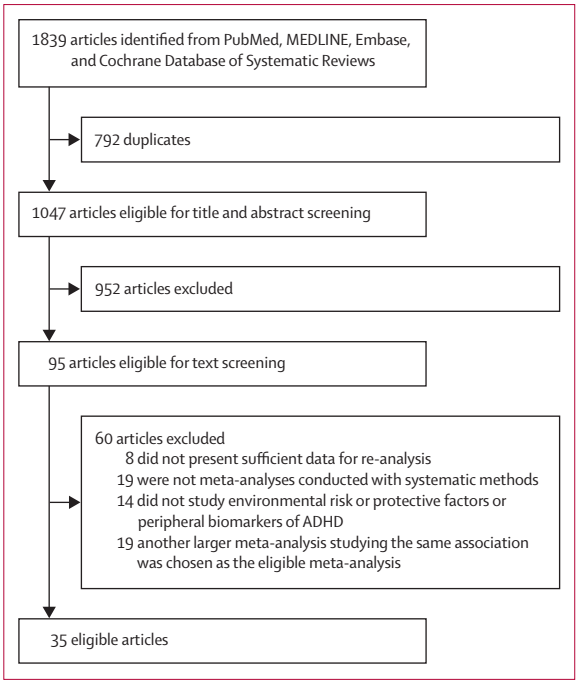

Figure 1: **Literature search**

Data extraction

For each eligible article, two investigators (JHK and JYK) independently extracted name of the first author; publication year; environmental risk factor, environmental protective factor, or peripheral biomarker of interest; number of ADHD cases and study population; maximally adjusted individual study estimate and corresponding 95% CI; and metrics used in the original analyses (eg, 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 (eg, cohort, case-control).

Data analysis

We used a series of statistical tests to assess the robustness and consistency of each identified association. Although environmental risk factors, environmental protective factors, and peripheral biomarkers might be of different use in clinical situations, we used the same assessment method to test the robustness of each association regardless of causality or temporal relationships with ADHD, as in previous umbrella reviews.[11,16] We re-analysed each eligible meta-analysis using the extracted individual study estimates. Metrics followed those of the original meta-analyses. We calculated the summary effect estimate and p values of eligible meta-analyses under both fixed and random effects models. Statistical significance was $p<0{\cdot}05$. We also assessed p values below $0{\cdot}001$ or $0{\cdot}00001$,[17,18] did Cochran's Q test, and calculated the I^2 statistic for heterogeneity between studies (I^2>50% indicates high heterogeneity).[19] We estimated the 95% prediction interval, the range in which we expect the effect of the association will lie for 95% of future studies.[20] We assessed the presence of small study effects (ie, large studies have significantly more conservative results than smaller studies) with the regression asymmetry test proposed by Egger and colleagues.[21] Small study effect was claimed when Egger $p<0{\cdot}1$, with the effect that the largest study was more conservative than the 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 individual studies ($p<0{\cdot}05$).[22] We did random-effects meta-analyses after applying 5%, 10%, 15%, and 20% credibility ceilings to account for potential methodological limitations of observational studies that might result in spurious significance.[23,24] All statistical tests were two-tailed. The software used

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See **Online** for appendix

	Convincing (class I)*	Highly suggestive (class II)*	Suggestive (class III)	Weak (class IV)	Not significant (NS)
Random effects p value	<0·000001	<0·000001	<0·001	<0·05	>0·05
Number of ADHD cases	>1000	>1000	>1000	..	..
p value of the largest study	<0·05	<0·05	..	..	..
Heterogeneity (I^2)	<50%	..	..	..	..
Small study effects	Not detected	..	..	..	..
Excess significance bias	Not detected	..	..	..	..
95% prediction interval	Excludes the null	..	..	..	..
p value with 10% credibility ceiling	<0·05	..	..	..	..

*For results in class I and II, further assessment included subgroup analysis of cohort studies, subgroup analysis of prospective cohort studies, and subgroup analysis of adjusted study estimates

Table 1: **Level of evidence for grading levels**

for the analysis was R version 3.5.1. and its packages.[25,26] 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.[14]

Determining the credibility of evidence

In accordance with previous umbrella reviews,[11,16,27,28] we classified the eligible meta-analyses according to the strength of the evidence of potential environmental risk factors, environmental protective factors, and peripheral biomarkers for ADHD into five classes: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), and not significant (NS; table 1). Criteria for each level of evidence were p values under a 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, we attempted further assessment for the robustness of the evidence by subset analyses of cohort studies (retrospective and prospective), prospective cohort studies, and study estimates adjusted for at least one covariate. We followed state-of-the-art methods of umbrella reviews.[11,16,27]

The study is registered with PROSPERO, number CRD42019145032.

Role of the funding source

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

Results

From database inception to October 31, 2019, we identified 1839 articles, 35 of which were eligible for inclusion (figure 1).[28–62] The 35 eligible articles provided 63 unique meta-analyses (40 potential environmental factors and 23 peripheral biomarkers; tables 2–3, appendix pp 10–12, 17–34). The 40 meta-analyses of environmental risk factors and environmental protective factors were based on 649 669 ADHD cases, 32 342 401 total population, median 16 850 ADHD cases per meta-analysis (IQR 1490–37 086, range 79–92 426), and median 83 884 people per meta-analysis (14 095–1 276 239, 1072–9 244 291). 29 meta-analyses were based on cohort studies, 15 of which also included case-control or cross-sectional studies. The median number of study estimates was six (4–8, 2–30). Effect metrics used were either RR, OR, or HR. 31 (78%) of 40 associations were statistically significant with p<0·05, 23 (58%) of 40 associations with p<0·001, and 12 (30%) with p<0·000001. 25 (80%) of 31 statistically significant associations included more than 1000 ADHD cases per association. 19 (48%) of 40 associations showed large heterogeneity (I^2>50%). 15 (38%) of 40 associations were statistically significant with no small study effects or excess significance bias. The 95% prediction interval excluded the null in only 14 (35%) of 40 associations, and 19 (48%) of 40 associations retained statistical significance with a 10% credibility ceiling.

The 23 meta-analyses of peripheral biomarkers were based on data of 13 807 ADHD cases and 23 649 controls, (median 175 ADHD cases per meta-analysis [IQR 136–798, range 53–2557]), and median 187 controls per meta-analysis [91–921, 39–8154]). Meta-analyses were only based on a case-control or cross-sectional design. The median number of study estimates of the meta-analyses was seven (5–9, 3–19). Effect metrics used were either WMD, Cohen's d, or Hedges' g. 14 (61%) of 23 associations were statistically significant under random effects model, six (26%) of which had p<0·001, and two (9%) had p<0·000001. Five (36%) of 14 statistically significant associations included more than 1000 ADHD cases per association. 15 (65%) of 23 associations showed large heterogeneity (I^2>50%). 11 (48%) of 23 associations were statistically significant with no small study effects or excess significance bias. The 95% prediction interval excluded the null in two (9%) of 23 associations, and eight (35%) of 23 associations retained statistical significance under 10% credibility ceiling.

AMSTAR 2 quality assessment was available for all but one association (maternal mobile phone use). Of 25 meta-analysis articles of environmental risk factors and environmental protective factors, 13 (52%) were graded as high quality, one (4%) moderate, and 11 (44%) low or critically low, mainly because the article did not report the protocol for the systematic review (table 2). When the quality assessment criterion for the protocol was ruled out, only three (12%) were graded as low or critically low. Two (22%) of nine meta-analysis articles of peripheral biomarkers were graded as high quality, and the rest as low or critically low (table 3). When we ruled out the protocol criterion for these, five (56%) were graded as high or moderate.

	Source	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 was ruled out
Convincing (class I)												
Maternal pre-pregnancy obesity	Jenabi et al (2019)[58]	40 880/1 464 097	11	Cohort	OR	1·63 (1·49 to 1·77)	p<0·000001	30%	1·35 to 1·95	0·92	None	Critically low/low
Childhood eczema	van der Schans et al (2017)[37]	10 636/54 429	6	Cohort, case-control	OR	1·31 (1·2 to 1·44)	p<0·000001	0%	1·15 to 1·5	0·94	None	Low/high
Hypertensive disorders during pregnancy	Maher et al (2018)[49]	37 128/1 395 605	8	Cohort, case-control	OR	1·29 (1·22 to 1·36)	p<0·000001	0%	1·2 to 1·38	0·73	None	High/high
Preeclampsia	Maher et al (2018)[49]	>1000/NR	6	Cohort, case-control	OR	1·28 (1·21 to 1·35)	p<0·000001	0%	1·19 to 1·39	0·76	None	High/high
Maternal acetaminophen exposure during pregnancy	Gou et al (2019)[55]	>1000/244 940	8	Cohort	RR	1·25 (1·17 to 1·34)	p<0·000001	26%	1·08 to 1·44	0·42	None	Low/high
Highly suggestive (class II)												
Maternal smoking during pregnancy	Huang et al (2018)[45]	50 044/3 011 050	20	Cohort, case-control	OR	1·6 (1·45 to 1·76)	p<0·000001	79%	1·15 to 2·22	0·004	Large heterogeneity*	High/high
Childhood asthma	Cortese et al (2018)[50]	32 539/355 686	11	Cross-sectional	OR	1·51 (1·4 to 1·63)	p<0·000001	52%	1·26 to 1·82	0·05	Large heterogeneity; small study effect	High/high
Maternal pre-pregnancy overweight	Jenabi et al (2019)[58]	23 525/814 880	9	Cohort	OR	1·28 (1·21 to 1·35)	p<0·000001	20%	1·14 to 1·43	0·068	Small study effect	Critically low/low
Suggestive (class III)												
Preterm birth	Allotey et al (2018)[41]	1542/45 298	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)[60]	25 547/1 758 906	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)[43]	39 097/1 836 001	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)[43]	23 064/1 212 802	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)[43]	56 502/2 858 185	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)[59]	>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
Child younger than school classmates	Caye et al (2019)[61]	>1000/NR	30	Cohort, case-control	RR	1·36 (1·25 to 1·47)	p<0·000001	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)[35]	37 414/9 244 291	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)[39]	6922/83 884	5	Cohort	OR	1·29 (1·12 to 1·48)	0·00038	0%	1·03 to 1·61	0·52	None	NR

(Table 2 continues on next page)

	Source	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
(Continued from previous page)												
Caesarean delivery	Zhang et al (2019)[62]	92 426/3 711 607	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)[35]	29 051/1 297 384	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)[26]	79/1072	2	Case-control, cross-sectional	OR	5·64 (3·08 to 10·33)	p<0·000001	0%	NA	NA	Loss of significance under 10% credibility ceiling	Moderate/ moderate
Preterm birth/low birth weight	Franz et al (2018)[44]	592/6163	12	Cohort, case-control	OR	3·04 (2·19 to 4·21)	p<0·000001	18%	1·6 to 5·75	0·83	None	High/high
Low education level of father	Russell et al (2016)[22]	513/12 769	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)[20]	NR/6255	6	NR	RR	2·09 (1·68 to 2·61)	p<0·000001	0%	1·53 to 2·86	0·69	None	Critically low/ critically low
Gestational diabetes	Zhao et al (2019)[56]	648/2516	4	Cohort	RR	2·00 (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)[22]	6960/108 812	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)[38]	6400/35 508	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)[38]	7937/51 709	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)[48]	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)[22]	7838/99 305	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

(Table 2 continues on next page)

	Source	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
(Continued from previous page)												
Childhood obesity	Cortese et al (2016)[33]	45 183/649 991	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)[54]	1305/40 053	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)[46]	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)[46]	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	Lønfeldt et al (2019)[52]	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)[38]	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)[29]	NR/248 134	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)[35]	26 728/124 988	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 ≤20 g per week	San Martin Porter et al (2019)[57]	NR/18 072	2	Cohort	OR	1·01 (0·68 to 1·5)	0·96	87%	NA	NA	Large heterogeneity	Critically low/low
Prenatal alcohol exposure ≤50 g per week	San Martin Porter et al (2019)[57]	NR/68 036	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
Prenatal alcohol exposure ≤70 g per week	San Martin Porter et al (2019)[57]	NR/74 502	7	Cohort	OR	0·94 (0·86 to 1·02)	0·14	41%	0·76 to 1·16	0·57	None	Critically low/low

AMSTAR 2=A Measurement Tool to Assess Systematic Reviews 2. HR=hazard ratio. NA=not available. NR=not reported. OR=odds ratio. RR=relative risk. *Presence of excess significance bias could not be assessed since necessary data were not reported. All statistical tests are two-tailed.

Table 2: **Potential environmental risk factors and environmental protective factors of ADHD**

	Source	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)[48]	2163/10 317	9	Case-control, cross-sectional	WMD	−6·93 (−9·34 to −4·51)	p<0·000001	94%	−14·99 to 1·14	0·47	Large heterogeneity	High/high
Suggestive (class III)												
Blood magnesium	Huang et al (2019)[53]	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)[40]	1160/2155	7	Case-control	WMD	1·00 (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)[34]	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)[28]	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)[53]	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)[28]	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)[31]	311/586	9	NR	Hedges' g	−0·42 (−0·59 to −0·26)	p<0·000001	0%	−0·62 to −0·22	0·38	None	Critically low/ critically low
Saliva cortisol	Scassellati et al (2012)[28]	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)[49]	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)[51]	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)[28]	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

(Table 3 continues on next page)

	Source	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
(Continued from previous page)												
Urine metanephrine	Scassellati et al (2012)[28]	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)[28]	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)[28]	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)[47]	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)[28]	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)[47]	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)[28]	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)[28]	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)[28]	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)[28]	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)[42]	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

AMSTAR 2=A Measurement Tool to Assess Systematic Reviews 2. NR=not reported. WMD=weighted mean difference. *Presence of excess significance bias could not be assessed as necessary data were not reported. All statistical tests are two-tailed.

Table 3: **Potential peripheral biomarkers of ADHD**

Five environmental risk factors were graded as convincing evidence (class I; table 2, figure 2): pre-pregnancy obesity (defined as body-mass index [BMI] ≥30 kg/m²;[58] OR 1·63, 95% CI 1·49–1·77), childhood eczema (1·31, 1·2–1·44), hypertensive disorders during pregnancy (including chronic hypertension, gestational hypertension, and pre-eclampsia;[49] 1·29, 1·22–1·36), pre-eclampsia (de novo or superimposed on chronic hypertension;[49] 1·28, 1·21–1·35), and maternal acetaminophen exposure during pregnancy (RR 1·25, 95% CI 1·17–1·34). Three environmental risk factors were graded as highly suggestive evidence (class II; table 2, figure 2): maternal smoking during pregnancy (OR 1·6, 95% CI 1·45–1·76), childhood asthma (1·51, 1·4–1·63), and pre-pregnancy overweight (defined as BMI 25·0–29·9 kg/m²;[58] 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, pre-eclampsia, 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 or 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 single parent family). Only breastfeeding showed statistically significant protective effects against ADHD (class IV). Only four associations had effect sizes larger than 2 (eating disorder, preterm birth or low birthweight, low education level of father, and head trauma), which were all class IV evidence.

Meta-analyses included studies diagnosing 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 that used self-report (childhood or adolescent obesity, head trauma, preterm or low birthweight, and maternal gestational diabetes).[30,33,44,56] The subset analyses excluding the self-report studies are provided in the appendix (p 13).

The only biomarker graded as high level of evidence was a lower concentration of serum vitamin D in patients with ADHD (WMD −6·93, 95% CI −9·34 to −4·51 [class II]; table 3, figure 2). Two biomarkers were graded as suggestive evidence (higher blood lead and lower blood magnesium in patients with ADHD; class III).

Subset analyses for class I and II associations were available for the eight meta-analyses of environmental risk factors (appendix p 14). In the cohort subset analyses, four maternal factors retained their level of evidence (pre-pregnancy obesity, overweight, maternal acetaminophen exposure during pregnancy, and maternal smoking during pregnancy), whereas the rest were downgraded to class III or IV, or the subset analysis was not available because there were fewer 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 factors 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 factors, environmental 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, pre-eclampsia, and maternal pre-pregnancy obesity [class I], maternal smoking during pregnancy, childhood asthma, maternal pre-pregnancy overweight, and serum vitamin D [class II]).

Maternal acetaminophen exposure during pregnancy was associated with a higher risk of ADHD in offspring with convincing evidence, retaining the level of evidence in all three subset analyses. Various potential mechanisms have been suggested, including 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.[55,63] Although the exact biological mechanism has not yet been identified, one hypothesis is that prenatal acetaminophen exposure affects normal neurodevelopment, which is consistent with the evidence that acetaminophen readily crosses the placenta[64] and blood–brain barrier,[65] and that prenatal acetaminophen exposure during the third trimester of pregnancy (when the fetal brain grows rapidly and is highly sensitive to stimulation)[66] is associated with a higher risk of ADHD than exposure in earlier trimesters.[55,67,68] This association was supported by a sibling-controlled study, in which children exposed to prenatal acetaminophen for more than 28 days had substantially poorer neurodevelopment than those exposed for less than 28 days.[66] One prospective cohort study reported positive dose-responsive associations with offspring ADHD diagnosis for maternal acetaminophen biomarkers.[69] However, this association should be interpreted in light of possible confounding by indication, since use of the medication could imply the presence of maternal comorbidities (eg, inflammation, infection), which might themselves increase the risk of ADHD in offspring.[55,70] Meanwhile, some studies reported the retained association with statistical significance even after adjusting for indications of acetaminophen.[55,67,68] Caution is required in interpreting the acetaminophen results, as our evidence grading did not consider the biological plausibility or potential confounders of an association, and the association itself does not necessarily indicate causality.

Components of maternal metabolic syndrome were associated with an increased risk of ADHD in offspring,

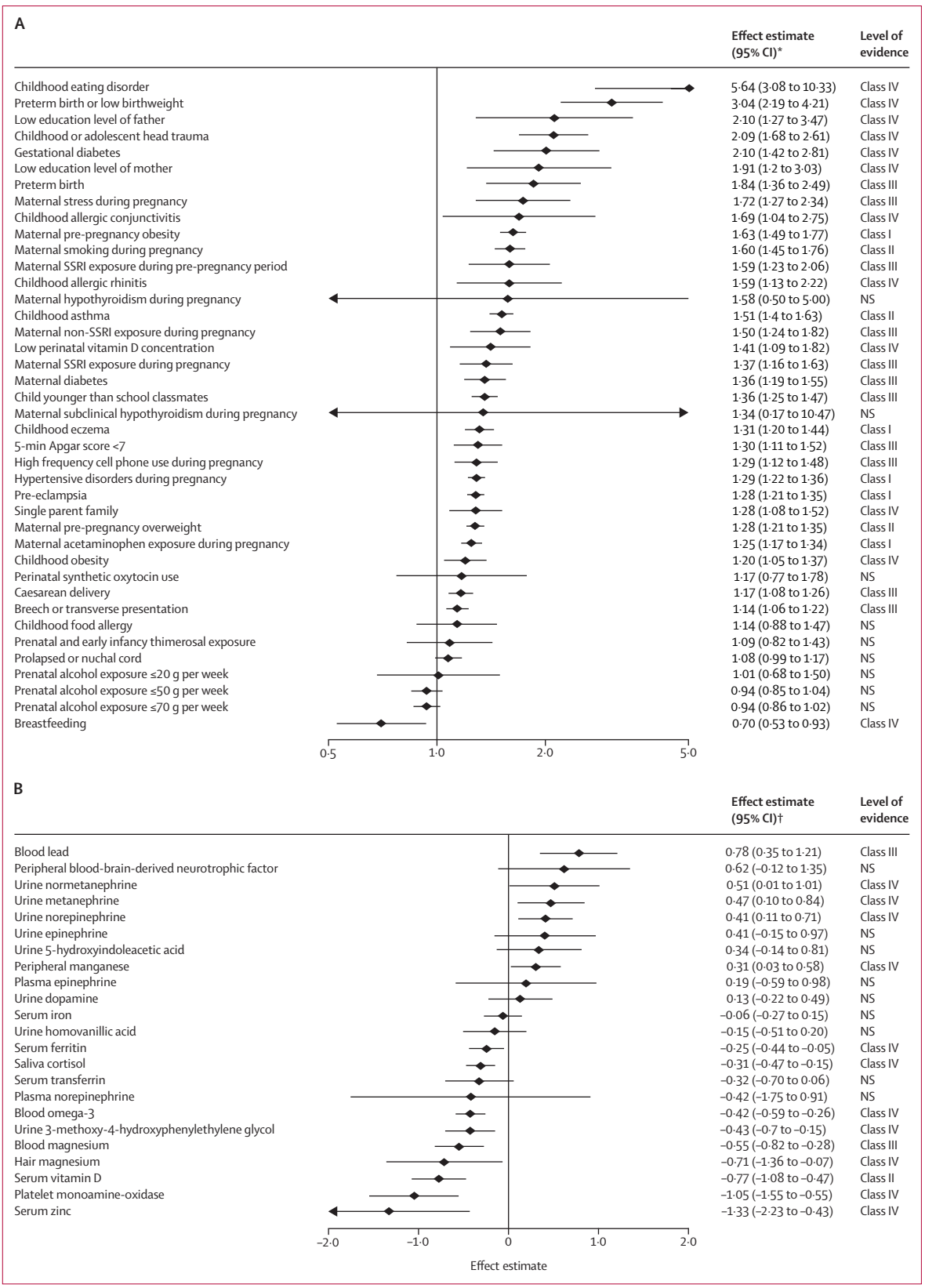

***Figure 2*: Summary estimates of meta-analyses of potential environmental risk factors, environmental protective factors, and peripheral biomarkers for ADHD**

A) Environmental risk factors and environmental protective factors for ADHD. B) Peripheral biomarkers for ADHD. *Metrics used were odds ratio, relative risk, and hazard ratio. †Metrics used were Cohen's d and Hedges' g. Meta-analyses that used weighted mean differences (serum vitamin D and blood lead) were converted to Cohen's d. NS=not significant.

with convincing evidence for pre-pregnancy obesity, pre-eclampsia, and hypertensive disorders during pregnancy, and highly suggestive evidence for pre-pregnancy overweight. One possible underlying mechanism involves a changed in-utero environment created by metabolic syndrome. Potential causes include reduced placental blood flow, maternal oxidative stress, and maternal inflammatory pathways.[71] As inflammatory agents induce increased permeability of the blood–brain barrier of the immature fetus, they can reach the fetal brain,[72] possibly resulting in neuroanatomical alteration.[71,73] Altered fetal developmental trajectories, especially in the brain, could increase the risk of long-term vascular, cognitive, and psychiatric sequelae in the offspring,[74–76] which could subsequently lead to higher risk of ADHD and other neurodevelopmental disorders, including autism spectrum disorder.[77] The causal relationship between pre-eclampsia and offspring with ADHD is supported by a sibling-matched study reporting similar effect sizes between the sibling-matched group (HR 1·13, 95% CI 1·05–1·22) and the unmatched population group (1·15, 1·12–1·19),[78] which implies that the association might be independent of genetic or familial confounding. On the other hand, the association of pre-pregnancy obesity or overweight and offspring with ADHD seems to be confounded by genetic or familial factors, as studies have reported attenuated, non-significant associations in sibling-matched groups (HR 1·15 [95% CI 0·85 to 1·56] for obesity, 0·98 [0·83 to 1·16] for overweight, regression coefficient –0·08 for pre-pregnancy BMI, –0·23 to 0·06).[79,80]

In accordance with evidence that ADHD is a common co-occurring condition in autism spectrum disorder,[81] some components of metabolic syndrome (pre-eclampsia, hypertensive disorders during pregnancy, and maternal pre-pregnancy overweight) and acetaminophen exposure during pregnancy had robust associations with autism spectrum disorder with a high level of evidence (appendix p 15).[11] This finding could support the pathological similarity between the two psychiatric disorders, previously characterised by reports of similarity of brain structural alterations in ADHD and autism,[73] and shared genetic influences that suggest similar biological pathways.[82] One hypothesis is that shared environmental risk factors of ADHD and autism spectrum disorder could have a transdiagnostic feature.[83,84] Further studies regarding the possible linkage between the disorders with the consideration of these 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. Broadly accepted contributors include neuroimmunological pathways[37] that account for the disruptive effect of allergic inflammatory cytokines,[85] and psychological mechanisms[50] that account for the elevated psychological stress.[86] These contributing factors damage ADHD-relevant brain circuits in early life, when the brain is particularly sensitive to stimulation.[87] 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.[50,87] Some twin studies have been done 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, 95% CI 0·04 to 0·37).[88] However, another study reported conflicting findings that cross-twin cross-trait correlation between ADHD and asthma is higher between dizygotic twins (correlation coefficient 0·13, 0·03 to 0·23) than monozygotic twins (0·05, –0·08 to 0·17), contradicting the notion of a shared genetic component in asthma and ADHD.[89] This result was supported by other familial studies.[90,91] Our findings should also be considered in light of the large between-study heterogeneity in the asthma meta-analyses. The heterogeneity might be attributed to the heterogeneous nature of asthma, including diverse clinical presentation, multiple causes, and variable developmental courses,[92,93] 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,[94] and in a twin-matched study,[95] childhood sleep problems were associated with subsequent hyperactivity.

Maternal smoking during pregnancy showed highly suggestive evidence for increased risk of ADHD, retaining the level of evidence in all three subset analyses. Potential mechanisms have been suggested for the harmful effect of maternal smoking on child neurodevelopment.[45] Meanwhile, results of three separate sibling studies, controlled for familial or genetic confounding,[96–98] reported non-significant, attenuated effect estimates, and a meta-analysis of these three studies reported an effect close to the null (OR 1·04, 95% CI 0·95–1·15).[45] Another sibling study reported that effect estimates gradually attenuated towards the null when adjusting for unmeasured confounders (HR 1·62 [95% CI 1·56–1·69] in unmatched population, 1·45 [1·24–1·68] for cousin comparison, 0·88 [0·73–1·06] for sibling comparison).[99] 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 the cause of ADHD.[100,101] Maternal psychiatric conditions, including ADHD, might be another possible confounding factor, in that they were associated with both smoking during pregnancy and ADHD in offspring.[102]

Of the potential peripheral biomarkers, evidence of association between ADHD and lower concentrations of

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 because of the paucity of ADHD cases and research in this field. The quality of meta-analyses of peripheral biomarkers was poorer than that of environmental factors, as many had no protocol registration or risk of bias assessment. These findings are consistent with the consensus that biomarkers are not yet reliable enough to be used clinically. Consensus studies in 2012[103] concluded that no single biomarker reliably predicts ADHD, and guidelines from the same time[104,105] do not mention or recommend any biomarkers for the management of ADHD (appendix p 16).

Our study has some limitations. First, due to the nature of observational studies, the identified associations do not necessarily imply causality. Although we identified robust associations consistently across multiple studies, the possibility of confounding cannot be ruled out. The associations of maternal smoking, obesity, and overweight were not replicated in familial studies, suggesting significant familial or genetic confounding underlying the association.[45,79,80,99] Second, we could not consider changes in classification for ADHD and its varieties and could not distinguish between specific symptoms for diagnosing ADHD. Third, we could not assess potential environmental factors or biomarkers of ADHD according to important characteristics such as sex, intellectual disability, and comorbid psychiatric disorders. Fourth, we assessed peripheral biomarkers but did not assess neurocognitive markers, which might act as biomarkers for ADHD.[15] Fifth, the identified factors might not be independent. Furthermore, we could only address associations in the published meta-analyses and might have missed associations not evaluated in other meta-analyses, or underestimated some genuine environmental factors or biomarkers. For example, other reviews have argued that preterm birth is the risk factor most strongly associated with risk of ADHD,[44,106] since the association was supported by sibling studies[107] and dose-response relationship.[108] However, we graded preterm birth[41] as suggestive evidence (class III), not meeting the criteria for highly suggestive (class II), because random effects p>0·000001, 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.

In this umbrella review, we mapped and established the hierarchy of evidence among 63 potential environmental risk factors, environmental protective factors, and peripheral biomarkers of ADHD. Among these factors and biomarkers, only pre-pregnancy obesity, pre-pregnancy overweight, maternal acetaminophen exposure during pregnancy, and maternal smoking during pregnancy retained high level of evidence in all subset analyses. However, these associations are not necessarily causative, and 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. PF-P provided overall supervision on the conduct of the study. All authors approved the final version of the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All data in this review were from publicly available systematic reviews.

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