**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](https://www.sciencedirect.com/topics/neuroscience/attention-deficit-hyperactivity-disorder) 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](https://www.sciencedirect.com/topics/medicine-and-dentistry/systematic-review), 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](https://www.sciencedirect.com/topics/medicine-and-dentistry/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](https://www.sciencedirect.com/topics/medicine-and-dentistry/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](https://www.sciencedirect.com/topics/medicine-and-dentistry/paracetamol) 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](https://www.sciencedirect.com/topics/medicine-and-dentistry/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](https://www.sciencedirect.com/topics/medicine-and-dentistry/atopy) 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](https://www.sciencedirect.com/topics/medicine-and-dentistry/heredity), and further high-quality studies are therefore required to establish causality.