Association Between Perinatal Hypoxic-Ischemic Conditions and Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis

Tingting Zhu, PhD1,2, Jing Gan, PhD1,2, Jichong Huang, MM1,2, Yafei Li, MM1,2, Yi Qu, PhD1,2, and Dezhi Mu, PhD1,2,3

Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder worldwide, but its etiology is still not fully understood. Previous studies have reported that perinatal hypoxic-ischemic conditions may be a potential cause of ADHD. Methods: An online search of potential English studies published before September 2015 was conducted using the PsycINFO, EMBASE, Web of Science, and PubMed databases. The combined odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with random-effects models. Results: Ten studies were included, with 45,821 cases and 9,207,363 controls. The metaresults found that the following were associated with ADHD: preeclampsia (OR 1.31; 95% CI 1.26-1.37), an Apgar score <7 at 5 minutes (OR 1.31; 95% CI 1.12-1.54), breech/transverse presentations (OR 1.14; 95% CI 1.06-1.23), and a prolapsed/nuchal cord (OR 1.10; 95% CI 1.06-1.15). Conclusion: Our results support that perinatal hypoxia-ischemia may contribute to ADHD. However, more clinical studies are warranted.

Keywords
hypoxia, ischemia, risk factor, ADHD, meta-analysis

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder characterized by inattentive and hyperactive-impulsive behaviours.1 The prevalence of ADHD during childhood and adolescence has highly variable rates worldwide. In the United States, 4-12% of all children aged 5-17 years had ADHD in 2008.2 A cohort study conducted with adolescents aged 11 years in Pelotas, Brazil, found a 4.1% prevalence of ADHD.3 Bianchini reported a prevalence of 3% in 6,183 schoolchildren in Italy.4 In the United Kingdom, Holden reported an estimated prevalence of 9.9 per 100,000 persons in 2009. This diversity may be due to the different ages of the subjects at assessment.5 Attention problems, hyperactivity, and learning difficulties are usually first noticed by teachers rather than parents because of the structured school setting. Also, the diagnosis of ADHD is based on various tools.

The symptoms of ADHD impair academic and social function, and persist into adulthood for approximately half of affected children.1,6 In addition, more than half of individuals with ADHD have 1 or more comorbid disorders. These include dyslexia, developmental coordination disorder, Tourette syndrome, autistic spectrum disorders, conduct and oppositional defiant disorders, and substance abuse.7,8 ADHD is also associated with disrupted parent–child relationships and increased parent stress levels.9,10 The high prevalence and chronic nature of ADHD combined with its related morbidity make it a public health priority.

The etiology of ADHD is complicated and still unknown. There are a number of well-recognized risk factors for ADHD, including a family history; male sex; traumatic brain injury; infections at infancy; and maternal exposure to alcohol, smoking, and other neurotoxic chemicals during pregnancy.11-13 Accumulative evidence suggests that hypoxic-ischemic insult to the fetus is associated with subsequent neurodevelopment after birth, such as cerebral palsy, intellectual disability, and autism.14-16 Recently, Miguel et al conducted an animal study

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that supported a positive association between neonatal hypoxia-ischemia and ADHD-like behavior in rats. However, the role of perinatal hypoxic-ischemic conditions in the development of ADHD in humans is unclear. The objective of this meta-analysis was to determine the association between perinatal hypoxic-ischemic conditions and ADHD. Our hypothesis was that the clinical risk factors for perinatal hypoxia-ischemia differ between individuals with ADHD compared to normal controls.

Materials and Methods

Eligibility Criteria

Only studies that compared at least 1 risk factor related to perinatal hypoxia-ischemia between cases and controls were included if the following criteria were met: (1) the article’s status was published, and it was written in English; (2) cases were individuals with ADHD regardless of age; (3) individuals without ADHD were the controls; (4) and risk factors which were akin to those of Getahun18 included placental abruption, an Apgar score <7 at 5 minutes, neonatal resuscitation, breech/transverse presentations or delivery, prolapsed/nuchal cord, preeclampsia respiratory distress syndrome, and fetal dystocia. It was expected that the included studies used validated scales or criteria to assess ADHD. In addition, the included studies reported the country of origin, study design, subjects’ ethnicity, and the number of patients/control subjects. Studies that attempted to identify the risk factors for a broader definition of an adverse outcome that may include ADHD, or the co-occurrence of ADHD and other impairments were excluded.

Search Strategy and Study Selection

The databases that were used for the literature search included PsycINFO, EMBASE, Web of Science, and PubMed. A further manual search was performed from references cited in these articles to identify any publications missed by the database search. The following keywords were used in the search strategy: “attention deficit hyperactivity disorder” or “ADHD” or “hyperkinetic disorder” and “pregnancy” or “perinatal” or “neonatal” or “birth asphyxia” or “preeclampsia” or “preeclampsia.” Studies were limited to those with human subjects published in English before September 2015. Two investigators conducted the search process independently. First, they excluded irrelevant studies by screening their titles and abstracts. Full texts of the remaining articles were further reviewed to assess their eligibility based on the inclusion criteria. Any disagreement about the inclusion eligibility was discussed with a third author to reach a consensus.

Data Extraction and the Risk of Bias

For data collection, 2 investigators independently used a form for data extraction. When the data collection became complicated, we compared the results of 2 investigators, and the difference was resolved by a third author who independently confirmed the information. The following information was extracted onto piloted forms: the first author, year of publication, sources of participants (cases and controls), sample size (the number of cases and controls, if available), study design (case-control, cross-sectional, or cohort study), case definition and ascertainment, subjects’ age at assessment, and primary outcome.

The risk of bias of all studies was critically assessed at the study level and considered in the quality assessment. The quality assessment of the mixed methods studies reviewed was performed using items from the Newcastle-Ottawa Scale.19

Statistical Analysis

The odds ratio (OR) was used as a common measure of the association between perinatal hypoxia-ischemia and the risk of ADHD among studies. For studies that reported hazard ratios, the hazard ratios were directly considered as ORs in the pooled analysis. We calculated the crude OR for studies in which only the original data were reported. For studies that reported ORs separately for the Apgar score at a different level, we combined these groups into a single group and calculated a combined OR using a fixed-effects model for the main analysis. Heterogeneity among studies was assessed by I² (significance level, >50%) and Tau² statistics (significance level, P < .10). The pooled OR was combined using a random-effects model, as a small number of studies or heterogeneity across studies in this meta-analysis. A sensitivity analysis was performed to evaluate if single studies could affect meta estimates after removing studies one by one. Planned subgroup analyses were stratified by the study design (case-control or cohort study), diagnosis of ADHD (Diagnostic and Statistical Manual of Mental Disorders [DSM] or International Classification of Diseases [ICD]), and type of effect estimates (crude or adjusted).

The potential publication bias was assessed by visual inspection of the funnel plots. Funnel plots were used to plot log ORs against their standard errors. We also performed the Begg rank correlation test and Egger linear regression test when the significance level was P < .10. All analyses were performed using Stata, version 12.0 (StataCorp, College Station, TX) and Review Manager 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

Results

Study Selection

The literature search yielded 1214 articles from databases and screening bibliographic references of the selected studies after ruling out duplicate publications. Thirty-four potential studies were eligible for further full-text reviewing after screening their titles and abstracts. After reading the full texts, 24 studies were excluded. Among them, 20 studies did not have a fetal hypoxic-ischemic risk factor, 1 study had overlapping datasets, 2 studies had cases of ADHD combined with another morbidity, and 1 study was unavailable. Finally, 10 studies11-13,18,21-26 met our inclusion criteria and were subsequently included in the meta-analysis. Figure 1 shows the flow diagram of the study selection.

Studies’ Characteristics and Quality

The included studies of the present meta-analysis were case-control or cohort studies, of which 4 were performed in Europe,11,23-26 2 in Asia,12,22 2 in America,13,18 1 in Brazil,11 and 1 in Australia.21 The sample size of cases ranged from 124 to 13623. For the diagnosis of ADHD, most studies used the criteria according to the DSM-IV or ICD, 10th revision (ICD-10),
except 2 studies used the ICD ninth revision\textsuperscript{13,18} and 1 study only mentioned that the definition of hyperactivity was a predominance of restless, inattentive, and chaotic behavior.\textsuperscript{26} Two studies reported that their cases received drug treatment for the disorder\textsuperscript{18,21} and other \textsuperscript{8,11-13,22-26} did not provide any information about the cases’ treatment status. A summary of the characteristics of the included studies is shown in Table 1.

The total number of controls was 785 (range, 124-1 170 073). Regarding the source of the controls, 3 studies enrolled students,\textsuperscript{11,12,22} 1 study used hospital controls,\textsuperscript{18} and the others enrolled subjects from a registry. Age-matched controls were recruited in 5 studies.\textsuperscript{11,12,18,21-22} However, most studies (n = 7) controlled statistically for a number of potentially confounding variables.\textsuperscript{11,18,21,23-25}

The participants’ age varied among the studies. Among the case-control studies, 1 enrolled adult participants,\textsuperscript{23} 1 enrolled adults,\textsuperscript{21} and the others enrolled those <18 years. For 3 cohort studies, the follow-up period varied between 2 years and 18 years. Although all studies reported the proportion of the cohort that was followed and the reasons for dropout, none of the studies reported whether the dropout rates were similar among groups. It should be noted that the data source used for ADHD diagnosis differed among the studies, with most relying on registry data and medical records,\textsuperscript{25,32} or a doctor’s diagnosis based on an interview with the parents and the child or adolescent.\textsuperscript{23,24,26-28}

The overall quality score of included studies all had score > 5 (see the supplemental data available online) according to the Newcastle-Ottawa Scale.

**Preeclampsia and ADHD**

Figure 2 shows the results of the combined ORs of preeclampsia. Among the 9 ORs from 8 studies, 5 showed a significantly positive relationship between preeclampsia and the risk of ADHD. However, ORs for the association varied from 1.24-3.83 among the studies. The meta-analysis suggests that
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sources of cases</th>
<th>Sources of controls</th>
<th>Case (number)</th>
<th>Control (number)</th>
<th>Matching factors</th>
<th>Age (years)</th>
<th>Diagnosis of ADHD</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silva et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Case control study</td>
<td>Monitoring of drugs of dependents system</td>
<td>Midwives notification system</td>
<td>ADHD and prescribed stimulant medication (12 991)</td>
<td>Non-ADHD (30 071)</td>
<td>Age, gender, socioeconomic status, birth year</td>
<td>&lt; 25</td>
<td>DSM-IV or ICD-10</td>
<td>Registry</td>
</tr>
<tr>
<td>Golmirzaei et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Case control study</td>
<td>cluster Sampling method from preschool children</td>
<td>Cluster sampling method from preschool children</td>
<td>ADHD (208)</td>
<td>Healthy children (196)</td>
<td></td>
<td>4-11</td>
<td>DSM-IV</td>
<td>Children were interviewed by a specialist in child and adolescent psychiatry</td>
</tr>
<tr>
<td>Getahun et al&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Nested case control study</td>
<td>Kaiser Permanente Southern California hospitals</td>
<td>Kaiser Permanente Southern California hospitals</td>
<td>ADHD and received prescriptions specific to ADHD (13 613)</td>
<td>Non-ADHD (68 065)</td>
<td>Age, maternal age, education, smoking during pregnancy, parity, prenatal care, household income, psychosocial disorder during pregnancy, child race/ethnicity, and gender</td>
<td>5-11</td>
<td>ICD-9</td>
<td>Checklist completed by parents and teachers and a clinical interview</td>
</tr>
<tr>
<td>Ketzer et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Case control study</td>
<td>12 public schools in Porto Alegre, Brazil</td>
<td>12 public schools in Porto Alegre, Brazil</td>
<td>ADHD-I (124)</td>
<td>Non-ADHD (124)</td>
<td>Gender, age, maternal age, previous abortion, bleeding during pregnancy, drug use during pregnancy, caesarian delivery, anesthesia, birth weight, prematurity, neonatal jaundice</td>
<td>6-17</td>
<td>DSM-IV</td>
<td>Parents and the child or adolescent interview</td>
</tr>
<tr>
<td>Halmøy et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Nested case control study</td>
<td>Medical Birth Registry of Norway</td>
<td>Medical Birth Registry of Norway</td>
<td>ADHD (2323)</td>
<td>Non-ADHD (1 170 073)</td>
<td>Year of birth, parity, age of mother at birth, maternal education, and marital status of mother</td>
<td>&gt;18</td>
<td>ICD-10</td>
<td>Registry</td>
</tr>
<tr>
<td>Amiri et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Case control</td>
<td>Child and adolescent psychiatric clinics</td>
<td>Primary schools’ students</td>
<td>ADHD (164)</td>
<td>Healthy students (166)</td>
<td></td>
<td></td>
<td>DSM-III-R and DSM-IV</td>
<td>interview with parents and children</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sources of cases</th>
<th>Sources of controls</th>
<th>Case (number)</th>
<th>Control (number)</th>
<th>Matching factors</th>
<th>Age (years)</th>
<th>Diagnosis of ADHD</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann and McDermott&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Cohort study retrospective</td>
<td>South Carolina Medicaid billing records</td>
<td>South Carolina Medicaid billing records</td>
<td>ADHD (7911) Non-ADHD (76 810)</td>
<td>Maternal infection, maternal education, race, sex, age, birth weight, maternal alcohol and tobacco use, sex, birth year, preterm birth, small for gestational age, congenital malformations, maternal variables (smoking during pregnancy, age, psychiatric history, income, school, residence, and cohabitation), and paternal psychiatric history</td>
<td>ADHD (8.45) control (9.46)</td>
<td>ICD-9</td>
<td>Medicaid billing records</td>
<td></td>
</tr>
<tr>
<td>Li et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Cohort study</td>
<td>6 national registers of all singletons born in Denmark</td>
<td>6 national registers of all singletons born in Denmark</td>
<td>ADHD (8234) Non-ADHD (7 882 237)</td>
<td>3-18</td>
<td>ICD-10</td>
<td>Registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gustafsson and Källén&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Case control study</td>
<td>Department of Child and Adolescent Psychiatry in the city of Malmö</td>
<td>Swedish Medical Birth Register</td>
<td>ADHD (124) Non-ADHD (31 775)</td>
<td>Maternal age, born outside Sweden, maternal smoking, year of birth, gestational week, sex</td>
<td>5-17</td>
<td>DSM-III-R and DSM-IV</td>
<td>Registry</td>
<td></td>
</tr>
<tr>
<td>Chandola et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Cohort study</td>
<td>Cardiff Births Survey Register</td>
<td>Cardiff Births Survey Register</td>
<td>Hyperactivity (129) Non-hyperactivity (24 656)</td>
<td>NR</td>
<td>3-6</td>
<td>predominance of restless, inattentive, and chaotic behavior</td>
<td>Registry</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; NR, no reported.

<sup>a</sup>Child’s oldest age in Medicaid.
offspring exposure to maternal preeclampsia compared with the reference group had a significantly increased risk for developing ADHD (OR: 1.31 [95% CI: 1.23-1.40]; P < .00001). No significant heterogeneity was observed (P = .49, I² = 24%).

Apgar Score <7 at 5 Minutes and ADHD

An Apgar score <7 at 5 minutes was considered an indicator of birth asphyxia. We combined different categories of the Apgar score at 5 minutes into a single group for the studies.21,23-24 Overall, 6 studies provided ORs for analysis. Figure 3 presents the results from random-effects models combining the ORs, which support a significant association between an Apgar score <7 at 5 minutes and ADHD (OR: 1.30 [95% CI: 1.11-1.52]; P = .0009). Substantial heterogeneity existed in the outcome (P = .01, I² = 63%).

Breech/Transverse Presentations and ADHD

Five ORs of breech/transverse presentations from 4 studies were pooled using the fixed-effects model. The ORs of each study and pooled results (OR: 1.14 [95% CI: 1.06-1.23]; P = .004) are presented in Figure 4. No significant heterogeneity was found (P = .49, I² = 0%).

1.3.6 Prolapsed/Nuchal Cord and ADHD

Figure 5 presents the results combining the ORs of a fetal prolapsed/nuchal cord. However, fewer studies reported on these outcomes, and none showed a significant relationship between a prolapsed/nuchal cord and the risk of ADHD. The overall combined ORs in relation to ADHD were 1.08 (95% CI: 0.99-1.17; P = .08). No significant heterogeneity was found (P = .14, I² = 45%).

Other Risk Factors

We identified only 1 study that evaluated the impact of placental abruption, respiratory distress syndrome, and fetal dystocia on ADHD.18 The authors of this study reported the following results associated with ADHD: placental abruption (OR 1.16; 95% CI 0.96-1.42), respiratory distress syndrome (OR 1.47; 95% CI 1.27-1.75), and fetal dystocia (OR 1.11; 95% CI 0.94-1.31).
Assessment of Biases and Variability Between Studies

During the sensitivity analysis, when we excluded the study of Getahun et al (the most influential study in terms of weight in meta-analysis), the breech/transverse presentations became not significantly associated ADHD. When we excluded the study of Silva et al (the OR of male subjects), the prolapsed/nuchal cord turned to be significantly associated ADHD. All of other results remained unchanged. The symmetrical funnel plots showed the absence of publication bias (Figure 6). Furthermore, Begg’s and Egger’s tests confirmed the results (all P > .1). The results keep similarly in the subgroup analysis according to the study design, the diagnosis of ADHD and type of effect estimates (see Table 2).

Discussion

Ten studies with 45 821 cases and 9 207 363 controls were included in the current meta-analysis. The pooled analysis indicated that associations were found for ADHD with preeclampsia (OR 1.31; 95% CI 1.23-1.40), an Apgar score <7 at 5 minutes (OR 1.30; 95% CI 1.11-1.52), breech/transverse presentations (OR 1.14; 95% CI 1.06-1.23), and a prolapsed/nuchal cord (OR 1.08; 95% CI 0.99-1.17).

Our analysis showed that offspring exposure to hypoxia-ischemia during the perinatal period might be associated with an increased risk of subsequent ADHD. However, substantial heterogeneity existed in the pooled analysis for an Apgar score <7 at 5 minutes. The results of some risk factors remained inconsistent in the sensitivity analysis and subgroup analysis, which suggested that the conclusion was unstable. This may be explained by the small number of studies in the analysis.

Perinatal ischemic-hypoxic condition is a common disorder that can be caused by many adverse events. Maternal preeclampsia is a severe form of hypertensive disorders in pregnancy, which occurs after 20 weeks of gestation and affects 5-10% of pregnancies. Preeclampsia can lead to poor trophoblast invasion and uteroplacental artery remodeling through several ways, which then compromise function. This in some way induces fetal hypoxia and undernutrition. The Apgar score is a sum of values based on 5 physical signs that reflect the clinical state of newborns. An Apgar score at 5 minutes that is \( \geq 7 \) (total score, 10) in neonates indicates a normal condition, whereas \( \leq 7 \) represents fetal distress. In addition, breech/
transverse presentations and a prolapsed/nuchal cord have been routinely considered as predictors of fetal distress.

The mechanism by which fetal hypoxia and ischemia lead to subsequent ADHD onset is significant structural and functional brain injuries during this critical period of fetal organ development. In animal models, concentrations of neuron-specific enolase and S100 suggest neuronal loss or damage. In a previous study, the density of dendritic spines of hippocampal CA1 pyramidal neurons was significantly lower in the hypoxia-ischemia brain injury group than in the controls. Diffusion tensor imaging in juvenile rats that experienced hypoxia-ischemia during late gestation showed poor microstructural integrity in the hippocampal CA3 subfield. Oligodendrocyte progenitor cell astrogliosis death, excess apoptotic cell death of subplate neurons, and the activation of microglia in the frontal cortex are also observed in hypoxic-ischemic animals. Miguel et al demonstrated that animals subjected to HI manifest cognitive impairments in task acquisition, deficits in sustained attention, and increases in impulsivity and compulsivity in response to task manipulation, which were correlated to brain volume loss in the total hemisphere, cerebral cortex, white matter, hippocampus, and striatum. Previous evidence from imaging studies in infants with hypoxia and ischemia demonstrated a marked reduction in the absolute grey matter volume, intraventricular volume, and periventricular leucomalacia. Abnormality of the brain anatomical morphology significantly contributes to the ADHD disorder.

To our knowledge, this is the first meta-analysis based on currently available observational studies in different settings that assessed the association of parameters related to fetal hypoxic-ischemic conditions with ADHD. However, this study has several limitations. First, we may have missed some studies because we only included studies published in English. Furthermore, we analyzed only several common risk factors related to fetal hypoxic-ischemic conditions. Second, the incidence of ADHD was assessed at a distinct time point during a single follow-up in the majority of studies so none investigated the onset and offset of ADHD episodes. Few studies followed the participants to adulthood, although ADHD predominantly occurs during childhood. Third, various assessments of ADHD used between studies suggest the likelihood of misclassification bias. Although the DSM, ICD, and National Institute of Mental Health’s Research Domain Criteria are commonly used to diagnosis ADHD, Whitely reported that the diagnosis of ADHD continues to fail reliability and validity tests. The DSM-IV diagnostic criteria do not specify age-appropriate levels of attention or impulsivity control. The authors pointed out that ICD-10 and DSM-IV criteria provide very similar lists of symptoms but recommend different ways of establishing a diagnosis, with a lower prevalence predicted. Finally, the relatively small number of studies in this meta-analysis is a major problem. This largely reduces the power of the test. Although a random-effects model was used, the results should accordingly be interpreted with caution. What’s more, the subgroup analysis could not be well performed to examine the independent contribution of multiple methodological factors accounting for the between-study variation in the hypoxic-ischemic-related risk for ADHD.

In conclusion, this meta-analysis of case-control and cohort studies suggests that perinatal hypoxic-ischemic conditions may increase risk for ADHD. Given the limited number of studies, more well designed studies are needed to confirm this association. Furthermore, this causal relationship in adults needs to be examined in future prospective studies.

### Table 2. Pooled OR and Heterogeneity in Subgroups Analyses

<table>
<thead>
<tr>
<th>Study design</th>
<th>Preeclampsia</th>
<th>Apgar score</th>
<th>Breech/transverse presentations</th>
<th>Prolapsed/nuchal cord</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall estimate; heterogeneity</td>
<td>Overall estimate; heterogeneity</td>
<td>Overall estimate; heterogeneity</td>
<td>Overall estimate; heterogeneity</td>
</tr>
<tr>
<td>Cohort</td>
<td>1.19 [1.07 1.32]; (n = 1)</td>
<td>1.43 [1.22 1.68]; ( \hat{\tau}^2 = 0% (n = 2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Case control</td>
<td>1.34 [1.28 1.41]; ( \hat{\tau}^2 = 0% (n = 8)</td>
<td>5.24 [1.03 1.49]; ( \hat{\tau}^2 = 62% (n = 5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diagnosis of ADHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM</td>
<td>1.58 [1.05 2.36]; ( \hat{\tau}^2 = 46% (n = 4)</td>
<td>1.85 [1.18 2.89]; ( \hat{\tau}^2 = 0% (n = 2)</td>
<td>0.93 [0.43 2.00]; ( \hat{\tau}^2 = 0% (n = 2)</td>
<td>—</td>
</tr>
<tr>
<td>ICD</td>
<td>1.28 [1.16 1.40]; ( \hat{\tau}^2 = 40% (n = 3)</td>
<td>1.39 [1.23 1.57]; ( \hat{\tau}^2 = 0% (n = 3)</td>
<td>1.10 [0.86 1.40]; ( \hat{\tau}^2 = 0% (n = 1)</td>
<td>—</td>
</tr>
<tr>
<td>ICD or DSM</td>
<td>1.34 [1.25 1.45]; ( \hat{\tau}^2 = 0% (n = 2)</td>
<td>1.06 [0.95 1.18]; ( \hat{\tau}^2 = 0% (n = 2)</td>
<td>1.33 [1.03 1.72]; ( \hat{\tau}^2 = 0% (n = 2)</td>
<td>—</td>
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</table>

**Effect estimates**

<table>
<thead>
<tr>
<th>Overall estimate; heterogeneity</th>
<th>Overall estimate; heterogeneity</th>
<th>Overall estimate; heterogeneity</th>
<th>Overall estimate; heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>1.67 [0.97 2.88]; ( \hat{\tau}^2 = 64% (n = 3)</td>
<td>1.74 [1.03 2.95]; (n = 1)</td>
<td>—</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.31 [1.25 1.37]; ( \hat{\tau}^2 = 0% (n = 6)</td>
<td>1.27 [1.09 1.49]; ( \hat{\tau}^2 = 65% (n = 6)</td>
<td>—</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; OR, odds ratio; n, number of estimates included; —, not available.
Author Contributions
TZ and JG contributed equally. TZ, JG, and DM conceived of and designed the study. TZ, YQ, DM, and JG performed literature searches and data collection. JH and YL conducted statistical analysis. TZ and JG wrote manuscript. YQ and DM revised the manuscript.

Authors' Note
Tingting Zhu, and Jing Gan contributed equally to this work.

Declaration of Conflicting Interests
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Supplemental Material
The online data are available at http://jcn.sagepub.com/supplemental.

References


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