

# Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis

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abstract

**CONTEXT:** Although very preterm (VP), extremely preterm (EP), very low birth weight (VLBW), and extremely low birth weight (ELBW) newborns seem to have a higher risk of later attention-deficit/hyperactivity disorder (ADHD), the magnitude of the risk is not well-defined.

**OBJECTIVE:** To systematically review and meta-analyze the risk of VP/VLBW and EP/ELBW individuals to develop a ADHD categorical diagnosis or dimensional symptomatology compared with controls with normal weight and/or birth age.

**DATA SOURCES:** We used PsycINFO, Medline, Embase, and Cochrane databases.

**STUDY SELECTION:** We selected cross-sectional, prospective, or retrospective studies with no time or language restriction.

**DATA EXTRACTION:** Independent reviewers screened and extracted data using predefined standard procedures.

**RESULTS:** In 12 studies ( $N = 1787$ ), researchers relying on a categorical diagnosis showed that both VP/VLBW and EP/ELBW subjects have a higher ADHD risk (odds ratio [OR] = 3.04 higher than controls; 95% confidence interval [CI] 2.19 to 4.21). In subgroup analyses, we demonstrated that the more extreme the cases, the higher the ORs (VP/VLBW: OR = 2.25 [95% CI 1.56 to 3.26]; EP/ELBW: OR = 4.05 [95% CI 2.38 to 6.87]). We drew data from 29 studies ( $N = 3504$ ) on ADHD symptomatology and found significant associations with inattention (standardized mean difference [SMD] = 1.31, 95% CI 0.66 to 1.96), hyperactivity and impulsivity (SMD = 0.74, 95% CI 0.35 to 1.13), and combined symptoms (SMD = 0.55, 95% CI 0.42 to 0.68) when compared with controls.

**LIMITATIONS:** Heterogeneity was significantly high for all analyses involving the 3 ADHD dimensions.

**CONCLUSIONS:** With our results, we provide evidence that VP/VLBW subjects have an increased risk of ADHD diagnosis and symptomatology compared with controls, and these findings are even stronger in the EP/ELBW group. Future researchers should address which risk factors related to prematurity or low birth weight lead to ADHD.



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Prematurity is an important public health issue because of its high prevalence rates and related morbidity and mortality.<sup>1</sup> In 2010, the worldwide prevalence of preterm births was estimated at 11.1% (14.9 million), and a significant amount of these were born very preterm (VP) (10.4%, 1.6 million) and extremely preterm (EP) (5.2%, 0.78 million).<sup>2</sup>

Preterm or low birth weight (LBW) children seem to have more cognitive and psychiatric disorders as well as an increased risk of attention-deficit/hyperactivity disorder (ADHD).<sup>3</sup> ADHD is a neurodevelopmental disorder characterized by a nonepisodic pattern of inattentive and/or hyperactive or impulsive symptoms occurring more frequently than expected for the patient's age.<sup>4</sup> The worldwide ADHD prevalence is estimated to be between 3.4<sup>5</sup> and 5.3%<sup>6</sup> in children and adolescents, and the disorder can persist over time, with an adult prevalence rate of ~2.5%.<sup>7</sup> Compared with those with typical development, children and adolescents affected by ADHD frequently present lower educational achievement and self-esteem and higher levels of social impairment, antisocial behavior, and substance abuse as well as greater involvement in criminal activities and traffic accidents.<sup>8,9</sup>

Researchers in some studies suggest a gradient correlation, by which the higher the level of prematurity or LBW, the higher the ADHD prevalence<sup>10</sup> or risk.<sup>11,12</sup> Thus, VP/very low birth weight (VLBW) and EP/extremely low birth weight (ELBW) individuals represent the highest risk groups for ADHD. There is also evidence from a longitudinal prospective cohort study<sup>13</sup> that ADHD diagnosis is more stable in these groups from childhood through adulthood than in term-born individuals.

Despite the data suggesting that VP/VLBW and/or EP/ELBW is clinically relevant to ADHD, no meta-analysis

specifically designed to address the risk of VP/VLBW individuals to develop ADHD has been published. Moreover, significant shortcomings are present in the few meta-analyses in which researchers evaluated associations between more general neurodevelopmental disorders and prematurity or LBW. In a previous meta-analysis of the cognitive and behavioral outcomes of preterm-born, school-aged children, Bhutta et al<sup>14</sup> limited their search to case-control studies and excluded articles in which primarily LBW children were evaluated. In addition, the small number of included studies (7 samples from 6 studies) makes their results less robust. Bhutta et al<sup>14</sup> showed that children born preterm had a 2.64-fold increased risk for ADHD and frequently manifested externalizing symptoms by the time they reached school age. In another meta-analysis,<sup>15</sup> VP/VLBW children's academic achievement and behavioral and executive functioning were evaluated, but its literature search was limited to a 10-year span, which could exclude relevant studies. The authors noted that the small number of studies limited the power of some correlational analyses, and they also detected potential publication bias in studies on teacher ratings of behavioral problems.

Although a definitive ADHD etiology has not yet been elucidated, a multifactorial interplay of genes and noninherited factors are implicated in its causal pathway.<sup>16</sup> Several pre- and perinatal factors and preterm morbidities (eg, necrotizing enterocolitis, periventricular hemorrhage, leukomalacia, bronchopulmonary dysplasia, neonatal chronic lung disease, low Apgar score, white matter injury, slow head growth, etc)<sup>17</sup> may play a significant role in the etiology of ADHD in premature individuals.

We conducted a systematic review and meta-analysis on the effects of VP/VLBW on ADHD diagnosis and

dimensional symptoms. Our primary aim with this study was to verify the risk of VP/VLBW and EP/ELBW subjects to be given a diagnosis of ADHD obtained by validated diagnostic instruments. Our second aim was to examine ADHD diagnosis according to validated dimensional rating scales. Additionally, we sought to describe the most frequent perinatal characteristics, such as clinical/neurologic comorbidities, found in VP/VLBW subjects that might be associated with the occurrence of ADHD. We hypothesized that there would be a strong and clinically relevant risk of VP/VLBW children, adolescents, and adults to develop categorically and dimensionally defined ADHD.

## METHODS

### Eligibility Criteria

Studies included in this systematic review were peer-reviewed, cross-sectional, prospective (including cohorts) or retrospective follow-up studies of subjects diagnosed with ADHD or dimensional symptoms and who were VP, VLBW, EP, or ELBW. The search parameters included no initial cutoff date, and the final search was performed in April 2017. No publication language was ruled out.

### Participants

We included studies with children, adolescents, and adults in which 1 or more of the following conditions was assessed: VP, VLBW, EP, or ELBW. Premature or LBW individuals must have been compared with a control group of subjects born near or at normal birth weight (NBW) ( $\geq 2500$  g) or near, at, or over 37 weeks of gestational age. A categorical ADHD diagnosis must have been established according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)*; *DSM-III-R*; *DSM-IV*; or *DSM-5* criteria. A hyperkinetic disorder diagnosis was also accepted according to

*International Classification of Diseases, Ninth Revision (ICD-9)* or ICD-10 criteria. Clinical assessment must have been performed either with validated diagnostic instruments (Supplemental Table 3) or with validated scales for assessing ADHD symptoms and questions addressing other pertinent DSM or ICD criteria. To select adequate instruments to assess ADHD dimensionally, we accepted a list of scales included in a recently published Cochrane meta-analysis on the dimensional diagnosis of ADHD,<sup>18</sup> and we included 2 other instruments: the Attention Problem scale of the Child Behavior Checklist (CBCL) and the Hyperactivity scale of the Strengths and Difficulties Questionnaire (SDQ). These scales were included because they are part of the 2 best-known instruments for assessing psychopathology in children and adolescents, and their accuracy has been tested for ADHD symptomatology<sup>19</sup> (Supplemental Table 4).

### Information Sources

The bibliographic search included the PsycINFO, Medline, Embase, and Cochrane databases. The search strategy for each database can be found in Supplemental Table 5. Hand searches for published, unpublished, and ongoing studies were performed by reviewing the bibliography sections of the included full texts. We also e-mailed the most productive researchers in the field to obtain information on any ongoing or unpublished studies. If the author did not respond after 2 weeks, a second e-mail was sent.

### Study Records

#### Data Management

The studies were uploaded to the Covidence production platform (<https://www.covidence.org/>), where duplicates were identified and manually excluded. The data were extracted to a Google spreadsheet according to predefined criteria

(described in this section) and independently entered by 2 authors.

#### Selection Process

The 2-step online selection process began with title and abstract screening: 3 independent reviewers (A.P.F., G.U.B., and H.B.) read the titles and abstracts and included studies according to the inclusion and exclusion criteria. Any discrepancies were resolved among the reviewers. An independent reviewer (L.A.R.) acted as arbitrator whenever consensus could not be achieved. The process concluded with full-text screening: 4 independent reviewers (A.P.F., G.U.B., H.B., and C.R.M.-M.) working in pairs read the full text of the studies selected in step 1 to determine if the inclusion criteria were met. At this point, any discrepancies were resolved among the reviewers. A third reviewer (L.A.R.) acted as arbitrator whenever consensus was not reached.

#### Data Collection Process

Data were collected and double-checked by 2 reviewers (A.P.F. and C.R.M.-M.), with a third reviewer (L.A.R.) acting as arbitrator. When multiple reports from the same group of individuals were identified, the following inclusion criteria were used: (1) the most complete data necessary for the meta-analysis, (2) age range for data collection (<18 years old), and (3) larger sample size.

Whenever necessary, the authors were contacted by e-mail to resolve questions emerging from the extraction process or to request additional data. If no response was received from the corresponding author, a second message was sent after 2 weeks. If there was no response, we sent an e-mail to the senior author before discarding the study from the data collection process.

### Included Data

We collected the following information from each selected study: first author and year of publication; country in which the sample was collected; place (ie, hospital, neighborhood, or study sample name) and year of data collection; study design; presence of multiple births; mean age (weeks) and mean weight (grams) at birth; sex; mean age or age range at ADHD evaluation, severity of prematurity or underweight (ie, whether VP, EP, VLBW, or ELBW), and information source (ie, parents, teachers, or self-report); the name of the diagnostic instrument and ADHD rating scale; and clinical or neurologic and psychiatric comorbidities.

### Study Factor and Outcomes

VP and VLBW were defined as gestational age <32 weeks and birth weight <1500 g, respectively.<sup>20</sup> EP and ELBW are subgroups of VP/VLBW with higher degrees of prematurity or LBW: <28 weeks and <1000 g, respectively.<sup>20</sup>

The primary outcome was categorically defined ADHD. The diagnosis could have been established through structured diagnostic interviews with parents or adult subjects. The same procedure was applied to ADHD rating scales filled out by subjects, parents, and/or teachers to collect data on ADHD dimensional symptoms.

### Risk of Bias Assessment

All studies included for data extraction were independently assessed for bias. Two researchers (A.P.F. and C.R.M.-M.) independently rated the studies according to a modified version of the Newcastle-Ottawa scale (NOS), which assesses the quality of nonrandomized studies for systematic reviews and meta-analyses.<sup>21</sup> A similar procedure was used in a recent publication.<sup>22</sup> On its original scale, a study is judged from 3 major perspectives: (1) the

selection of study groups, (2) the comparability of the groups, and (3) ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.<sup>21</sup> We used only the first 2 perspectives because the third item was already part of the inclusion criteria for our review (Supplemental Fig 6). All 4 subitems of the “selection” perspective could receive a maximum score of 1 star, whereas “comparability” could receive 2 stars. Thus, each study could have received a minimum of 0 stars (low quality and high risk of bias) and a maximum of 6 stars (high quality, low risk of bias).

### Data Synthesis

Effect sizes were calculated as odds ratios (ORs) with 95% confidence intervals (CIs) for categorical data according to the number of ADHD and non-ADHD subjects among the VP and/or VLBW subjects, EP and/or ELBW subjects, and controls. To avoid 0 cases, the Cochrane-recommended approach of including 0.5 was applied.<sup>23</sup> For rating scales with continuous data, we calculated the standardized mean difference (SMD) with a 95% CI. Given the expected diversity of methodology in the studies, we used DerSimonian and Laird’s random-effects models,<sup>24</sup> which incorporate the effect of heterogeneity in the overall result to estimate the pooled effect sizes for both categorical and dimensional variables. When researchers provided data from more than 1 information source (ie, parents, teachers, and patients) in their studies, a priori preference was given to parent data. To evaluate the effect of individual studies on effect size, the jackknife method was applied. Jackknife sensitivity analysis is a common procedure used in meta-analysis to test the stability of the outcomes. This is done by recalculating the effect size by removing a different study each time

and then repeating the analyses.<sup>25</sup> Heterogeneity was assessed with the  $I^2$  statistic. To further evaluate the effects of heterogeneity, we performed meta-regression analyses, examining the effects of age, article quality, the occurrence of multiple births, information source, country, and rating scale. For the final multivariate meta-regression model, we selected only those covariables associated with a  $P \leq .2$  in univariate analyses.<sup>26</sup> In addition, we evaluated publication bias using Egger’s statistical test.<sup>27</sup> Meta-analysis was computed in the R software meta-package (version 4.7.0)<sup>28</sup> Meta-regression analyses were performed in Stata 13.0 (StataCorp, College Station, TX).

### RESULTS

Of 519 references identified in the literature search, 34 studies were included in the final analysis. In Fig 1, we present the Preferred Reporting Items for Systematic Reviews and Meta-Analysis<sup>29</sup> trial selection flowchart. Studies included in the final analysis are reported in Table 1 (characteristics of studies included as categorical ADHD diagnosis for VP/VLBW or EP/ELBW) and Table 2 (characteristics of studies included as ADHD rating scales with continuous data for VP/VLBW or EP/ELBW). The 94 full texts excluded from the final analysis and the reasons for their exclusion can be found in Supplemental Table 11. The most frequent reason for eligibility phase exclusion was “measure not assessing or deriving strictly DSM or ICD ADHD diagnosis or dimensional scores” ( $n = 37$ ) (the list of instruments accepted for inclusion can be found in Supplemental Tables 3 and 4). E-mail correspondence with the most productive researchers in the field identified no ongoing or unpublished studies.

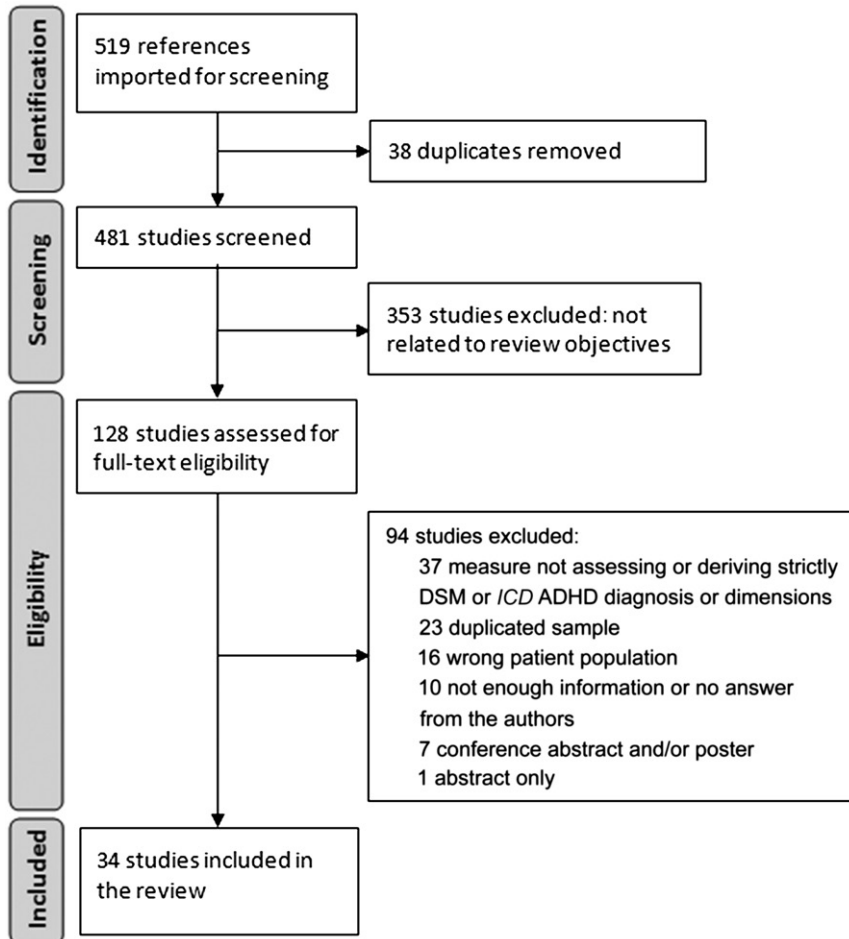
Seven studies<sup>13,32,33,35–37,40</sup> were entered as both diagnostic

instruments (categorical data) and rating scales (continuous data) in the meta-analysis. The Extremely Premature Infants Cure (EPICure) Study was entered in both dimensional and categorical analyses because the same population was assessed at different times and with distinct evaluation methods: by Samara et al<sup>41</sup> in 2008 (dimensional) and Johnson et al<sup>34</sup> in 2010 (categorical). The same was done for the Central-West Canadian Cohort by Boyle et al<sup>42</sup> in 2011 (dimensional) and Van Lieshout et al<sup>39</sup> in 2015 (categorical). Woodward et al<sup>40</sup> 2017 was also entered in both categorical and dimensional analyses because information from the dimensional scale (SDQ) was collected from the subjects at 2 years of age, and a categorical diagnosis was obtained at 9 years of age with the Development and Well-being Assessment (DAWBA). In 1 publication<sup>36</sup> researchers included 2 cohorts, but data were only available under request from the 2004 Pelotas cohort data managers. The “Rainbow Babies and Children’s Hospital” name was given to 2 different cohorts. The participants were born between 1977 and 1979 for one<sup>49</sup> and between 1992 and 1995 for the other.<sup>50</sup>

Twelve studies involving 1787 subjects were included in the categorical diagnosis analysis. Subjects’ mean age and birth weight ranged from 26<sup>37</sup> to 30.6<sup>13</sup> weeks and from 818<sup>37</sup> to 1320 g,<sup>13</sup> respectively. Researchers reported patient assessment during childhood in 8 studies,<sup>13,32,34–38,40</sup> during adolescence in 3 studies,<sup>30,31,33</sup> and during adulthood in 1 study.<sup>39</sup> Researchers reported female predominance in 5 studies,<sup>30,31,35,37,39</sup> male predominance in 4 studies,<sup>13,33,38,40</sup> and did not report on sex in 3 studies.<sup>32,34,36</sup>

Twenty-nine studies (3504 individuals) were included for analysis of ADHD symptomatology





**FIGURE 1**  
Study selection flowchart.

according to ADHD rating scales. The age and birth weight ranged from 24.9<sup>55</sup> to 31 weeks<sup>62</sup> and from 719<sup>47</sup> to 1320 g,<sup>13</sup> respectively. Researchers assessed ADHD during childhood in 23 studies,\* during adolescence in 4 studies,<sup>33,45,47,54</sup> and during adulthood in 2 studies.<sup>42,49</sup> We again found a predominance of female subjects in the 15 studies.†

In both the categorical (Table 1) and the dimensional (Table 2) studies, clinical or neurologic correlates and psychiatric comorbidities were only sporadically reported, so no further analysis could be performed.

\*Refs 13,32,35–37,40,41,43,44,46,48,50–53,55–62.

†Refs 35,37,42,45,47–51,53,56,58–60,62.

### Prematurity, LBW, and ADHD Diagnosis

We found a significant risk of both VP/VLBW and EP/ELBW subjects to develop ADHD (pooled OR = 3.04 [95% CI 2.19 to 4.21],  $I^2 = 17%$ ,  $P = .27$ ), as shown in Fig 2. The subgroup analysis demonstrated that the more extreme the case, the higher the OR (VP/VLBW: OR = 2.25 [95% CI 1.56 to 3.26],  $I^2 = 0%$ ,  $P = .82$ ; EP/ELBW: OR = 4.05 [95% CI 2.38 to 6.87],  $I^2 = 34%$ ,  $P = .21$ ). The subgroup analysis according to raters showed an OR = 3.13 (95% CI 2.10 to 4.68),  $I^2 = 27%$ ,  $P = .20$  for parents and an OR = 2.53 (95% CI 1.31 to 4.89),  $I^2 = 0%$ ,  $P = .41$  for patients (Supplemental Fig 7). No potential publication bias was found

in this group of studies according to Egger's test ( $t = 0.89$  [ $P = .39$ ]).

The sensitivity analysis is presented in Supplemental Table 6. In the EP/ELBW group, the procedure did not change the OR significantly, but the exclusion of Burnett et al<sup>30</sup> (2014) and Scott et al<sup>37</sup> (2012) dropped the heterogeneity from 34% to 0% ( $P = .50$ ). In the overall analysis, there was no significant change in the OR, but the heterogeneity dropped from 17% ( $P = .27$ ) to 0% ( $P = .56$  and  $P = .85$ ) with the exclusion of Breeman et al<sup>13</sup> (2016) and Scott et al<sup>37</sup> (2012), respectively.

### Prematurity, LBW, and ADHD Symptomatology

The forest plot of the overall pooled SMD for inattention, hyperactivity or impulsivity (H/I), and combined symptoms are presented in Figs 3–5. Compared with controls, the SMD was significantly higher for H/I (SMD = 0.74 [95% CI 0.35 to 1.13],  $I^2 = 95%$ ,  $P < .01$ ), inattention (SMD = 1.31 [95% CI 0.66 to 1.96],  $I^2 = 97%$ ,  $P < .01$ ), and combined symptoms (SMD = 0.55 [95% CI 0.42 to 0.68],  $I^2 = 81%$ ,  $P < .01$ ) because no intervals crossed the 0 axis. On the other hand, the comparison among the 3 dimensions is not significant because all 95% CIs are included in the same range, as demonstrated in Figs 3–5.

The overall heterogeneity was high for all 3 dimensions except the combined dimension in the VP/VLBW group (moderate  $I^2 = 54%$ ,  $P < .01$ ). No potential publication bias was found, as demonstrated by Egger's test ( $t = 2.10$  [ $P = .07$ ] and  $t = 1.81$  [ $P = .10$ ] for inattention and H/I, respectively). However, a potential bias was detected for the combined dimension ( $t = 2.38$  [ $P = .02$ ]).

The sensitivity analysis for the combined presentation can be found in Supplemental Table 7. The exclusion of Dahl et al<sup>45</sup> (2006) and Hack et al<sup>49</sup> (2004) reduced the

**TABLE 1** Characteristics of Studies Included as Categorical ADHD Diagnosis for VP/VLBW or EP/ELBW Subjects

Author, y	Sample (Birth y)	Country	N	Mean Age at Birth, wk (Mean or Range)	Mean wt at Birth (g)	Age at Evaluation, y (Mean or Range)	Male (%)	Scale	Rater	Clinical or Neurologic Comorbidities, n (%)	Psychiatric Comorbidities, n (%)	NOS	
												Case	Control
Breeman et al, <sup>13</sup> 2016 <sup>a</sup>	The Bavarian Longitudinal Study (1985–1986)	Germany	260	30.6	1320	6–8	53.1	MPI	Parents	SGA: 108 (41.5); SevD: 50 (19.2)	NS	—	5
Burnett et al, <sup>30</sup> 2014	Victorian Infant Collaborative Study Group (1991–1992)	Australia	215	26.6	1218	17.9	45	CHIPS	Subject	MNBI: 22 (10); SGA: 34 (16); PCU: 31 (67)	MDD: 28 (14); BP: 1 (0.5); DD: 6 (3); GAD: 10 (5); Soc.P: 2 (1); Spe.P: 8 (4); PTSD: 3 (1); PD: 5 (2); agoraphobia: 1 (0.5); OCD: 4 (2)	4	—
Cooke and Abernethy, <sup>31</sup> 1999	Liverpool Maternity Hospital (January 1980 to June 1981)	United Kingdom	87	28.6	1103	13	46	CAPA	Parents	PVH: 19 (21.8); MGL: 2 (2.2); convulsions: 7 (8); PBC: 22 (25.2%)	NS	—	4
Hatch et al, <sup>32</sup> 2014 <sup>a</sup>	New York City metropolitan area University Hospital in Trondheim (1986–1988)	United States	197	NS	978.06	3–4	NS	K-SADS-PL	Parents	NS	NS	4	—
Indredavik et al, <sup>33</sup> 2010 <sup>a</sup>	University Hospital in Trondheim (1986–1988)	Norway	65	29	1180	14	54	K-SADS-PL	Parents	IWH: 11 (4)	NS	5	—
Johnson et al, <sup>34</sup> 2010 <sup>b</sup>	EPiCure Study: United Kingdom and Ireland (March to December 1995)	United Kingdom	219	≤26	NS	11	NS	DAWBA	Parents	NS	Aut.D: 16 (8); SAD: 5 (2.5); Spe.P: 3 (1.5); Soc.P: 1 (0.5); PTSD: 1 (0.5); GAD: 4 (2); MD: 3 (1.5); ODD: 11 (5); CD: 1 (0.5); TD: 2 (1)	—	5
McNicholas et al, <sup>35</sup> 2015 <sup>a</sup>	Dublin Maternity Hospital (1995–1996)	Ireland	64	30	1172	11.6	37.5	DAWBA	Parents	IWH: 12 (18.7); ACU: 40 (62.5)	ADNS: 8 (12.5); CD: 1 (1.5); Asp.D: 3 (4.6)	—	4
Murray et al, <sup>36</sup> 2016 <sup>ac</sup>	2004 Pelotas cohort	Brazil	48	≤32	≤1500	6.7	NS	DAWBA	Parents	NS	NS	—	5
Scott et al, <sup>37</sup> 2012 <sup>a</sup>	Rainbow Babies and Children's Hospital (2001–2003)	United States	148	26	818	5.96	46	P-CHIPS	Parents	NS	ODD: 27 (19); CD: 8 (6); Soc.P: 9 (6); Spe.P: 24 (6); SAD: 8 (6); GAD: 4 (3)	—	5
Treyvaud et al, <sup>38</sup> 2013	Victorian Infant Brain Studies (2001–2003)	Australia	177	27.5	975	7	53	DAWBA	Parents	SGA: 16 (9); GBA: 117 (66.1); NDD: 9 (5.08)	SAD: 6 (3); Spe.P: 7 (4); GAD: 4 (2%); depression: 1 (0.5); ODD: 3 (2)	—	4
Van Lieshout et al, <sup>39</sup> 2015 <sup>d</sup>	Central-West Ontario (1977–1982)	Canada	84	27.05	829	32.02	37	MINI	Subject	SGA: 26 (31); ACU: 46 (59)	Anx.D: 14 (16.6); AB: 7 (8.3); APP: 17 (20.2); depression 13 (15.4)	—	4

**TABLE 1** Continued

Author, y	Sample (Birth y)	Country	N	Mean Age at Birth, wk (Mean or Range)	Mean wt at Birth (g)	Age at Evaluation, y (Mean or Range)	Male (%)	Scale	Rater	Clinical or Neurologic Comorbidities, n (%)	Psychiatric Comorbidities, n (%)	NOS
Woodward et al, <sup>40</sup> 2017 <sup>a</sup>	Christchurch Women's Hospital (November 1998 to December 2000)	New Zealand	223	27.81	1054.4	9	51	DAWBA	Parents	MSWMA: 17 (17); IVH grade 3–4: 6 (6); SPNE: 7 (7)	CD 7 (7); Anx.D: 7 (7); depression 3 (3); ASD: 3 (3)	Case-Control Cohort

AB, antisocial behavior; ACU, antenatal corticosteroid use; ADNS, anxiety disorders (not specified); Anx.D, anxiety disorder; APP, avoidant personality problems; ASD, autism spectrum disorder; Asp.D, Asperger disorder; Aut.D, autistic disorder; BP, bipolar disorder; CAPA, Child and Adolescent Psychiatric Assessment; CD, conduct disorder; CHIPS, Cohen-Hoberman Inventory of Physical Symptoms; DD, dysthymic disorder; GAD, generalized anxiety disorder; GBA, global brain abnormality; IVH, intraventricular hemorrhage; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version; MCL, minor cystic leucomalacia; MDD, major depressive disorder; MINI, Mini International Neuropsychiatric Interview; MNBI, major neonatal brain injury; MPI, Mannheim Parent Interview; MSWMA, moderate to severe white matter abnormality; NDD, neurodevelopmental disability; NS, not stated; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; PBC, positive blood culture; P-CHIPS, Children's Interview for Psychiatric Syndromes-Parent Version; PCU, postnatal corticosteroid use; PD, panic disorder; PTSD, posttraumatic stress disorder; PVH, periventricular hemorrhage; SAD, separation anxiety disorder; Sev.D, severe disability (IQ  $\leq$  2 SDs, cerebral palsy grade 3 or 4, or blindness or deafness); SGA, small for gestational age; Soc.P, social phobia; Spe.P, specific phobia; SPNE, suspected or proven necrotizing enterocolitis; TD, tic disorder; —, not applicable.

<sup>a</sup> These studies also contributed with data from ADHD rating scales for the meta-analysis of dimensional data.

<sup>b</sup> Results of this study are also reported in Samara et al<sup>41</sup> (2008).

<sup>c</sup> Results for the Pelotas cohort were obtained after requirement. Contacts with the Avon Longitudinal Study of Parents and Children investigators were not successful.

<sup>d</sup> Results of this study are also reported in Boyle et al<sup>42</sup> (2011).

heterogeneity from moderate to low levels in the VP/VLBW group. In the EP/ELBW group, the exclusion of Grunewaldt et al<sup>48</sup> (2014) reduced the heterogeneity from 90% to 72%, whereas the study's exclusion reduced heterogeneity in the overall analysis from 81% ( $P < .01$ ) to 62% ( $P < .01$ ).

The most important modifications in the sensitivity analysis for H/I (Supplemental Table 8) were the lack of significance in the VP/VLBW analysis with the exclusion of Brogan et al<sup>44</sup> (2014), Hack et al<sup>49</sup> (2004), Hanke et al<sup>51</sup> (2003), Indredavik et al<sup>33</sup> (2010), and Levy-Shiff et al<sup>54</sup> (1994). The exclusion of Grunewaldt et al<sup>48</sup> (2014) reduced the heterogeneity from 92% ( $P < .01$ ) to 0% ( $P = .45$ ) in the EP/ELBW group. Regarding inattention (Supplemental Table 9), the exclusion of Brogan et al<sup>44</sup> (2014), Hack et al<sup>49</sup> (2004), and Indredavik et al<sup>33</sup> (2010) resulted in a lack of significance in the VP/VLBW analysis. Heterogeneity dropped from high to moderate after the exclusion of Grunewaldt et al<sup>48</sup> (2014) and Indredavik et al<sup>33</sup> (2010) in the EP/ELBW and VP/VLBW groups, respectively. The exclusions altered neither the significance of the overall SMD nor the heterogeneity in either dimension.

### Meta-regression

A meta-regression was not performed for categorically defined ADHD because low heterogeneity was found in the meta-analysis of this group.

With respect to the ADHD rating scales, we performed individual analyses for continuous and categorical covariables to better understand their heterogeneity. We included 1 covariable into the model at a time for each of the ADHD symptom dimensions: age, article quality, country, occurrence of multiple births, and information source (raters). As shown in Supplemental Table 10, countries

**TABLE 2** Characteristics of Studies Included as ADHD Rating Scales With Continuous Data for VP/ILBW or EP/ELBW Subjects

Author, y	Sample (Birth y)	Country	N	Mean Age at Birth, wk (Mean or Range)	Male (%)	Scale	Rater	Clinical or Neurologic Comorbidities, n (%)	Psychiatric Comorbidities, n (%)	Case-Control	NOS Cohort		
Anderson et al, <sup>45</sup> 2011	State of Victoria (January to December 1997)	Australia	189	26.5	833	8.1	NS	Conners	Parents	CP: 22 (12); IVH grade 3–4: 7 (4); GPL: 6 (3%); NE: 10 (5); RP: 97 (51%); BD: 119 (63); ACU: 166 (88); PCU: 70 (37)	NS	—	5
Boyle et al, <sup>42</sup> 2011 <sup>a</sup>	Central-West Ontario (1977–1982)	Canada	142	26.8	835	23.2	43.7	Barkley, YASR	Subject	SGA: 35 (26.8); NI: 23 (27)	NS	—	4
Breeman et al, <sup>13</sup> 2016 <sup>b</sup>	The Bavarian Longitudinal Study (1985–1986)	Germany	260	30.6	1320	6–8	53.1	CBCL	Parents	SGA: 108 (41.5); SevD: 50 (19.2)	NS	—	5
Brogan et al, <sup>44</sup> 2014	Premature Infants' Skills in Mathematics study (September 2001 to August 2003)	United Kingdom	117	28.6	1218	9.7	55	DuPaul ADHD-RS, SDQ	Parents, teachers	NS	NS	4	—
Dahl et al, <sup>45</sup> 2006	Two countries of Norway (1998–2004)	Norway	99	29.3	1188	13–18	44.4	CBCL, YSR	Parents, subject	CP: 8 (8.1); IVH grade 3–4: 2 (3.9); BD: 11 (13.6); sepsis: 10 (10.1); PDA: 13 (13.3)	NS	4	—
de Kieviet et al, <sup>46</sup> 2012	VU University Medical Center Amsterdam (September 2001 to July 2003)	Netherlands	66	29.3	1241	7.5	50	CBCL	Parents	SGA: 18 (27.3); sepsis: 42 (63.6); BD: 19 (28.8); IVH: 14 (21.2)	NS	5	—
Grunau et al, <sup>47</sup> 2004	British Columbia's Children's Hospital (January 1981 to February 1986)	Canada	53	25.8	719	17.3	32	CBCL	Parents	ACU: 53 (80.3) SGA: 9 (17)	NS	5	—
Grunewaldt et al, <sup>48</sup> 2014	Trondheim University Hospital (1999–2001)	Norway	31	26.1	773	10.2	48	ADHD-RS	Parents	IVH: 11 (47); sepsis: 7 (30.4); PDA: 7 (30); ACU: 18 (58); PCU: 12 (39)	NS	—	4
Hack et al, <sup>49</sup> 2004	Rainbow Babies and Children's Hospital (1977–1979)	United States	241	29.7	1179.51	20	48.1	ADHD-RS, YASR	Parents, subject	NS	NS	—	4



**TABLE 2** Continued

Author, y	Sample (Birth y)	Country	N	Mean Age at Birth, wk (Mean or Range)	Mean wt at Birth, (g)	Age at Evaluation, y (Mean or Range)	Male (%)	Scale	Rater	Clinical or Neurologic Comorbidities, n (%)	Psychiatric Comorbidities, n (%)	Case-Control	NOS	Coort
Hack et al, <sup>50</sup> 2009	Rainbow Babies and Children's Hospital (1992–1995)	United States	219	26.4	810	8	41	CSI-4	Parents	BD: 93 (43); sepsis: 108 (49); NE: 11 (5); IVH or PL: 51 (23)	ODD: 12 (6); CD: 19 (9); GAD: 7 (3); MDD: 4 (2); Aut.D: 4 (2); Asp.D: 3 (1); Soc.P: 16 (7); SAD: 9 (4); Spe.P: 108 (50)	5	—	—
Hanke et al, <sup>51</sup> 2003	Department of Pediatrics in Marburg (January 1994 to December 1996)	Germany	60	29	1124	6.2	45	CBCL, HKS	Parents	SGA: 11 (18.3); IVH: 16 (26.6); BD: 20 (33.3)	NS	4	—	—
Hatch et al, <sup>32</sup> 2014 <sup>b</sup>	New York City metropolitan area	United States	197	NS	978.06	3–4	NS	ADHD-RS	Parents, teachers	NS	NS	4	—	—
Huang et al, <sup>52</sup> 2012	Kaohsiung Medical University Hospital and Kaohsiung Municipal Hsiao-Kang Hospital	Taiwan	20	28.95	<1500	2	64	DBRS-Toddler	Parents	0	0	3	—	—
Indredavik et al, <sup>33</sup> 2010 <sup>b</sup>	University Hospital in Trondheim (1986–1988)	Norway	65	29	1180	14	54	ADHD-RS	Parents	SGA: 24 (37); CP: 8 (12); IVH: 11 (4)	NS	5	—	—
Leijon et al, <sup>53</sup> 2016	Southeast region of Sweden (January 1998 to December 1998)	Sweden	51	28.8	1105	7.8	37.2	CBCL	Parents	BD: 14 (27); RDS: 23 (45); sepsis: 14 (28); SGA: 29 (27); IVH: 1 (2); PL: 2 (5); RP: 2 (4)	NS	5	—	—
Levy-Shiff et al, <sup>54</sup> 1994	Kaplan Hospital and Beilinson Hospital	Israel	90	29	1190	13.3	NS	Conners	Parents	NS	NS	1	—	—
Månsson et al, <sup>55</sup> 2014	EXPRESS (April 2004–March 2007)	Sweden	344	24.9	780	2.5	54.7	CBCL	Parents	SGA: 62 (18); CP: 21 (6.1); IVH: 30 (8.7); PL: 14 (4.1); BD: 80 (23.2); NE: 18 (5.2); RP: 115 (33.4)	NS	4	—	—
McNicholas et al, <sup>35</sup> 2015 <sup>b</sup>	Dublin Maternity Hospital (1995–1996)	Ireland	64	30	1172	11.6	38	SDQ	Parents, subject, teachers	IVH: 12 (18.7)	ADNS: 8 (12.5); CD: 1 (1.5); Asp.D: 3 (4.6)	—	4	—
Murray, <sup>36</sup> 2016 <sup>b,c</sup>	2004 Pelotas cohort	Brazil	48	≤52	≤1500	6.7	NS	SDQ	Parents	NS	NS	—	5	—
Nadeau et al, <sup>56</sup> 2001	Ste-Justine Hospital (January 1987 to October 1990)	Canada	61	27.4	1024.3	7	49	CBCL, TRF	Parents, teachers	NS	NS	4	—	—

**TABLE 2** Continued

Author, y	Sample (Birth y)	Country	N	Mean Age at Birth, wk (Mean or Range)	Male (%)	Scale	Rater	Clinical or Neurologic Comorbidities, n (%)	Psychiatric Comorbidities, n (%)	Case-Control	NOS	Cohort
Perkinson-Gloor et al, <sup>57</sup> 2015	University Children's Hospital Basel (June 2001 to December 2005)	Switzerland	58	29.7	69	SDQ	Parents	RDS: 45 (77.6); AP: 46 (79.3); BD: 3 (5.2)	NS	—	—	3
Samara et al, <sup>41</sup> 2008 <sup>a</sup>	Study (March through December 1995)	United Kingdom	241	≤25	50.2	SDQ	Parents, teachers	CP: 41 (17.4); VM: 76 (31.5)	NS	—	—	5
Scott et al, <sup>37</sup> 2012 <sup>b</sup>	Rainbow Babies and Children's Hospital (2001–2003)	United States	148	26	46	CBCL	Parents	NS	ODD: 27 (19); CD: 8 (6); Spe.P: 24 (6); Soc.P: 9 (6); SAD: 8 (6); GAD: 4 (3)	—	—	5
Shum et al, <sup>58</sup> 2008	Mater Children's Hospital	Australia	45	26.4	48.8	ADHD-RS	Parents, teachers	NS	NS	3	—	—
Stjernqvist and Sverningsen, <sup>59</sup> 1999	Southern Swedish population (1985–1986)	Sweden	65	27.1	41	CBCL	Parents	SGA: 9 (15); IVH: 13 (21); BD: 11 (18)	NS	5	—	—
Sykes et al, <sup>60</sup> 1997	Royal Maternity Hospital (1978–1981)	Ireland	243	30.4	41	TRF	Teachers	IVH: 6 (3)	NS	2	—	—
Teplin et al, <sup>61</sup> 1991	NICU of the University of North Carolina Hospitals (1980)	United States	28	28	50	Conners	Parents	SGA: 10 (37); MSD: 3 (12); VI: 3 (12); HL: 2 (7)	NS	4	—	—
Torrioli et al, <sup>62</sup> 2000	Pollicinico Gemelli (1991–1993)	Italy	36	31	41.6	Conners	Parents	NS	NS	1	—	—
Woodward et al, <sup>40</sup> 2017 <sup>b</sup>	Christchurch Women's Hospital (November 1988 to December 2000)	New Zealand	223	27.81	51	SDQ	Parents	MSWMA: 17 (17); IVH grade 3–4: 6 (6); SPNE: 7 (7)	CD 7 (7); Anx.D: 7 (7); depression 3 (3); ASD: 3 (3)	—	—	6

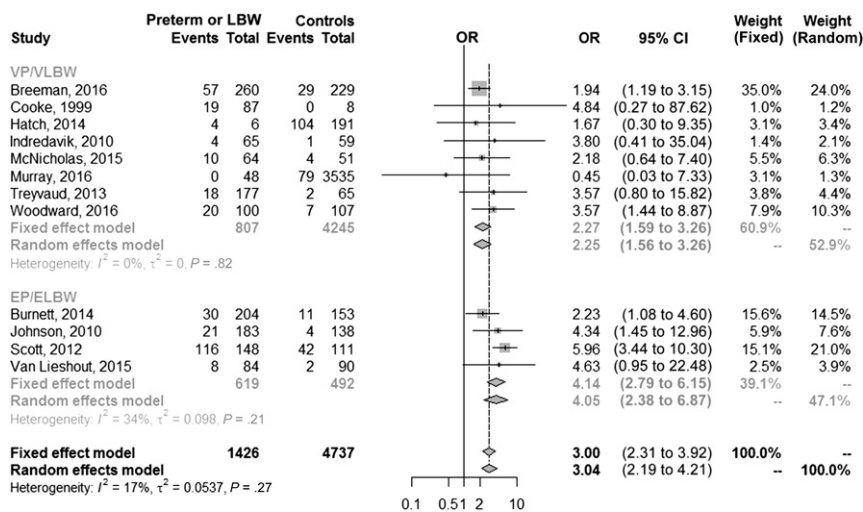
AB, antisocial behavior; ACU, antenatal corticosteroid use; ADHD-RS, ADHD rating scale-IV; ADNS, anxiety disorders (not specified); AP, apnea of prematurity; APP, avoidant personality problems; Asp.D, Asperger disorder; Aut.D, autistic disorder; BD, bronchopulmonary dysplasia; CD, conduct disorder; CP, cerebral palsy; CPL, cystic periventricular leukomalacia; CSI-4, Child Symptom Inventory-4; DBRS-Toddler, Disruptive Behavior Rating Scale-Toddler; EXPRESS, Extremely Preterm Infants in Sweden Study; GAD, generalized anxiety disorder; HL, hearing loss; HKS, Questionnaire of Hyperactivity Symptoms; IVH, intraventricular hemorrhage; MDD, major depressive disorder; MSD, mild spastic diplegia; MSWMA, moderate to severe white matter abnormality; NE, necrotizing enterocolitis; NI, neurosensory impairment; ODD, oppositional defiant disorder; PCU, postnatal corticosteroid use; PDA, patent ductus arteriosus; PL, periventricular leukomalacia; PTSD, posttraumatic stress disorder; RDS, respiratory distress syndrome; RP, retinopathy of prematurity; SAD, separation anxiety disorder; SeVd, severe disability (IQ ≤2 SDs, cerebral palsy grade 3 or 4, or blindness or deafness); SGA, small for gestational age; Soc.P, social phobia; Spe.P, specific phobia; SPNE, suspected or proven necrotizing enterocolitis; TD, tic disorder; VI, visual impairment; VM, ventriculomegaly; YASR, Young Adult Self-Report and Young Adult Behavior Checklist; YSR, youth self-report; —, not applicable.

<sup>a</sup> Results of this study are also reported in Van Lieshout et al.<sup>38</sup> (2015).

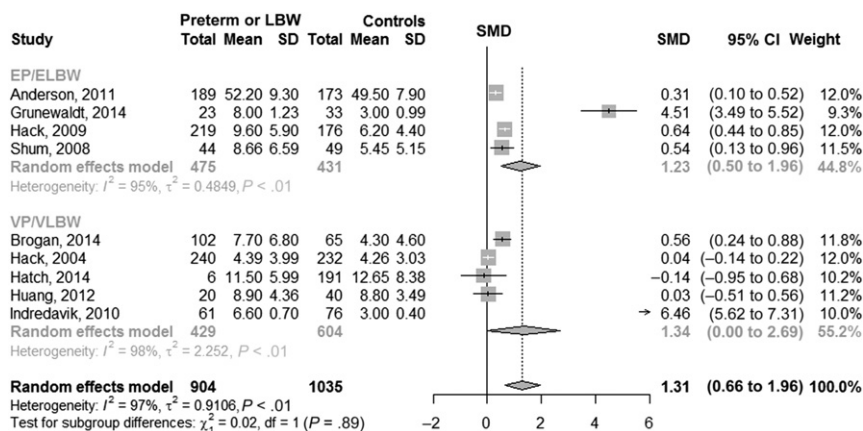
<sup>b</sup> These studies also contributed with data from ADHD rating scales for the meta-analysis of categorical data.

<sup>c</sup> Results for the Pelotas cohort were obtained after requirement. Contacts with the Avon Longitudinal Study of Parents and Children investigators were not successful.

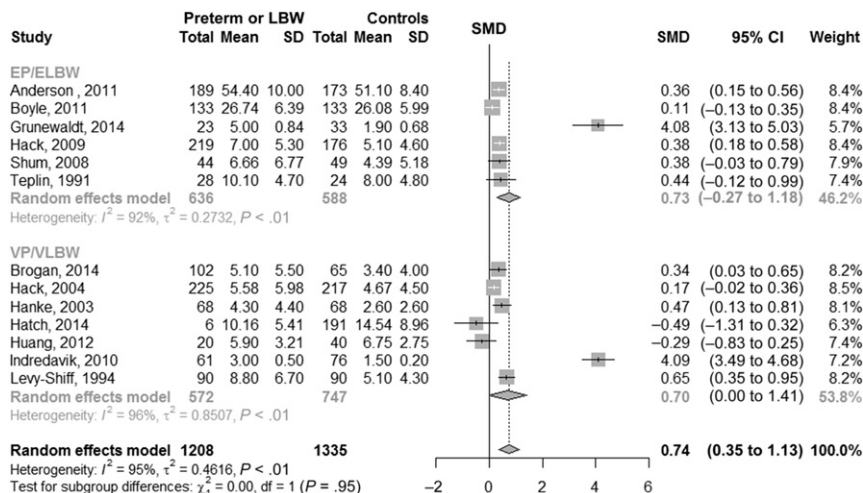
<sup>d</sup> Results of this study are also reported in Johnson et al.<sup>34</sup> (2010).



**FIGURE 2**  
Forest plot for ADHD diagnosis categorically defined.



**FIGURE 3**  
Forest plot for ADHD inattentive symptoms. df, degrees of freedom.



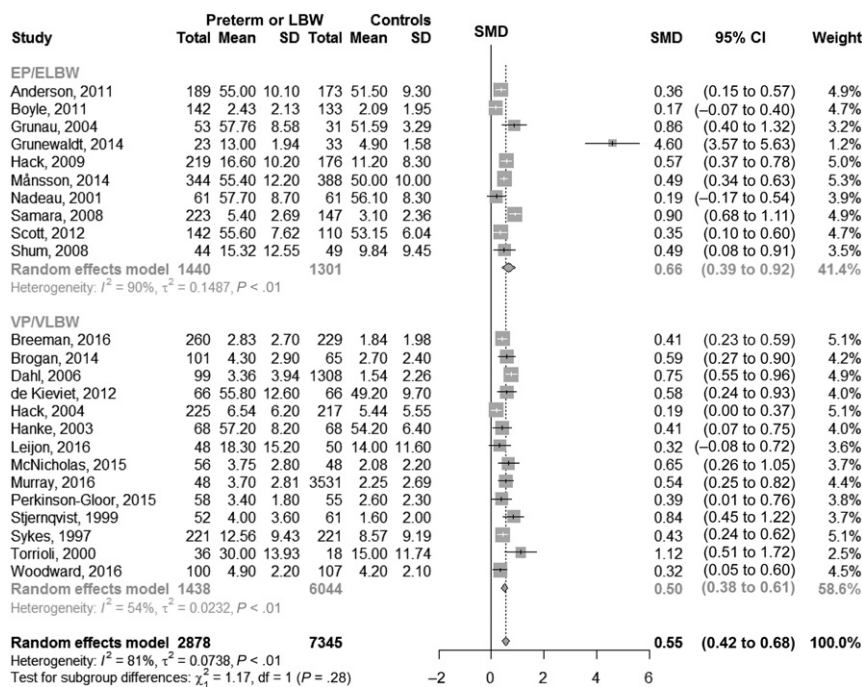
**FIGURE 4**  
Forest plot for ADHD H/I symptoms. df, degrees of freedom.

reaching a flexible  $P \leq .2$  were to be included in a final multivariate meta-regression model; however, this was not feasible because of the lack of additional covariables.

## DISCUSSION

In this systematic review and meta-analysis, we evaluated the risk of VP/VLBW and EP/ELBW individuals to develop ADHD, emphasizing well-defined categorical and dimensional diagnoses and providing evidence of robust associations. In 12 categorical diagnosis studies in which researchers assessed a total of 1787 subjects, it is suggested that VP/VLBW and EP/ELBW individuals are ~3 times more likely to be diagnosed with ADHD than term-born controls. In the VP/VLBW group, this likelihood is approximately doubled, whereas in the EP/ELBW group it is increased fourfold. Furthermore, in 29 studies on ADHD symptoms involving a total of 3504 individuals, researchers demonstrated that both inattention and H/I symptoms are similarly associated with VP/VLBW newborns, with large effect sizes found for the inattention and H/I dimensions and a moderate effect size for the total symptom scores.

Researchers in previous studies have suggested similar findings. In a meta-analysis of the cognitive and behavioral outcomes of preterm-born, school-aged children, Bhutta et al<sup>14</sup> (2002) also found a significantly higher risk of an ADHD diagnosis in preterm infants than controls (OR = 2.64, 95% CI 1.85 to 3.78). In addition, they found that preterm children were at significant risk of reduced cognitive performance and other non-developmentally expected behaviors at school age. Interestingly, they found a gradient correlation because gestational age and birth weight were directly proportional to the mean cognitive test scores. Moreover, in a meta-analysis on academic achievement,



**FIGURE 5** Forest plot for ADHD combined symptoms. df, degrees of freedom.

behavioral problems, and executive function, Aarnoudse-Moens et al<sup>15</sup> (2009) found that attention problems measured by teachers and parents via the CBCL or Teacher Report Form (TRF) were more pronounced in VP/VLBW children than in NBW controls. They also found a strong correlation between adverse outcomes and level of maturity at birth: smaller and more premature children were more prone to internalizing and externalizing behavior problems and poor academic achievement than heavier, more mature infants.

The idea of a gradient correlation<sup>10–12</sup> between prematurity or LBW and ADHD is endorsed by our finding of higher ADHD risk in the EP/ELBW group than the VP/VLBW group. Regarding the ADHD presentations, we found a similar risk for both inattentive and H/I types. Researchers conducting previous investigations have reported that EP had only a risk to develop the ADHD inattentive type<sup>34,50</sup> whereas others have reported a risk for both ADHD inattentive

type and H/I.<sup>34,43</sup> Furthermore, we found a predominance of female subjects in the VP/VLBW groups, although ADHD is typically associated with a high prevalence among male subjects in the general population.<sup>63</sup> Researchers in several studies have suggested that preterm-born individuals with ADHD have phenotypic specificities that diverge from their nonpremature ADHD counterparts. These include a predominance of inattention symptoms, less psychiatric comorbidity,<sup>64,65</sup> higher diagnostic stability from childhood to adulthood,<sup>13</sup> more perinatal clinical or neurologic complications, and major disabilities.<sup>13,15,30,66,67</sup> In addition, the preponderance of male subjects, which is typically seen in nonpremature ADHD, was also not observed in preterm subjects.<sup>64</sup>

Despite the fact that both clinical or neurologic and psychiatric comorbidities were reported in some of the studies, further analyses were not possible because of the heterogeneity of the data described.

It is important to note that our findings suggesting a robust risk of VP/VLBW subjects to develop ADHD are similar to those found in other behavioral and psychiatric disorders. In a previous meta-analysis, Burnett et al<sup>68</sup> (2011) showed that a prevalence of any psychiatric diagnosis in preterm or LBW individuals was 3.66 times higher (95% CI 2.57 to 5.21) than NBW controls. Similarly, they found a high risk for anxiety or depressive disorder (OR = 2.86, 95% CI 1.73 to 4.73), although they did not provide data on ADHD or other psychiatric diagnoses. Another meta-analysis<sup>69</sup> found a significant association between autism diagnosis and LBW but not preterm birth. The reasons for increased vulnerability to ADHD and behavioral and psychiatric problems in preterm or LBW individuals remain unknown, but a number of hypotheses have been put forward. These include pre- and postnatal adversities, such as the environmental problems they must face, as well as parental and biological issues such as hypothalamic-pituitary-adrenal axis dysregulations and perinatal systemic inflammation, which could cause structural and functional brain disorders such as ADHD and other psychiatric and developmental disorders.<sup>17,68,70–72</sup>

Certain limitations should be considered when interpreting our findings. First, potentially important articles were excluded during the eligibility phase for not using validated diagnostic instruments or the rating scales selected in our protocol. Second, many studies were excluded because of different data definitions (ie, different categorizations for prematurity or birth weight levels). Third, although excluding gray literature from our review may have led to the overrepresentation of studies with statistically significant findings,<sup>73</sup> the OPEN consortium<sup>74</sup> demonstrated



in a recent systematic review that the exclusion of such studies has a negligible impact on effect sizes. Fourth, the heterogeneous reporting of clinical or neurologic correlates in VP/VLBW individuals precluded us from comparing those that did and did not develop ADHD for these variables. Fifth, substantially high heterogeneity was found for all 3 ADHD dimensions, indicating that there is clinical or methodological diversity among studies.<sup>23</sup> It is important to note that potential explanatory variables (age, article quality, country, occurrence of multiple births, and information source) entered in meta-regression analyses could not explain such variability. Sixth, our analyses included studies spanning a 30-year period (1977–2007). Although the lack of publication date limits increased the number of subjects in the analysis, the VP/VLBW subjects might not have the same perinatal profile over time given the advances in care management.<sup>75</sup> Such a limitation was also reported in Bhutta et al's<sup>14</sup> 2002 meta-analysis. Moreover, we also assumed that the different classification systems and versions (DSM-III, DSM-III-R, DSM-IV, DSM-5, ICD-9 or ICD-10) had similar ADHD diagnostic performance. Seventh, the ADHD risk found in our meta-analysis adequately represents the risk in high-income countries, but it cannot be generalized to middle- or

low-income countries. Among the 34 included studies, only the 2004 Pelotas cohort<sup>36</sup> came from a middle-income country. In middle- and low-income countries, the risk mechanisms could vary because of different determinant profiles.<sup>36</sup> As for the strengths of our review, we performed a broad literature search of cohort, case-control, and cross-sectional studies with no language restriction, allowing us to find a substantial number of articles. Most importantly, our strict inclusion criteria allowed only studies with a well-defined ADHD categorical diagnosis in the meta-analyses, unlike previous systematic reviews and meta-analyses.<sup>14,15</sup>

## CONCLUSIONS

In conclusion, with our findings we provide robust evidence that VP/VLBW individuals have an increased risk of ADHD both in categorical and dimensional analyses, and there is an even stronger association in the EP/ELBW group. In terms of clinical applicability, we suggest that premature infants need specific neonatology, pediatric, and psychiatric prevention and management interventions to minimize the ADHD burden. Future researchers in this field should clarify specific causal determinants associated with prematurity and LBW that could lead to the development of ADHD.

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## ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder  
CBCL: Child Behavior Checklist  
CI: confidence interval  
DAWBA: Development and Well-being Assessment  
DSM: *Diagnostic and Statistical Manual of Mental Disorders*  
ELBW: extremely low birth weight  
EP: extremely preterm  
EPICure: Extremely Premature Infants Cure  
H/I: hyperactivity or impulsivity  
ICD: *International Classification of Diseases*  
LBW: low birth weight  
NBW: normal birth weight  
NOS: Newcastle-Ottawa scale  
OR: odds ratio  
SDQ: Strengths and Difficulties Questionnaire  
SMD: standardized mean difference  
TRF: Teacher Report Form  
VLBW: very low birth weight  
VP: very preterm

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Dr Franz conceptualized and designed the study, helped in data collection, and drafted the initial manuscript; Drs G. Bolat, H. Bolat, Silveira, Procyanoy, Matijasevich, and Santos helped in data collection and critically reviewed the manuscript; Dr Rohde conceptualized and designed the study, helped in data collection, and critically reviewed the manuscript; Dr Moreira-Maia conceptualized and designed the study, helped in data collection, conducted the analyses, and reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered with PROSPERO (identifier CRD42016049421) ([http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42016049421](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016049421)).

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