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A Systematic Review and Meta-analysis of Prenatal, Birth, and Postnatal Factors Associated with Attention-Deficit/Hyperactivity Disorder in Children

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Abstract

Previous studies have shown mixed results on the relationship between prenatal, birth, and postnatal ("pregnancy-related") risk factors and attention-deficit/hyperactivity disorder (ADHD). We conducted meta-analyses to identify potentially modifiable pregnancy-related factors associated with ADHD. A comprehensive search of PubMed, Web of Science, and EMBASE in 2014, followed by an updated search in January 2021, identified 69 articles published in English on pregnancy-related risk factors and ADHD for inclusion. Risk factors were included in the meta-analysis if at least three effect sizes with clear pregnancy-related risk factor exposure were identified. Pooled effect sizes were calculated for ADHD overall, ADHD diagnosis, inattention, and hyperactivity/impulsivity. Odds ratios (OR) were calculated for dichotomous measures and correlation coefficients (CC) for continuous measures. Prenatal factors (pre-pregnancy weight, preeclampsia, pregnancy complications, elevated testosterone exposure), and postnatal factors (Apgar score, neonatal illness, no breastfeeding) were positively associated with ADHD overall; the findings for ADHD diagnosis were similar with the exception that there were too few effect sizes available to examine pre-pregnancy weight and lack of breastfeeding. Prenatal testosterone was significantly associated with inattention and hyperactivity/impulsivity. Effect sizes were generally small (range 1.1–1.6 ORs, −0.16–0.11 CCs). Risk factors occurring at the time of birth

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Declarations

Conflict of Interest All authors report no potential conflicts of interest.

Research Involving Human Participants and/or Animals This study includes analyses of data previously published in the literature.

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(perinatal asphyxia, labor complications, mode of delivery) were not significantly associated with ADHD. A better understanding of factors that are consistently associated with ADHD may inform future prevention strategies. The findings reported here suggest that prenatal and postnatal factors may serve as potential targets for preventing or mitigating the symptoms of ADHD.

Attention-deficit/hyperactivity disorder (ADHD) in childhood is characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity that significantly interfere with learning and social relationships. As outlined in the 5th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5; American Psychiatric Association, 2013), symptoms must present by the age of 12 years, interfere with functioning in two or more settings, and not be better explained by another mental disorder such as anxiety disorder or schizophrenia. Although the specific diagnostic criteria have evolved over time (e.g., DSM-IV criteria required that symptoms present before the age of seven years rather than 12 years), the core features of inattention, hyperactivity and impulsivity have been retained. ADHD has been diagnosed in 9.4% of children aged 2–17 years in the United States (Danielson et al., 2018) and has significant public health relevance based on its impact throughout the lifespan on overall health, social relationships, education, and employment (Erskine et al., 2016; Schoenfelder & Kollins, 2016). Efforts to reduce the impact of ADHD could thus benefit individuals, families, schools, communities, and society.

Although ADHD is known to have a significant genetic contribution, many environmental and experiential risk factors have been shown to be associated with increased risk for ADHD (Milberger et al., 1997; Froehlich et al., 2011; Faraone et al., 2021). Findings on the association of specific risk factors with ADHD are often mixed, possibly due to different methodologies across studies. For example, many studies rely on cross-sectional designs, leaving questions about whether the ADHD symptoms or the risk factor exposure occurred first. Another source of heterogeneity across studies is that published manuscripts frequently rely on different measures of ADHD (e.g., symptom counts versus diagnostic cutoffs) or how the risk factor of interest was measured (e.g., parent report versus medical records). A more comprehensive understanding of potentially modifiable risk factors for ADHD may lead to prevention efforts that target reductions in the impact of inattention, hyperactivity, and impulsivity at both the individual and public health levels.

Maternal health before and during pregnancy plays a critical role in the development of healthy newborns and can have lasting effects on children’s physical and mental development (Dean & Davis, 2007; Marques et al., 2015; Sullivan et al., 2014). Pregnancy-related factors including prenatal, birth, and postnatal factors have been reported in individual studies to be linked to numerous negative outcomes, including neurodevelopmental disorders and behavioral problems (Dean & Davis, 2007; Sullivan et al., 2014). Numerous mechanisms, including hypoxia (Smith et al., 2016), inflammation (Instanes et al., 2017), nutrition (Sullivan et al., 2014), and exposure to atypical hormone levels (e.g., elevated testosterone, Martel et al., 2008; Roberts & Martel, 2013; Silva et al., 2014), have been proposed as the pregnancy-related factors linked with brain development which could be related to the expression of ADHD symptoms. In addition, because pregnancy-related factors may be associated with maternal mental and overall health, the

relationship between these factors and the onset of ADHD symptoms in childhood may also be influenced by shared genetics.

Research on the relationship between pregnancy-related factors and ADHD has taken place for over 40 years, with mixed findings on the association between specific risk factors and symptoms of ADHD. Pregnancy-related risk factors affecting child development with potential to increase risk for ADHD in children include prenatal factors (e.g., pregnancy complications), events occurring at birth (e.g., labor complications) and postnatal factors (e.g., no breastfeeding). Although a large literature exists on preterm birth and low birth weight as risk factors for neurodevelopmental disorders, including ADHD (see Sciberras et al., 2017), risk factors with potential for more targeted prevention strategies were prioritized for these analyses. Furthermore, specific risk factors for preterm birth (Goldenberg et al., 2008), including maternal weight, pre-eclampsia, maternal stress (Robinson et al., this issue), and prenatal drug exposure (Maher et al., under review in this issue), were included in the current series (this article and others in the same special issue) of meta-analyses. A better understanding of risk factors that are consistently associated with ADHD may inform future prevention strategies. In this study, we use meta-analysis to summarize the findings across studies of pregnancy-related factors and indicators of ADHD, including ADHD diagnosis, inattention, and hyperactivity/impulsivity.

Methods

Document Search, Retrieval, and Coding

This manuscript serves as the first in a six-part series that presents findings from meta-analyses conducted on the association between six risk factor categories and ADHD. This manuscript reports on pregnancy-related risk factors, and subsequent manuscripts in the series report on the following risk factor categories: chemical (Dimitrov et al., under review in this issue), parent mental health (Robinson et al., this issue), parent substance use disorders (Maher et al., under review in this issue), parenting (Claussen et al., this issue), and child health factors (So et al., under review in this issue). All manuscripts in the series are based on identical core methods; only this manuscript will describe the series' methodologic components in detail. Explanations of additional methods that are specific to this manuscript are labeled here as pregnancy-related.

In January–February, 2014, we searched PubMed, Web of Science (WOS), and EMBASE for studies reporting on associations between potentially modifiable risk factors and ADHD diagnosis or symptoms. This review was not registered and a review protocol was not prepared. We employed two types of search strategies, a targeted risk factor search and a general ADHD risk study approach. The targeted risk factor search was designed to identify studies of ADHD and specific potential risk factors known to the authors from the literature or linked with ADHD in popular media. Search strings included variants of ADHD terms (e.g., attention deficit, ADHD, hyperactivity) combined with specific suspected risk factor terms (e.g., preterm birth, pesticide, trauma). To capture risk factors potentially missed by the targeted approach, we also employed a more general search to identify any additional relevant studies of risk for ADHD. Search strings included the same variants of ADHD terms used in the targeted searches (e.g., attention deficit, ADHD, hyperactive) combined

with methods and analytic terms that identify studies of risk (e.g., exposure, odds). All searches were restricted to terms that appeared in the titles or abstracts, to human research participants, and publications in English. No restriction was placed on publication date. The full set of search strings for the second strategy is provided in a Supplementary table. Relevant publications discovered through iterative reference mining of retrieved articles were subsequently added to the collection of eligible studies. Specific search terms for *pregnancy-related* risk factors used in the initial search included *weight, obesity, BMI, body mass index, blood pressure, labetalol, toxemia, eclampsia, preeclampsia, long duration of labor, fetal distress, Apgar, Pitocin, Syntocinon, oxytocin, birth* (AND (*date* OR *month* OR *season*)), *indue*, labor, low birth weight, low birthweight, LBW, premature, preterm, intrauterine growth, birth* AND *complicate, hemorrhage.* Articles on breastfeeding and prenatal exposure to testosterone were identified from the results of the general search strategy and from iterative reference mining.

No automation tools were used to identify articles for inclusion or exclusion. Publications identified in the searches were reviewed for inclusion or exclusion in three stages (see Fig. 1 for pregnancy-related study triage). Studies were excluded at the first stage if the title or abstract clearly identified the article as out of scope, such as studies of memory loss related to aging, evaluations of interventions or treatments, and studies of ADHD as a risk factor for later outcomes. All articles included after title and abstract review, including articles about which coders were unsure, were retrieved for full-text review. Additional reasons for exclusion during full-text review included investigations of risk factors outside the scope of this meta-analysis (e.g., genetic studies) and non-empirical publications (i.e., theoretical or review articles). Data from all publications included after the second stage were extracted for potential analysis. Studies were excluded if they used the same population to examine the same risk factor; in these cases, the earlier publication was included in the analysis unless a later publication reported on a larger sample of the same population. Publications were also excluded during or after data extraction as necessary, for example, if sufficient data with which to compute a standardized effect size were not reported.

Because the risk factors of interest in this meta-analysis were ethically inappropriate for experimental manipulation, all eligible studies were non-experimental and thus studies of association rather than causation. To rule out the potential that ADHD caused or influenced the purported risk factor, we included only longitudinal or retrospective studies in which the measurement time period for the risk factor clearly preceded the measurement time period for ADHD. Among *pregnancy-related* risk factors, the notable exception was prenatal testosterone, which was measured by finger-length ratio in childhood. Studies using this methodology were included because it is widely accepted that finger-length ratio is a strong indicator of prenatal testosterone exposure levels (Lutchmaya et al., 2004).

Coders were trained and tested to criterion before data extraction began. During the first phase, the double-coding rate for articles was set to be at least 25%. After coders demonstrated consistent success using the coding forms, the minimum double-coding rate was reduced to 15%. Inter-rater agreement was continuously monitored via inter-rater reliability metrics and Cohen’s kappa, and coders were retrained if the coefficient was less than 0.70. A series of hierarchical coding forms (available from the authors) were used

to capture all relevant data from each publication. A study-level form included questions concerning basic publication identification information, inclusion criteria verification, key study methods and setting information, and study population characteristics. An outcome-level form captured characteristics of the ADHD outcome, including how it was measured, the case definition (if applicable), and at what age the measurement occurred. Multiple outcome-level forms were used when more than one ADHD measure was included in a study. Effect-size-level forms captured characteristics of the risk factor exposure and the statistical relationship reported between the risk factor and ADHD outcome. Effect size information was extracted whenever possible, regardless of whether the risk factor was the main variable of interest in a study or was simply included as a covariate or statistical control.

Meta-Analysis Methods

All meta-analyses were conducted using R versions 3.1.3 through 4.0.3 (R Core Team, 2015–2020) using the rmeta package (Lumley, 2018). We calculated standardized summary statistics and variances for each relevant result within each included study using conventional meta-analytic techniques. For continuous outcomes, results including group means, sample sizes, and standard deviations were transformed into a t-statistic, such that:

$$t = \frac{x_e - x_u}{\sqrt{\frac{s_e^2}{n_e} + \frac{s_u^2}{n_u}}}$$

where x represents the exposed or unexposed group mean, s^2 represents a group standard deviation and n a group sample size. Results reported as a non-standardized regression coefficient (β) allowed for a t-statistic calculated as:

$$t = \beta / se(\beta)$$

where se represents the standard error. Results were also included if a standardized regression coefficient (β) or correlation coefficient was reported. All t-statistics were converted to a correlation coefficient (r) for meta-analysis as follows:

$$r = \sqrt{t^2 / \left(t^2 + df\right)}$$

For dichotomous outcomes, odds ratios were calculated. When effect sizes with standard errors, confidence intervals, or sample sizes were available, but not raw count data, the study was included and represented by its effect size and standard error.

When multiple effect sizes for the same risk factor and type of ADHD outcome were reported in a study (e.g., if data from two different measures of hyperactivity were reported, or if results were reported separately for boys and girls), the average of the relevant effect sizes was used, reflecting the relationship between a risk factor and type of ADHD outcome. When multiple effect sizes were reported for different time points (i.e., risk factor or ADHD outcome measured at different ages), only one time point was selected for analysis; in these

cases, the ADHD outcomes closer in time to the risk factor measurement (but at least 6 months apart, to maintain the integrity of the longitudinal measurement inclusion criteria) were selected, to maximize the analyses' ability to detect an effect if present. When selecting among multiple time points for risk factor measurements, we similarly selected the later age measurement (but at least 6 months prior to the ADHD measurement). The exception to that rule was when multiple prenatal time periods were reported for a risk factor, in which case we selected the earliest measurement, because earlier exposures are generally associated with the greatest impact on neurodevelopment (Rice & Barone, 2000). When a single article reported analyses from different samples (e.g., three distinct longitudinal studies), effect sizes were treated as separate studies for these meta-analyses.

For continuous or dichotomous outcomes, pooled effect sizes and 95% confidence intervals were calculated via a complete pooling approach. Each effect size was weighted by its conditional variance (Hedges & Olkin, 1985) to give more weight to studies with larger sample sizes. The variance across effect sizes was assessed by calculating a heterogeneity statistic, Q, which describes the variation across study estimates (DerSimonian & Laird, 1986). We fit separate random-effects models for each set of ADHD risk factors. Random-effects models include a weighting term (tau) to account for the between-study variation in effect size (Sutton et al., 2000), thus the random-effects model is considered to produce a more conservative estimate of effect size (i.e., pulled toward the null) than a fixed-effect model (Berlin et al., 1989).

Results are presented for each analysis for which there were at least three measures of association (hereafter referred to as effect sizes) between a particular risk factor and ADHD. Our meta-analyses were conducted separately for statistics with outcomes that were measured dichotomously (e.g., ADHD diagnosis) versus outcomes that were measured continuously (e.g., ADHD symptoms). Some risk factors only had a sufficient number (i.e.., at least three) of independent effect sizes to produce an overall effect size for either dichotomous or continuous statistics. Whenever possible (i.e., when at least three relevant effect sizes were available), additional analyses of subsets of studies within a risk factor category were conducted. For a pregnancy-related example, 12 studies reporting dichotomous statistics were included for pregnancy complications, 10 of which relied on ADHD diagnosis as the outcome measure. We were thus able to compute effect sizes between pregnancy complications and 1) any ADHD measure (referred to as "overall") and 2) specific to ADHD diagnosis (referred to as "diagnosis only"). Similarly, for the general risk factor category "mode of delivery," we had 24 articles, six of which were specific to breech delivery. Thus, we were able to compute test statistics for the more general mode of delivery and the more specific breech delivery risk factor. Among the pregnancy-related factors, only prenatal testosterone exposure had at least three effect sizes for separate analyses of the inattentive and hyperactive-impulsive symptoms that characterize ADHD.

In January, 2021, we conducted a literature search using the same search criteria as the original review, to identify papers published from 2014 through early 2021. We restricted our inclusion criteria to categories of risk factors where we had already generated effect sizes, based on the methodology described above.

Results

A total of 59 articles related to prenatal, birth, and postnatal risk factors were identified through the original directed searches and iterative reference mining. Most of the articles were identified through the initial directed searches for each risk factor except for testosterone, for which six of 10 articles reviewed were identified through iterative reference mining. After excluding 16 articles based on title and abstract review and three additional articles based on full-text review, a total of 40 articles published between 1979 and 2014 were included. An additional 29 articles were included based on the second literature search conducted in 2021, for a total of 69 articles included (Fig. 1). Three articles included two separate study samples; therefore, data are presented on 72 samples. Table 1 includes information about each article including sample size, basic demographics of the study sample (i.e., age, sex, country), and how ADHD and perinatal risk factors were measured. Many articles included findings for multiple categories of risk factors (e.g., pregnancy complications and neonatal illness; see Table 1).

The perinatal risk factors included in this study, and the number of eligible articles for each were: pre-pregnancy weight (8), preeclampsia (14), pregnancy complications (12), prenatal testosterone exposure (measured by finger length ratio); 8), perinatal asphyxia (8), labor complications (10), mode of delivery (24), low Apgar score (14), neonatal illness (14), and no breastfeeding (9). For presentation of results, risk factors were categorized as prenatal measures (pre-pregnancy weight, preeclampsia, pregnancy complications, prenatal testosterone exposure), events occurring at birth (perinatal asphyxia, labor complications, mode of delivery), and postnatal measures (Apgar score, neonatal illness, no breastfeeding). Although exposure definitions varied by study, the most common definitions by risk factor are included in Table 2. All studies of testosterone and ADHD were based on measurement of finger length ratio. A lower 2nd digit (2D):4th digit (4D) ratio (2D:4D) has been shown to be associated with elevated prenatal testosterone exposure in both boys and girls (Lutchmaya et al., 2004); thus, negative effect sizes reported for testosterone represent a positive association between testosterone exposure and ADHD.

Effect sizes resulting from random-effects meta-analysis for each pregnancy-related risk factor are summarized in Table 2. Forest plots with effect sizes and confidence intervals for individual studies, alongside the summary effect size for each risk factor are presented as supplementary material (see supplemental Figs. 1-25). Heterogeneity statistics (not shown) were non-significant for all analyses, suggesting there was not significant heterogeneity across the studies. Risk factors that were significantly associated with increases in measures of ADHD overall (e.g. all included measures of ADHD) included pre-pregnancy weight, preeclampsia, pregnancy complications, prenatal testosterone exposure, Apgar score, neonatal illness, and lack of breastfeeding. Preeclampsia, pregnancy complications, testosterone, Apgar score, and neonatal illness were also associated with ADHD diagnosis. Testosterone was the only risk factor with at least three effect sizes for measures of inattentive or hyperactive/impulsive symptoms (not presented in Table 2). Higher levels of prenatal testosterone (i.e., lower finger length ratio indicating higher levels of testosterone) was associated with higher levels of inattentive symptoms (six studies; total sample size 1,062; correlation coefficient: −0.16; CI: −0.22, −0.09; $p<0.05$), as well as hyperactive/

impulsive symptoms (seven studies; total sample size 1,139; correlation coefficient: −0.14; CI: −0.20, −0.08; $p<0.05$). Pre-pregnancy weight, perinatal asphyxia, labor complications, and mode of delivery (including the overall category, as well as breech delivery, Cesarean section, and vacuum delivery), were not significantly associated with ADHD.

Discussion

All prenatal and postnatal risk factors examined had significant positive associations with ADHD. Although risk factors occurring at birth (e.g., mode of delivery) consistently had a positive relationship with ADHD, these factors were not significantly associated with ADHD outcome measures. Notably, the risk factors identified as significantly associated with ADHD tended to represent those with more chronic exposure, rather than acute events such as mode of delivery, or labor complications. This finding aligns with a previous hypothesis that the pregnancy-related factors more frequently associated with ADHD tend to be more chronic in nature, possibly suggesting an increased “dose” of exposure (Milberger et al., 1997). Although neonatal illness is not necessarily chronic, and Apgar score measures infant health immediately at birth, these risk factors may represent poor overall health outcomes and poor neurologic outcomes (Leinonen et al., 2018; Ehrenstein et al., 2009).

The mechanism by which each pregnancy-related factor is associated with ADHD has not been comprehensively investigated and likely varies. In many cases, individual factors might influence neurodevelopment through multiple mechanisms of action. Hypoxia or ischemia can result from preeclampsia or other pregnancy complications (e.g., placental abruption), perinatal asphyxia at birth, and neonatal illness (including respiratory distress syndrome), and might increase the risk for ADHD through impact on the development of the basal ganglia specifically (Ananth et al., 1999; Bos-Veneman et al., 2010; Getahun et al., 2013; Ilekis et al., 2007). Hypoxia may also act more broadly on the brain, as perinatal oxygen deprivation has been shown to be associated with reductions in gray matter volume, intraventricular volume, and periventricular leukomalacia (Getahun et al., 2013). Inflammatory cytokines associated with preeclampsia may influence neural development through inflammatory mechanisms (Silva et al., 2014; Sullivan et al., 2012). The impact of preeclampsia may vary by the timing of onset during pregnancy, and severity of symptoms (Ilekis et al., 2007), factors that were not addressed in the studies included in this meta-analysis.

A recent meta-analysis looking at the association of maternal weight with neurodevelopmental outcomes including ADHD also found an increased risk for ADHD among children whose mothers were overweight or obese prior to pregnancy (Sanchez et al., 2018). Maternal weight may influence child outcomes through multiple pathways. Genetic and environmental risk factors are shared between ADHD and obesity (Faraone et al., 2021). Maternal obesity may influence neurodevelopment through exposure to increased levels of nutrients, hormones, and inflammatory factors (Rivera et al., 2015). In addition, a higher pre-pregnancy BMI is associated with other pregnancy-related risk factors associated with ADHD, including gestational hypertension and preeclampsia, maternal mental health, preterm birth, and neonatal illness, as well as congenital anomalies, possibly through increased risk of gestational diabetes (Mina et al., 2015; Ramachenderan et al., 2008).

The category of pregnancy complications included a wide range of exposures, including excessive vomiting (Bhatia et al., 1991), maternal illness (Pineda et al., 2007), antepartum hemorrhage (Chandola et al., 1992), placental abruption (Motlagh et al., 2010; Getahun et al., 2013), and total number of complications (Kadziela-Olech & Piotrowska-Jastrzebska, 2005). Maternal illness may impact maternal nutrition, and inflammation, both of which can impact early neurodevelopment (Marques et al., 2015). Antepartum hemorrhage and placental abruption may result in oxygen deprivation (Getahun et al., 2013; Walfish et al., 2009) and both are associated with maternal drug use and preterm birth (Ananth et al., 1999; Walfish et al., 2009) which may also be risk factors for ADHD (Vanderbilt & Gleason, 2010; Maher et al., under review in this issue).

Prenatal exposure to increased levels of testosterone may be due to aspects of maternal health, including production by maternal ovaries, elevated levels of insulin (possibly related to obesity or polycystic ovarian syndrome; Lathi et al., 2014), maternal use of anabolic steroids, or exposure to environmental substances with estrogenic or androgenic activity, or in cases of congenital adrenal hyperplasia (Padmanabhan et al., 2006). Elevated prenatal testosterone levels, often indicated by a lower second-digit-to-fourth-digit finger length ratio (2D:4D), have been proposed as a theory for the boys' elevated risk of ADHD and other neurodevelopmental disorders (de Bruin et al., 2006; Martel et al., 2008). Typically, males have a lower 2D:4D ratio compared to females, and it has been proposed that boys may be more susceptible to elevated levels of testosterone because the central dopamine system has a longer period of development in boys, allowing for increased exposure to elevated hormone levels (Martel et al., 2008; Roberts & Martel, 2013). The analyses presented here included combined estimates across sexes. Future studies could consider the relationship of testosterone on ADHD symptomatology in boys and girls separately.

Although Apgar score is an indicator of the infant's health status rather than a directly modifiable risk factor, it was included in these analyses because of its widespread use in practice and research. In one analysis of perinatal risk factors for ADHD, a low Apgar score was found to be the most predictive of ADHD, followed by post-term birth (Hanc et al., 2018). Because Apgar score is associated with many pregnancy-related complications (Ehrenstein et al., 2009), it is unlikely to represent a unique risk factor. Interventions and approaches aimed at increasing Apgar scores or other overall indicators of newborn health could be evaluated for potential longer-term impacts on ADHD.

Similar to the categories of pregnancy complications and Apgar score, the "neonatal illness" risk factor category is not specific to a single event or exposure. The neonatal illness category included neonatal or postnatal complications (Ben Amor et al., 2005; Bos-Veneman et al., 2010; Wagner et al., 2009), neonatal intensive care (Froehlich et al., 2009; Hoffman et al., 2010; Sciberras et al., 2011), neonatal resuscitation (Getahun et al., 2013), incubator use (Kim et al., 2009), severe neonatal illness indicated by any hospitalization during the first month of life (Pineda et al., 2007), and whether "the child had any congenital or neurologic problem or any kind of anomaly at birth" (Pires et al., 2013). Both the groups of complications and some of the specific complications included circumstances in which oxygen was limited, or other early stressful events (Ben Amor et al., 2005) that might

increase risk for ADHD. Additionally, infants with neonatal illness may have other risk factors for ADHD, such as preterm birth and low birthweight (Wagner et al., 2009).

Findings similar to those reported here, of an increased risk for ADHD among children who were not breastfed, were documented in a meta-analysis focused exclusively on breastfeeding that included only one overlapping article with the analyses presented here (Tseng et al., 2019). The association of a lack of breastfeeding with ADHD might be related to multiple mechanisms including nutritional factors, hormone exposure, immunity transfer, as well as social factors (Silva et al., 2014; Tseng et al., 2019). In addition, breastfeeding is related to improved maternal-child attachment which is associated with improved attention (Hayatbakhsh et al., 2012), and with reductions in child maltreatment (Hayatbakhsh et al., 2012) and maternal depression (Dias & Figueiredo, 2015) which are both risk factors for ADHD (Claussen et al., this issue; Robinson et al., this issue). Admission to the NICU is also associated with decreased breastfeeding (Maia et al., 2011) and increased risk for ADHD (Chiorean et al., 2020). The sensory experience associated with breastfeeding has also been proposed as a mechanism for improving cognitive development (Mimouni-Bloch et al., 2013). The studies included in the meta-analysis reported here reported on breastfeeding and did not include a group of children provided breastmilk in the absence of breastfeeding; thus, the mechanism contributing to these findings cannot be determined.

Only factors occurring at the time of birth were not associated with increased risk for ADHD including labor complications, mode of delivery, and perinatal asphyxia. Although asphyxia has been shown to have a wide-range of effects on neurodevelopment, including cognitive impairments, no significant association was found for perinatal asphyxia and ADHD. There may be multiple causes of asphyxia but the timing, severity, and causes of asphyxia were not analyzed as specific factors in this study. Although asphyxia can be severe, it can also be short in duration, and may be associated with more select damage to the brain that might be more easily repaired (Korkman et al., 1994). One author suggested that asphyxia may be associated with either severe damage, where the children might be excluded from the study because of very low Intelligence Quotient (IQ), or minimal or no neural damage, which would be more likely in children included in the research protocols (Korkman et al., 1994). In fact, of the five studies of perinatal asphyxia included in the meta-analysis, two excluded children based on their IQ (Motlagh et al., 2010; Pineda et al., 2007), and two excluded children with autism spectrum disorder or pervasive developmental disorder (Getahun et al., 2013; Pringsheim et al., 2009). Furthermore, more severe asphyxia, or prolonged complications associated with asphyxia, may have been captured in the categories of Apgar score, and neonatal illness, which was often characterized by receiving care in the neonatal intensive care unit (NICU). Of note, preeclampsia may cause chronic exposure to asphyxia-type conditions (Ilekis et al., 2007), and was associated with ADHD in these meta-analyses. Like asphyxia, labor complications and mode of delivery are relatively acute events that may restrict oxygen delivery to the baby, potentially impacting the brain. However, neither of these, including specific modes of delivery (e.g., breech), were associated with ADHD outcomes.

At least five limitations are associated with these meta-analyses. First, as with all studies based on published literature, these results cannot be assumed to generalize beyond the

populations in the included studies. Second, despite conducting the literature search with an intent to capture all relevant articles, the findings are not comprehensive of all potential risk factors. Some risk factors may have been missed by our search strategies, and some articles and risk factors were excluded due to insufficient data for the meta-analysis (e.g., fewer than three articles on maternal infection and ADHD were identified) or resource limitations for the overall project. Since the initial review in 2014, there may be new studies of additional risk factors, including maternal autoimmune disease, that may be associated with ADHD (Nielsen et al., 2021). Third, many of the categories of risk factors were broad, some contained a variety of more specific exposures (including some for which evidence on modifiability is still lacking), and there were a variety of measures of association types reported. In particular, the categories of pregnancy complications and neonatal illness each included a number of different exposures, which potentially occurred at different times during pregnancy and the neonatal period. Future research could examine the association of more specific risk factors (e.g., maternal diabetes, neonatal hypothermia) or timing of exposure with ADHD outcomes. Fourth, although there is a strong genetic component to ADHD, and evidence for gene-environment interaction, genetic factors were beyond the scope of these analyses. Incidentally, one study identified perinatal complications as nonshared environmental factors that increased risk of ADHD in individuals compared with their siblings (Ben Amor et al., 2005). Future studies can include other related and potentially confounding factors such as child age, sex, and other parental factors including family history of ADHD. Fifth, many of the pregnancy-related risk factors examined are associated both with each other, (Ehrenstein et al., 2009) and with other identified risk factors for ADHD, including maternal mental health (Blom et al., 2010; Robinson et al., this issue), and parental substance use (Maher et al., under review in this issue). Our analytic approach examined risk factors separately (vs. multi-level modeling) to ensure that findings across risk factors and papers could be meaningfully compared. Future research could include multi-level modeling to better understand the relationships between risk factors.

Despite these limitations, the findings reported here highlight the association between prenatal and postnatal risk factors and ADHD. Each of the pooled odds ratios for the prenatal and postnatal factors was between 1.3 and 1.5; the corresponding range for pooled correlation coefficients was −0.16–0.11. These findings represent small, but significant, effect sizes (Chen et al., 2010; Cohen, 1988), and agree with the finding of Faraone et al. (2021) that ADHD is most often caused by the combined effect of multiple risk factors, with each contributing a small risk. Although the prevalence of pregnancy-related risk factors associated with ADHD vary widely, the most common include pregnancy weight, with approximately 50% of mothers being overweight or obese prior to pregnancy (Jo et al., 2015), pregnancy complications, present in approximately half (46.9%) of pregnancies (Ananth et al., 2013), lack of breastfeeding among about 16% of infants (Centers for Disease Control and Prevention, 2020), and NICU admittance for 12% of newborns (U.S. Department of Health and Human Services, 2013). Less common pregnancy-related risk factors include preeclampsia, which occurs in approximately 3% of pregnancies (Ananth et al., 2013), and a low Apgar score (< 7), present in less than one percent of infants (Li et al., 2013). The prevalence for testosterone exposure is less certain. Studies examining the effect of testosterone on ADHD diagnosis and symptoms used the 2D:4D finger ratio as a proxy

for testosterone exposure. We are not aware of an established threshold for this ratio or an associated prenatal testosterone exposure level that could be used to provide a prevalence estimate. Given the prevalence of the pregnancy-associated factors found to be associated with ADHD, and the impact of ADHD, and the long-term association of perinatal risk factors with ADHD symptoms and associated outcomes (Tervo et al., 2017) these factors may serve as potential targets for preventing or mitigating the symptoms of ADHD, and to inform future research to better understand more specific factors (e.g. specific modifiable pregnancy complications).

In addition to the association of specific pre- and postnatal risk factors and ADHD, these risk factors may be more broadly associated with neurodevelopment and other related disorders. For example, pre-pregnancy maternal weight has been shown to be associated with autism spectrum disorder, developmental delay, emotional/behavioral problems, and cognitive delay (Sanchez et al., 2018). Pregnancy complications including preeclampsia have been shown to be associated with increased risk for autism spectrum disorder (ASD) and other developmental delays (Walker et al., 2015), and exposure to elevated prenatal levels of testosterone have also been shown to be associated with ASD, total behavioral difficulties, and conduct problems (de Bruin et al., 2006; Fink et al., 2007). Low Apgar scores have been shown to be associated with cerebral palsy, epilepsy, intellectual disability, and sensorineural deficits (Leinonen et al., 2018). Breastfeeding has been associated with reduced problem behaviors including social problems, aggressive behaviors (Hayatbakhsh et al., 2012), as well as motor development (Sacker et al., 2006). Thus, prevention activities to reduce these risk factors may have greater impact than only reducing ADHD. Furthermore, the pregnancy-related risk factors examined here are also associated with maternal health, supporting prenatal care, neonatal care, and breastfeeding.

Attention to prenatal and maternal health and neonatal care is fundamental to establishing the foundation for lifelong physical and mental health (Brundage & Shearer, 2019). Optimizing maternal and child health can be challenging due to somewhat independent systems serving women (e.g., obstetrics) and children (e.g., pediatrics). Improving both maternal and child health could be facilitated through an “integrated family care” approach (Brundage & Shearer, 2019). In addition to promoting maternal health and prenatal care, an integrated approach could allow for sharing of health information from the prenatal and early neonatal period with pediatricians. In this way, the identified prenatal and early postnatal risk factors could inform future screening and prevention efforts to improve outcomes related to ADHD and neurodevelopment more generally. Early identification of infants at risk for ADHD and other neurodevelopmental disorders may improve the time to referral for intervention services and could improve outcomes among children at risk for these disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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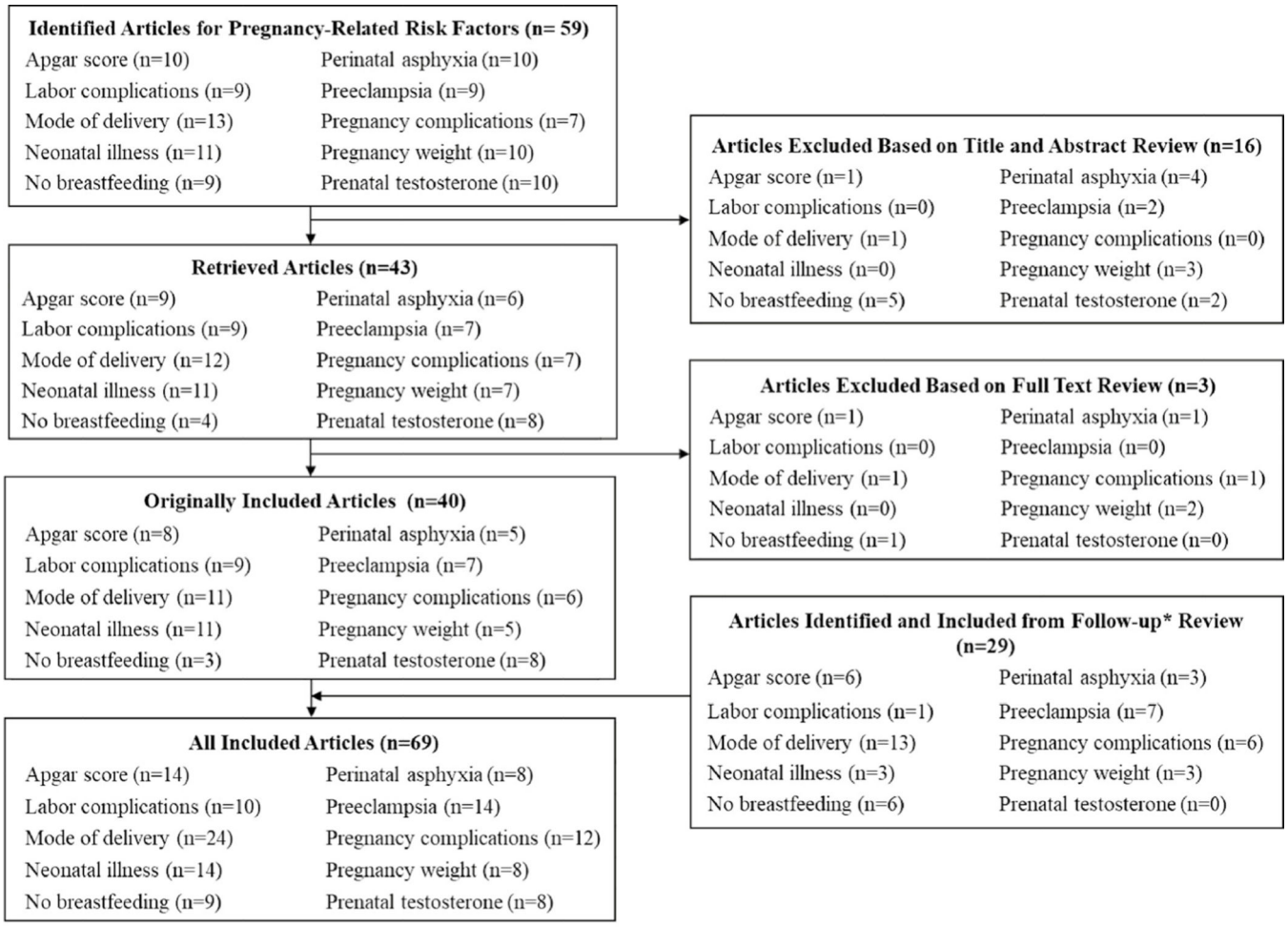

Fig-1.

Flowchart of triage process for articles identified for meta-analyses of prenatal, birth, and postnatal risk factors associated with attention-deficit/hyperactivity disorder

Note: Articles overlap across categories and therefore the n representing the sum of the individual risk factors is greater than the overall n for each box. Articles were identified through a comprehensive search of PubMed, Web of Science, and EMBASE and iterative reference mining in 2014, and an updated search of PubMed, Web of Science, and EMBASE in January 2021.

Table 1

Characteristics of studies included in meta-analyses of prenatal, birth, and postnatal risk factors for attention-deficit/hyperactivity disorder

Study	Risk Factors (Included)	Sample size	Age at Outcome Measurement (Years)	Male (%)	ADHD Measurement (Included)	Sample (country)	Measurement
Ben Amor et al. (2005)	Labor Complications; Neonatal Illness	100	8.8–10.1	34–90	Diagnosis (clinical, DSM-IV)	Clinical, outpatient research survey/interview including siblings without ADHD as control (Canada)	Retrospective parent report of perinatal factors
Bhatia et al. (1991)	Mode of Delivery; Pregnancy Complications	224	3–12	85.7	Diagnosis (clinical, DSM-III)	Clinical, outpatient research survey/interview of children screened in pediatric hospital (India)	Retrospective parent report of pregnancy-related factors
Böhm et al. (2019)	Preeclampsia	13,192	7	50.6	Parent report of physician-diagnosed ADHD; SDQ^{P}	Cohort Study (MCS) (United Kingdom)	Maternal report
Bos-Veneman et al. (2010)	Labor Complications; Neonatal Illness	65	12.2	88	ADHD symptoms (ADHD Rating Scale-TV)^{P}	Clinical, outpatient research survey/interview of children identified in psychiatric clinic (The NetherlandsNetherlandsNetherlands)	Retrospective parent report of perinatal factors
Brionet al. (2011)	Pregnancy Weight	4,873	3–4 (47 months)	n/a	ADHD symptoms (SDQ)^{P}	Birth cohort (ALSPAC; United Kingdom)	Self-report of pre-pregnancy weight at enrollment during pregnancy
	Pregnancy Weight	2,483	3	n/a	Inattention (CBCL attention problems)^{P}	Birth cohort (Generation R; The Netherlands)	Self-report of pre-pregnancy weight at enrollment postpartum
Chandola et al. (1992)	Apgar Score; Neonatal Illness; Pregnancy Complications	24,672–24,785	3–6	51–68.2	Hyperactivity (Referral to clinic for hyperactivity)	Birth cohort (CBS; Wales)	Pregnancy-related information recorded on birth records prior to maternity hospital discharge
Chen et al. (2019)	Perinatal Asphyxia	4,750	10.8	77.5	Clinical diagnosis (ICD-9)	Taiwan Longitudinal Health Insurance Database (Taiwan)	Health insurance database
Claycomb et al. (2004)	Labor Complications; Mode of Delivery	130	8.49–10.65	n/a	Diagnosis (ADHD prescription medication bottle)	Research survey with recruitment through advertisements (USA)	Retrospective parent report of perinatal factors
Clements et al. (2015)	Apgar Score, Mode of Delivery	7,874	2–19	71.2–73.5	Diagnosis (ICD-9, DSM-IV)	Matched case control study using electronic health records (USA)	Electronic health records
Curran et al. (2016)	Mode of Delivery	1,722,548	<3	51.4	Diagnosis (ICD-10) or medication treatment	Cohort study using linked data from National Patient Register and Multi-generation Register (Sweden)	Medical birth register
Dachew et al. (2019)	Preeclampsia	6,597	7	n/a	Diagnosis (DAWBA, DSM-IV)^{P}	ALSPAC (United Kingdom)	Medical record review
de Bruin et al. (2006)	Testosterone	153	9.08	100	Diagnosis (clinical, DSM-IV)	Clinical, outpatient research study of children identified in psychiatric clinic; controls recruited from a school (The Netherlands)	Right hand 2nd:4th digit ratio

Study	Risk Factors (Included)	Sample size	Age at Outcome Measurement (Years)	Male (%)	ADHD Measurement (Included)	Sample (country)	Measurement
D'Souza et al. (2019)	No Breastfeeding	6,246	2	n/a	Inattention/hyperactivity (SDQ)[P]	Longitudinal prospective birth cohort (Growing Up in New Zealand; New Zealand)	Prospective maternal report
Fianu and Joelsson (1979)	Mode of Delivery	1,921	n/a	n/a	ADHD symptoms (Impulsivity, Hyperkinetic syndrome. Retrospective report of behavior from birth to study date)[P]	Case reports of premature and breech delivery collected at birth (Sweden)	Retrospective parent report of behavior and achievement from birth to study date
Fink et al. (2007)	Testosterone	58	5–7	43.1	Hyperactivity (SDQ)[P]	School based research study (United Kingdom)	Right hand 2nd:4th digit ratio
	Testosterone	56	6–11	51.8	Inattention (CBCL attention problems)[P]	School based research study (Austria)	Right hand 2nd:4th digit ratio
Froehlich et al. (2009)	Neonatal Illness	2,528	8–15	63.5	Diagnosis (DISC-IV, or parent report of previous diagnosis, and treatment with ADHD medication in past year)[P]	National survey (NHANES; USA)	Retrospective parent report of care in NICU
Getahun et al. (2013)	Apgar Score; Labor Complications; Mode of Delivery; Neonatal Illness; Perinatal Asphyxia; Preeclampsia; Pregnancy Complications	81,678	8	50.5–74.3	Diagnosis (medical record of diagnosis and at least 2 ADHD prescriptions)	Nested case-control study (USA)	Medical records (Kaiser Permanente Southern California)
Guhn et al. (2020)	Apgar Score, Mode of Delivery	134,094	5.7	51	ADHD symptoms (EDI)[T]	Cohort study using linked records (Canada)	Linked population-based vital statistics (birth records), and child survey data
Gurevitz (2014)	Mode of Delivery	116	7.77–8.17	65.5–69	Diagnosis (clinical, DSM-IV)	Retrospective study (Israel)	Review of well-baby clinic records
Gustafsson and Källen (2011)	Apgar Score; Mode of Delivery; Preeclampsia	32,012	5–17	51–87	Diagnosis (clinical, DSM-m-R or DSM-IV)	Case-control study linking medical records (Sweden)	Medical birth registry
Gustavson et al. (2019)	Pregnancy Complications	99,947	7.4–17.3	51.2	ADHD diagnosis (ICD-10); ADHD rating scale (DSM-IV)	Norwegian Mother and Child Cohort Study (Norway)	Prospective maternal report
Han et al. (2015)	Labor Complications	19,940	Elementary school age (<9—>12)	49.4	ADHD symptoms (Korean version of the DuPaul Rating Scale, K-ARS)[P]	School-based survey of parents (South Korea)	Parent report
Hanć et al. (2018)	Apgar Score	278	6–18	100	Diagnosis (ICD-10, DSM-IV; Conners' Parent Rating Scale, Diagnostic Structured Interview for	Poland	Medical registry

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Study	Risk Factors (Included)	Sample size	Age at Outcome Measurement (Years)	Male (%)	ADHD Measurement (Included)	Sample (country)	Measurement
					ADHD and Hyperkinetic Disorder)		
Hoffman et al. (2010)	Neonatal Illness	578	12–15	47.7–80.4	Diagnosis (parent report of previous diagnosis)[P]	National survey (NHANES; USA)	Retrospective parent report of care in NICU
Ji et al. (2018)	Mode of Delivery, Pregnancy Complications	1,479	7–12	48.1	Diagnosis (ICD-9, ICD-10 codes in medical records)	Prospective birth cohort study using medical records (BBC; USA)	Medical records
Jin et al. (2014)	Mode of Delivery, Perinatal Asphyxia	5,648	5–15	39.2	Clinical ADHD diagnosis (DSM-IV)	School-based sample, Zhabei District, Shanghai (China)	Retrospective parent report
Jo et al. (2015)	Pregnancy Weight	1,311	6	49.9	Diagnosis (Parent report) and ADHD symptoms (SDQ)[P]	Nationally distributed longitudinal study (IFPS II, USA)	Maternal report
Joelsson et al. (2016)	Apgar Score	48,943	6–20	n/a	ADHD diagnosis (ICD-9, ICD-10)	Nationwide register study based on a nested case-control design (Finland)	Linkages of three national registers: FHDR FMBR, Finnish Central Population Register
Julvez et al. (2007)	No Breastfeeding	199	4	50.2	ADHD symptoms (ADHD-DSM-IV questionnaire)[T]	Birth cohort (Spain)	Maternal report of breastfeeding obtained by questionnaire at 1 and 4 years, or at 6 months, 14 months, and 2 years (child age)
Kadziela-Olech and Piotrowska-Jastrzebska (2005)	Apgar Score; Labor Complications; Pregnancy Complications	100	7.3–7.8	85	Diagnosis (Behavioral Scale of ICD-10 criteria)[P, T]	School-based Research study (Poland)	Retrospective parent report of pregnancy-related factors
Küllén et al. (2011)	Apgar Score; Pregnancy Weight; Mode of Delivery; Preeclampsia	78,250–681,292	n/a	n/a	Diagnosis (prescription of methylphenidate or atomoxetine recorded in drug register)	Data linkage with medical records (Sweden)	Medical birth registry
Kimetal. (2009)	No Breastfeeding; Mode of Delivery; Neonatal Illness	2,419	n/a	48.6	Diagnosis (DISC-IV)[P]	School-based research study (Seoul Child and Adolescent Mental Health Survey; Korea)	Retrospective parent report of pregnancy-related factors
Kosidou et al. (2017)	Apgar Score; Preeclampsia; Pregnancy Weight	558,910	3–17	68.8	ADHD diagnosis or treatment (ICD-10)	Matched case-control study using health and population data registers for all children bom in Sweden from 1984 to 2008 (Sweden)	Medical Birth Register (MBR)
Li et al. (2011)	Apgar Score	7,246,218	≥3	82	Diagnosis (ICD-10 diagnosis of hyperkinetic disorder recorded in one of two national registers)	Population-based cohort study (Sweden)	Medical birth registry
Lin et al. (2017)	Perinatal Asphyxia, Mode of Delivery	21,243	1.3–5.7	54.6	Hyperactivity (CPRS-48)[P]	School-based cohort Study (LCCS; China)	Questionnaire

Study	Risk Factors (Included)	Sample size	Age at Outcome Measurement (Years)	Male (%)	ADHD Measurement (Included)	Sample (country)	Measurement
Linnet et al. (2006)	Apgar Score	1,355	3.5	n/a	Hyperactivity (PBQ)^{P}	Birth cohort (Denmark)	Midwife report at delivery
Liu et al. (2012)	Testosterone	219	11	54.8	Inattention (CBCL; TRF)$^{P, T}$	School-based research study (China)	Right hand 2nd:4th digit ratio
Maher et al. (2020)	Preeclampsia	10,692	3	51.4	ADHD symptoms (SDQ)^{P}	Nationally representative longitudinal study of children (GUI; Ireland)	Questionnaire, interview (maternal-report)
Mann and McDermott (2011)	Preeclampsia	84,721	6.49	46.7–71.9	Diagnosis (ICD-9, Medicaid billing data)	Data linkage with medical records (USA)	Medicaid billing data
Martel et al. (2008)	Testosterone	250	14.67	56.2–63.7	Diagnosis (clinical, K-SADS-E) and symptoms (K-SADS-E; ADHD Rating Scale)$^{P, T}$	Clinical research study (USA)	Right hand 2nd:4th digit ratio
Martel (2009)	Testosterone	312	13.31	50–63.1	Diagnosis (clinical, K-SADS-E) and ADHD symptoms (ADHD Rating Scales; BASC,CRS)$^{P, T}$	School, clinic, and community based research study (USA)	Right hand 2nd:4th digit ratio
McFadden et al. (2005)	Testosterone	31–61	7–15	60.7	Diagnosis (inattentive or combined type, DSM-IV-TR)	Clinical research study (USA)	Right hand 2nd:4th digit ratio
McIntosh et al. (1995)	Labor Complications	209	9.5–10.4	53–85	Diagnosis (DSM-III-R)	School-based research study (USA)	Retrospective parent report of perinatal factors (The Maternal Perinatal Scale)
Melchior et al. (2015)	No Breastfeeding	1,113	5	51.4–53.4	ADHD symptoms (SDQ)^{P}	DEN mother-child cohort study (France)	Maternal report questionnaire
Mimouni-Bloch et al. (2013)	No Breastfeeding	159	9.5–10.36	50.5–73.2	Diagnosis (clinical)	Clinic-based research study, with sibling and non-psychiatric clinical control groups (Israel)	Retrospective parent report of breastfeeding
Motlagh et al. (2010)	Pregnancy Weight; Perinatal Asphyxia; Preeclampsia; Pregnancy Complications	117	11.8–12.2	46–73	Diagnosis (clinical, SADS-PLV)	Clinic-based research study, with population-based controls (USA)	Retrospective parent report of pregnancy and perinatal factors
Murray et al. (2016)	Apgar Score, Mode of Delivery	6,849	7	n/a	ADHD symptoms (SDQ), Diagnosis (DAWBA)^{P}	ALSPAC Birth cohort (United Kingdom)	Birth records
	Apgar Score, Mode of Delivery	3,509	7	n/a	ADHD symptoms (SDQ), Diagnosis (DAWBA)^{P}	Pelotas birth cohort (Brazil)	Maternal interview
Park et al. (2014a)	Neonatal Illness	900	6–15	73.8–85.4	ADHD diagnosis (DSM-IV; K-SADS-PL, DISC-IV)^{P}	Research study with clinical recruitment of ADHD sample from hospital and school-based non-ADHD sample (South Korea)	Parent report

Study	Risk Factors (Included)	Sample size	Age at Outcome Measurement (Years)	Male (%)	ADHD Measurement (Included)	Sample (country)	Measurement
Park et al. (2014b)	No Breastfeeding	874	8–11	58.2	ADHD Diagnosis (DSM-IV; DISC-IV)[P]	School sample across five regions (South Korea)	Maternal report
Pineda et al. (2007)	Neonatal Illness; Perinatal Asphyxia; Preeclampsia; Pregnancy Complications	486	7.9–8.3	47.2–74.5	Diagnosis (DSM-IV; DICA-PR, BASC, DSM-IV ADHD Symptom Questionnaire, ADHD Checklist; all were being treated with methylphenidate)	Clinic-based research study; controls recruited from schools (Colombia)	Retrospective parent report of pregnancy-related factors as part of BASC
Pires et al. (2013)	Neonatal Illness	366	7.9	50.8	ADHD diagnosis/ symptoms (CBCL, TRF)[P, T]	School-based research study (Brazil)	Retrospective maternal report of neonatal illness
Pohlabelnetal. (2017)	Mode of Delivery, Preeclampsia	15,577	2–12	50.6	Parent report of diagnosis	European IDEFICS prospective multicenter cohort study (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain and Sweden)	Parent questionnaire
Pringsheim et al. (2009)	Mode of Delivery; Perinatal Asphyxia	353	9.9–10	76.7–83.4	Diagnosis (clinical, DSM-IV-TR)	Clinic-based case-control research study. Cases had ADHD+Tourette syndrome (TS); controls had TS only (Canada)	Retrospective report of perinatal factors included as part of demographic form for all new patients
Roberts & Martel, 2013	Testosterone	109	4.82	46.7–72.2	ADHD symptoms (K-DBDS, DSM-IV)[P]	Community-based research study (USA)	Right hand 2nd:4th digit ratio
Rodriguez et al. (2008)	Pregnancy Weight	12,976	7–12	50	ADHD symptoms (SDQ; Rutter)[T]	Follow-up of pregnancy cohorts (Sweden, Denmark, Finland)	Pre-pregnancy weight collected prospectively
Rodriguez (2010)	Pregnancy Weight	907	5	53	ADHD symptoms (DSM-IV, SDQ)[P, T]	Follow-up of pregnancy cohort (Sweden)	Early pregnancy weight recorded in Swedish Medical Birth Register
Russell et al. (2014)	Mode of Delivery	8,443	7.2	50.3–82.2	Diagnosis (parent report of previous diagnosis)[P]	Birth cohort (MCS; United Kingdom)	UK Birth Registration and Maternity Hospital Episode Data
Say et al. (2016)	Mode of Delivery, Preeclampsia, Pregnancy Complications	180	3–18	71–78	Clinical diagnosis (DSM-IV)	Case-control study recruited from pediatric clinics and child/adolescent psychiatry clinics (Turkey)	Maternal report
Sciberras et al. (2011)	Neonatal Illness	3,477	6.8	51	Diagnosis (parent report of previous diagnosis)[P]	Nationally representative population-based birth cohort (LSAC; Australia)	Retrospective parent report of whether the child required intensive care at birth
Shih et al. (2020)	Mode of Delivery	16,376	8	52.5	Diagnosis (parent report of previous diagnosis)[P]	National prospective longitudinal cohort study (Taiwan)	Parent report

Study	Risk Factors (Included)	Sample size	Age at Outcome Measurement (Years)	Male (%)	ADHD Measurement (Included)	Sample (country)	Measurement
Silva et al. (2014)	Apgar Score; Labor Complications; Mode of Delivery; Perinatal Asphyxia; Preeclamp-sia	43,062	0–25	77	Diagnosis (use of stimulant medication recorded in MODDS)	Population-based, record linkage case-control study (Australia)	Prospectively ascertained pregnancy and perinatal information obtained from MNS
Stadler et al. (2016)	No Breastfeeding	474	7–13	63.9	Diagnosis (DSM-5; KSAD-S-E, Conners, DuPaul ADHD Rating Scale IV)^{P}	Case control cohort (USA)	Maternal report
St. Sauver et al. (2004)	Labor Complications	5,631	n/a	50.1–75.4	Diagnosis (algorithm based on ADHD symptoms, diagnosis, use of stimulants)	Birth cohort (USA)	Birth certificate (perinatal information) records linked to school and medical records
Stevenson et al. (2007)	Testosterone	187	n/a	27.8	ADHD symptoms (DSM-IV)^{S}	School (college)-based research study (USA)	Right hand 2nd:4th digit ratio
Sucksdorff et al. (2018)	Preeclampsia, Pregnancy Complications, Mode of Delivery, Neonatal Illness	49,533	6–20	n/a	ADHD diagnosis (ICD-9, ICD-10)	Nested case-control study based on the Finnish Prenatal study of ADHD (Finland)	Linkages of three national registers: FHDR FMBR, Finnish Central Population Register
Wagner et al. (2009)	Labor Complications; Neonatal Illness	748	8.13	49.2	ADHD symptoms (HBQ, CBQ, DISC-IV)^{P}	Wisconsin Twin Panel (USA)	Perinatal risk factors coded from medical records using OCS, NCS
Wang et al. (2019)	Mode of Delivery, No Breastfeeding	401	8.6	79–84	Diagnosis, (SNAP and clinical interview; DSM-IV)^{P}	Community based case-control study (China)	Face to face interview
Wiggs et al. (2016)	Pregnancy Complications, Neonatal Illness	464	6–17	55	Diagnosis (DSM-IV ADHD Rating Scale, Conners' Rating Scale - Revised Short Form, K-SADS-E)^{P,T,S}	Research study recruited from community and clinics (USA)	Parent report
Zhu et al. (2015)	Mode of Delivery, No Breastfeeding, Pregnancy Complications, Pregnancy Weight	1,765	4	54	ADHD symptoms (Conners' Hyperactivity Index^{P}	Research study recruited prenatally from hospital (China)	Parent interview and medical records

ADHDT The Attention Deficit Hyperactivity Disorder Test, *ALSPAC* Avon Longitudinal Study of Parents and Children, *BASC* Behavior Assessment System for Children, *BBC* Boston Birth Cohort, *C-ASQ* Conners abbreviated symptom questionnaire, *CBCL* Child Behavior Checklist, *CBQ* Children Behavior Questionnaire, *CBS* Cardiff Birth Survey, *CPRS-48* Conners' Parent Rating Scale-Revised, *CRS* Conners Rating Scale, *DAWBA* Development and Wellbeing Assessment, *DEN* Étude sur les Déterminants pré - et postnatals pré coces du développement psychomoteur et de la santé de l'Enfant, *DICA-PR* Diagnostic Interview for Children and Adolescents - Parent Revised Version, *DSM-IIIR* Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, *DSM-TV* Diagnostic and Statistical Manual of Mental Disorders, 4th edition, *DSM-TV-TR* Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision, *DSM-5* Diagnostic and Statistical Manual of Mental Disorders,

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5th edition, *EDI* Early Development Instrument, *FHDR* Finnish Hospital Discharge Register, *FMBR* Finnish Medical Birth Register, *GUI* Growing Up in Ireland, *HBQ* MacArthur Health and Behavior Questionnaire, *IFPSII* The Infant Feeding Practices Study n, *IDEFICS study* Identification and prevention of dietary- and lifestyle-induced health effects in children and infants, *K-DBDS* Kiddie-Disruptive Behavior Disorder Schedule, *K-SADS-E* Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiological Version, *LCCS* The Longhua Child Cohort Study, *LSAC* Longitudinal Study of Australian Children, *MCS* Millennium Cohort Study, *MNS* Midwives Notification System, *MODDS* Monitoring of Drugs of Dependence System, *n/a* not available, *NCS* Neonatal Complications Scale, *NHANES* National Health and Nutrition Examination Survey, *NICU* Neonatal intensive care unit, *OCC* Odense Child Cohort, *OCS* Obstetrical Complications Scale, *PBQ* Preschool Behavior Questionnaire, *SADS-PLV* Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version, *SDQ* Strengths and Difficulties Questionnaire, *TBCS* Taiwan Birth Cohort Study, *TRF* Teacher Report Form

P Parent report;

T Teacher report;

S Self report

Table 2

Results of meta-analyses of studies examining selected prenatal, birth, and postnatal risk factors for attention-deficit/hyperactivity disorder (ADHD)

	Risk factor	Outcome Measure	Most common risk factor definition	ADHD Overall		ADHD Diagnosis only	
				Total sample size (number of studies)	Pooled effect size (95% CI)*	Total sample size (number of studies)	Pooled effect size (95% CI)*
Prenatal risk factors	Pre-pregnancy weight	Dichotomous	Pre-pregnancy body mass index in the obese category (≥ 30 kg/m2)	1,102,386 (9)	OR: 1.49(1.14; 1.94)**		
	Preeclampsia	Dichotomous	Preeclampsia	972,772 (14)	OR: 1.26 (1.09; 1.46)**	962,080 (13)	OR: 1.27 (1.10;1.47)**
	Pregnancy complications	Dichotomous	Placental abruption most common (others included)	253,517 (12)	OR: 1.47(1.17; 1.86)**	226,967 (10)	OR: 1.49 (1.16; 1.91)**
	Testosterone	Continuous	Finger length ratio (2nd digit (2D):4D ratio). A lower ratio represents greater testosterone exposure	1,405 (9)	CC: −0.14 (−0.20; −0.09)**	526 (3)	CC:−0.16 (−0.25; −0.08)**
Risks occurring at birth	Perinatal asphyxia	Dichotomous	Perinatal asphyxia	157,051 (8)	OR: 1.31 (0.99; 1.74)	135,808 (7)	OR: 1.24 (0.92;1.66)
	Labor complications	Dichotomous	Labor/delivery complications	139,110 (6)	OR: 1.16(0.92; 1.48)	same as overall	
		Continuous		1,122 (4)	CC: 0.01 (−0.08; 0.11)		
	Mode of delivery	Dichotomous	Breech delivery, cesarean delivery, and vacuum delivery	2,201,243 (24)	OR: 1.11 (0.99; 1.24)	1,989,443 (18)	OR: 1.12 (0.98; 1.27)
	Breech delivery	Dichotomous	Breech delivery	247,599 (6)	OR: 1.02 (0.78; 1.34)	133,183 (3)	OR: 1.03 (0.76–1.41)
	Cesarean delivery	Dichotomous	Cesarean delivery	2,123,517 (22)	OR: 1.12 (1.00; 1.25)		
	Vacuum delivery	Dichotomous	Vacuum delivery	197,957 (5)	OR: 1.10(0.87; 1.39)		
Postnatal risk factors	Apgar score	Dichotomous	Apgar score of <7 at 5 min	8,189,263 (15)	OR: 1.30 (1.09; 1.54)**	8,163,236 (13)	OR: 1.29 (1.08; 1.53)**
	Neonatal illness	Dichotomous	Neonatal intensive care unit (NICU) admission	166,891 (11)	OR: 1.50 (1.18; 1.92)**	142,106 (10)	OR: 1.46 (1.14; 1.87)**
		Continuous		913 (3)	CC: 0.11 (0.05; 0.18)**		
	No breastfeeding	Dichotomous	Never breastfed	13,229 (9)	OR: 1.55 (1.15; 2.10)**		

Note: all heterogeneity statistics were not significant and therefore are not reported

*Odds ratio (OR) for dichotomous outcomes and correlation coefficient (CC) for continuous outcomes; completed via complete pooling. CI=confidence interval

**Significant at $p < 0.05$