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Systematic Review and Meta-analysis of the Relationship Between Exposure to Parental Substance Use and Attention-Deficit/Hyperactivity Disorder in Children

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is characterized by persistent patterns of inattention, hyperactivity, and impulsiveness. Among US children and adolescents aged 3–17 years, 9.4% have a diagnosis of ADHD. Previous research suggests possible links between parental substance use and ADHD among children. We conducted a systematic review and meta-analysis of 86 longitudinal or retrospective studies of prenatal or postnatal alcohol, tobacco, or other parental substance use and substance use disorders and childhood ADHD and its related behavioral dimensions of inattention and hyperactivity-impulsivity. Meta-analyses were grouped by drug class and pre- and postnatal periods with combined sample sizes ranging from 789 to 135,732. Prenatal exposure to alcohol or tobacco and parent substance use disorders were consistently and significantly associated with ADHD among children. Other parental drug use exposures resulted in inconsistent or non-significant findings. Prevention and treatment of parental substance use may have potential for impacts on childhood ADHD.

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Keywords

Attention-deficit/hyperactivity disorder; Meta-analysis; Parent substance use; Parent alcohol use; Parent tobacco use

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood psychiatric disorder in the USA. ADHD is diagnosed among 9.4% of US children and adolescents aged 3–17 years (Bitsko et al., 2022a). Analyses of the Institute for Health Metrics and Evaluation Disease Expenditure 2013 project database revealed that ADHD was the condition that accounted for the second-highest amount of pediatric personal health care spending at $20.6 billion that year (Bui et al., 2017). Individuals with ADHD exhibit impairment in academic, family, and social settings and are at an increased risk for minor and major injury (Faraone et al., 2021; Xiang et al., 2005), hospital admission, and emergency room visits (Faraone et al., 2021; Leibson et al., 2001), and in late adolescence and early adulthood, dangerous driving behaviors, including motor vehicle accidents, traffic violations, and impaired driving (Woodward et al., 2000). In adulthood, there is a consistent association of childhood ADHD with chronic diseases, such as obesity and hypertension, as well as mental disorders (Faraone et al., 2021). Thus, effective prevention of ADHD has the potential to impact individuals, families, communities, and the health sector.

Individual studies and meta-analyses have implicated genetics in the development of ADHD (Faraone et al., 2021). For example, a meta-analysis of dopamine system gene studies revealed a significant association between ADHD and both DRD4 and DRD5 (Maher et al., 2002). Although the pooled effect sizes were statistically significant, odds ratios were 1.41 for DRD4 and 1.57 for DRD5, suggesting other causal pathways including environmental influences and gene-environment interactions as contributing factors (Faraone et al., 2021). Therefore, evidence on these potentially modifiable environmental risk factors could inform prevention efforts.

Among such potential environmental risk factors for ADHD is substance exposure. Prenatal substance exposure may include tobacco and alcohol (about 10% and 15% of pregnancies affected, respectively) as well as illicit substances (about 5% of pregnancies affected), most commonly cannabis[1] (Gosdin et al., 2022; NIDA, 2022). Children may also experience direct substance exposure postnatally. For example, almost half of children may be exposed to second-hand smoke (Homa et al., 2015). Finally, parental substance use may impact the child by its effect on parenting and the home environment, especially when the use is chronic and severe enough to meet criteria for a disorder. Parental substance use disorders affect more than 1 in 10 children and are associated with and compounded by social determinants of health risks such as poverty (Lipari & Van Horn, 2017; U.S. Department of Health & Human Services, 1999) which present further risks for child development.

[1]Although medical/nonmedical adult cannabis use is legalized in some states, it has historically been included as an illicit substance. We use cannabis throughout the article for consistency, including for studies that use the term marijuana.

For the development of ADHD, parental substance use may represent a constellation of prenatal and postnatal risk factors via different pathways. Prenatal (i.e., during pregnancy) exposure to substances such as alcohol, tobacco, and cannabis can adversely affect the developing brain and nervous system, affecting children's cognition and behavior (Lange et al., 2018; U.S. Department of Health and Human Services, 2014; Ryan et al., 2018; Smith et al., 2016). Studies have linked parental tobacco smoking with later ADHD among children (Day et al., 2000; Desrosiers et al., 2013). What is unclear is whether those associations are due to exposure to secondhand smoke and associated effects on child health (U.S. Department of Health and Human Services, 2006) or to other factors that contribute both to parental smoking and to a child developing ADHD. ADHD, particularly if untreated, is associated with risk for later substance use, so parents of children with ADHD may also be at increased risk for substance use given shared genetics between ADHD and substance use disorders (Wimberley et al., 2020).

Having a parent with a substance use disorder may increase a child's risk for ADHD by the associated impact on the parent–child relationship and home environment. For example, research has linked parent substance use to harsh, negative parenting practices (Smith et al., 2016) and to ADHD (Carbonneau et al., 1998; Knopik et al., 2006). Claussen et al.'s meta-analysis of parenting and family environmental factors (Claussen et al., 2022) concluded that lower parental sensitivity and warmth, higher parental negativity and harsh discipline, and higher parental intrusiveness and reactivity were all associated with higher risk of ADHD among children. Other risks such as parental stress and mental disorders as well as lack of economic resources are associated with both parental substance use and ADHD (Lipari & Van Horn, 2017; Robinson et al., 2022; Rowland et al., 2018).

The existing research on the association between parental substance use and childhood ADHD has encompassed a variety of different research methods and time periods. A synthesis of what is known about the relationship between parental substance use, both pre- and postnatally, and the development of ADHD could inform interventions and approaches to preventing or reducing the impact of ADHD. In the present paper, we examine the association of parental substance use and ADHD-related outcomes in several ways: prenatal exposure to substances, direct postnatal environmental exposure such as parental smoking, and the impact of parental substance use disorders. A deeper understanding of the associations between parental substance use and ADHD may identify potential public health interventions to address the associated risks.

Methods

Procedure

This paper is one of a series of articles using the same methodology to examine potential modifiable risk factors for ADHD, including factors related to pregnancy, parenting, parent mental health, chemical exposures, and child health factors (Bitsko et al., 2022b; Claussen et al., 2022; Robinson et al., 2022; So et al., 2022; Dimitrov et al., in press); more specific details on study methods are included in Bitsko et al. (2022b). These categories of risk factors were divided across multiple papers because of the large literature available for each and were grouped by type of exposure and potential mechanism. The current study

focuses on a group of risk factors related to parental substance use. Since identical methods were used across papers, findings can be directly compared and provide a summary of modifiable risk factors for ADHD. To identify relevant publications pertaining to potential risk factors for ADHD diagnosis and symptomology, we conducted literature searches of multiple publication databases: PubMed, Web of Science, and EMBASE. We used a top-down approach with search strings including terms to capture ADHD and terms that identify studies of potential "risk" factors, as well as a bottom-up approach, with search strings including ADHD or related terms and specific or general terms representing substance use (specifically, smok* OR tobacco OR nicotine OR alcohol* OR drinking OR ethanol OR substance OR marijuana OR cocaine OR amphetamine OR heroin OR caffeine, see Bitsko et al., 2022a, b for details). Across databases, articles were limited to those in English using Human subjects. We reviewed citations in each article in the comprehensive search to identify additional relevant articles (i.e., iterative reference mining). We excluded articles for meta-analytic synthesis that lacked a sufficient diagnostic or assessment description and had a poor exposure description, those where exposure was concurrent with the outcome assessment, and those lacking appropriate data (e.g., effect size, sample size). For studies with overlapping study samples, the earlier study was included unless a later publication included a larger sample size. We coded retained articles into a database describing all samples and individual test statistics for included studies. ADHD outcomes included ADHD diagnosis, hyperactivity/impulsivity symptoms, inattentive symptoms, and ADHD overall, which pooled findings across all the ADHD outcomes to include as many effect sizes as possible. For prenatal smoking, studies that did not account for postnatal smoking were excluded; included studies either adjusted for postnatal smoking or defined exposure groups taking postnatal smoking into account. The initial literature review was conducted in 2014 and provided the data for our initial meta-analysis. In January of 2021, we conducted an updated literature review to identify studies published since the initial review, limited to risk factors that had been included in our original analyses (as described below). Overall, articles from 1984 to 2020 were reviewed for inclusion.

Meta-analysis Methods

Selected studies were retained for potential analysis if sufficient data were presented for calculation of a common effect size statistic across each risk factor set. In the selected studies, statistical reporting of ADHD associations included dichotomous and continuous measurement (e.g., dichotomous for studies using odds ratios or categorical analyses; continuous for correlation coefficients or beta weights) which were analyzed separately. If multiple effect sizes were included in a study (e.g., separately for boys and girls), they were aggregated prior to the meta-analysis. For multiple effect sizes presented across time points during pregnancy, we prioritized inclusion of the earliest effect size given that early exposures typically have a greater impact on neurodevelopment (Rice & Barone, 2000).

Standardized summary statistics (i.e., odds ratio for dichotomous outcomes or a combined correlation coefficient for continuous outcomes) and variances (95% confidence intervals) for each study were calculated. For each risk factor, when at least 3 eligible effect sizes were present, forest plots were generated separately diagnosis or symptoms (referred to as "ADHD overall"), as well as for studies that separately assessed ADHD diagnosis,

inattention, or hyperactivity/impulsivity. For each outcome, a single pooled effect size for all studies was calculated accompanied by its 95% confidence interval, with each study weighted by its conditional variance (inverse variance method). As in other studies in this supplement, weighted random-effects models were used for these analyses, with weights based on the inverse of both within-study variation and among-study variation, to provide a more conservative effect size estimate compared to a fixed-effect model (Berlin et al., 1989). Between-study heterogeneity was assessed by calculating Cochran's heterogeneity statistic, Q (Cochran, 1954). See Bitsko et al. (2022a, b), for further details on our meta-analytic approach.

Results

Our literature search yielded 86 studies of parental substance use (Table 1) that met all inclusion criteria and provided enough summary information for meta-analysis; this included 67 articles from our original literature review in 2014 and an additional 19 articles identified in 2021 (see Fig. 1), with publication dates ranging from 1988 to 2019. The literature search yielded studies of prenatal cannabis, cocaine, heroin, general substance use (i.e., studies grouping different substances together without specifying type), and alcohol, as well as prenatal or postnatal tobacco, and parental substance use disorders. Other postnatal exposure such as cannabis did not yield sufficient studies for inclusion. The characteristics of included studies can be found in Table 1. We examined four categories ADHD outcomes: ADHD overall (diagnosis or symptoms), ADHD diagnosis specifically, or presence of the specific ADHD symptoms of inattention and hyperactivity/impulsivity. Summary statistics of each random-effects meta-analysis performed are presented in Table 2. Forest plots depicting the individual study effect sizes and confidence intervals in addition to the estimated common effect size and confidence interval are provided in Supplemental Figs. 1-26. Where continuous or dichotomous effect sizes are presented, the associated statistics are correlation coefficients and odds ratios, with confidence intervals, respectively.

Prenatal Cannabis Exposure

Only continuous effect sizes were available. In a synthesis of four studies, prenatal cannabis exposure was significantly associated with ADHD overall (diagnosis or symptoms) (CC = 0.04 (0.01, 0.07)), as well as with inattention (CC = 0.06 (95% CI 0.02, 0.10)). The test of heterogeneity for both ADHD overall and inattention was not significant.

Prenatal Cocaine Exposure

A significant relationship was found via synthesis of seven studies of continuous effect sizes for ADHD overall (CC = 0.06 (95% CI 0.02, 0.10)) and seven studies of continuous effect sizes for inattention (CC = 0.09 (95% CI 0.05, 0.13)). Analysis of smaller samples of four and three pooled studies each did not show a significant relationship between prenatal cocaine exposure and hyperactivity-impulsivity or with the dichotomous ADHD overall outcome. The test of heterogeneity for hyperactivity-impulsivity was significant ($Q_{(3)}$ = 14.05, p = 0.003).

Prenatal Heroin Exposure

For prenatal heroin exposure, only continuous ADHD overall had a sufficient number of effect sizes for analysis (3 studies) and the association between prenatal heroin and ADHD overall was not significant.

Prenatal General Substance Use

Studies that examined the impact of any substance exposure rather than a specific substance exposure did not yield significant results for dichotomous ADHD overall or ADHD diagnosis. No other factors had sufficient studies for analyses.

Prenatal Alcohol Exposure

Using dichotomous effect sizes, prenatal alcohol exposure was significantly associated with ADHD overall across 42 studies (OR = 1.62 (95% CI 1.33, 1.97)) and ADHD diagnosis across 25 studies (OR = 1.68 (95% CI 1.23, 2.29)). In smaller analyses of inattentive (6 studies) and hyperactive-impulsive symptoms (4 studies) with dichotomous effect sizes, effect sizes did not reach significance. Using continuous effect sizes, prenatal alcohol exposure was significantly associated with ADHD overall across 20 studies (CC = 0.09 (95% CI 0.05, 0.13)), inattention across 13 studies (CC = 0.21 (95% CI 0.10, 0.32)), and hyperactivity-impulsivity in 11 studies (CC = 0.18 (95% CI 0.09, 0.27)). The tests of heterogeneity were significant for ADHD overall dichotomous ($Q_{(41)} = 81.4$, $p < 0.001$) and continuous ($Q_{(19)} = 109.5$, $p < 0.001$) with ADHD diagnosis ($Q_{(24)} = 38.8$, $p = 0.03$) and using continuous effect sizes with inattention ($Q_{(12)} = 105.69$, $p < 0.001$) and hyperactivity-impulsivity ($Q_{(10)} = 86.9$, $p = 0.003$).

Prenatal Tobacco Exposure

All included measures of the association of prenatal tobacco exposure and ADHD were significant. Using dichotomous effect sizes, prenatal tobacco exposure was significantly associated with ADHD overall across 11 studies (OR = 1.67 (95% CI 1.23, 2.26)) and ADHD diagnosis across 6 studies (OR = 1.74 (95% CI 1.15, 2.62)). Prenatal tobacco exposure using continuous effect sizes was associated with ADHD overall in 7 studies (0.11 (95% CI 0.03, 0.19)) and hyperactivity-impulsivity across four studies (CC = 0.17 (95% CI 0.08, 0.26)). Both continuous analyses were significantly heterogeneous, ADHD overall ($Q_{(6)} = 63.79$, $p < 0.001$) and hyperactivity-impulsivity ($Q_{(3)} = 8.9$, $p = 0.03$).

Postnatal Tobacco Exposure

Postnatal tobacco exposure was associated with ADHD overall for dichotomous effect sizes across 9 studies (OR = 1.45 (95% CI 1.05, 2.00)) and with inattention using continuous effect sizes from 3 studies (CC = 0.09 (95% CI 0.04, 0.14)), but not with ADHD overall using continuous effect sizes from 5 studies or ADHD diagnosis based on dichotomous effect sizes from four studies. The heterogeneity for continuous ADHD overall was significant ($Q_{(4)} = 77.8$, $p < 0.001$).

Parental Substance Use Disorders

All relevant studies used dichotomous effect sizes. Parental substance use disorders were strongly associated with ADHD overall across 9 studies (OR = 2.71 (95% CI 1.68, 4.38)) and ADHD diagnosis across 8 studies (OR = 2.90 (95% CI 1.68, 5.00)). Tests of heterogeneity were not significant.

Discussion

The findings of the meta-analysis add to the evidence that parental substance use can present a risk for children's healthy development and add to the body of research that documented effects of substance exposure on children's cognitive and behavioral development (Sharapova et al., 2018; U.S. Department of Health and Human Services, 2014; Ryan et al., 2018). Our study documented associations of several substances with ADHD symptoms and diagnosis using consistent methodology across the different exposures and summarizing literature published over 3 decades (1988–2019).

Parental substance use may be associated with childhood ADHD through different paths, such direct or indirect exposure (Skoglund et al., 2014; Wimberley et al., 2020). The study adds to the existing literature by examining multiple substances and multiple mechanisms of exposure together. Both prenatal and postnatal substance use exposure and parental substance use disorder are known risk factors for poor health and developmental outcomes among children (Lipari & Van Horn, 2017; NIDA, 2022). In our findings, prenatal exposure to alcohol, tobacco, and cannabis were consistently and significantly associated with overall ADHD among children, as was the presence of parent substance use that reached criteria for substance use disorders. Postnatal exposure may also represent risk, but the associations for postnatal tobacco exposure were significant in some analyses but non-significant in other analyses. Not all substances were associated with effects; for prenatal cocaine, results were mixed, and available data on prenatal exposure to heroin or to drugs in general revealed no significant association with later ADHD. Analyses for specific symptoms of inattention or hyperactivity were limited due to fewer studies available; for prenatal alcohol, analyses for continuous outcomes were significant while dichotomous outcomes were not.

Inconsistent results for several factors were likely impacted by methodological differences. The differences in significance for prenatal alcohol when comparing continuous with dichotomous outcomes may be related to fewer studies in the analyses of dichotomous outcomes (4 and 6) compared to the analyses for continuous outcomes (11 and 13) since the overall estimates were significant for both dichotomous and continuous outcomes. The inconsistently significant findings for postnatal tobacco exposure and for prenatal cocaine exposure may be related a smaller number of studies included in some analyses, as well as significant heterogeneity observed in the overall analysis (which was not significant) that was not observed in the analysis of inattention which was significant. It appears from the forest plots that eliminating a single study (Keyes et al., 2014, see Supplemental Figure S23) likely reduced heterogeneity which may have led to the significant finding in the sub-analysis of inattention.

Given the associated risk for ADHD, parental substance use, including substance use disorders, can be used as an indicator to identify affected children and parents as populations who could benefit from intervention and support. An understanding of the mechanisms that account for the relationship between parental drug use and ADHD is still developing. Several mechanisms could explain the relationship of parental drug use with ADHD and have been studied extensively for the most prevalent drug exposures, tobacco and alcohol. One possible mechanism is the prenatal teratogenic effects of the substance on the developing brain. In humans, limited information is available; in animal studies, exposure to nicotine prenatally leads to deficits in cognition, attention, and memory consistent with ADHD symptoms in children (Liang et al., 2006; Paz et al., 2007) and to an increase in physical activity level (Ernst et al., 2001). Previous evidence links the lasting behavioral impact of prenatal exposure to nicotine to a prenatal upregulation of nicotinic cholinergic receptors leading to abnormal cell differentiation and brain structural and functional changes (Shea & Steiner, 2008; Toro et al., 2008). The teratogenic effects of alcohol in fetal alcohol spectrum disorder (FASD), including increased risk of hyperactivity and inattention, are well-established (Lange et al., 2018) but the biological mechanisms linking the exposure to lasting effects outside of FASD are not well-understood.

Another mechanism that might explain the relationship between prenatal substance exposures and ADHD is the existence of common sets of genes underlying both the predisposition to use substances and ADHD (Wimberley et al., 2020). Parents with increased genetic liability for ADHD may be more likely to have a substance use disorder, including use during pregnancy. Family studies have revealed ADHD-related behavioral traits, such as short attention spans and high impulsivity and behavioral activity, in children of parents with substance use disorders (Earls et al., 1988). Potentially mediating this commonality, several neurobiological systems (e.g., dopaminergic, serotonergic, and monoamine oxidase) have been implicated as contributors to the etiology of addictive and other behavioral disorders. The dopamine system has been posited as the major component in the mechanisms of substance use disorder (Volkow et al., 2019). Substances generally stimulate dopaminergic neurons and their rewarding effects are associated with dopamine release. Genetic studies indicate that the dopamine system genes may substantially contribute to behavioral variation and are a possible genetic link between the ADHD and substance use disorder liabilities (Maher et al., 2002; Volkow et al., 2019). Phenotypic correlation between novelty seeking and impulsivity, a component of ADHD, is highly heritable (Jang et al., 2022; Wimberley et al., 2020), and novelty seeking has been associated with substance use (Foulds et al., 2017). Studies of children of twins provide support for the role of prenatal drinking, smoking, and ADHD in increasing ADHD prevalence in offspring independent of genetic risk (Knopik et al., 2006). Similarly, studies of siblings discordant for exposure support a prenatal-environmental relationship between alcohol or tobacco exposure and ADHD in offspring (D’Onofrio et al., 2007). Two very large cohort studies support a relationship between prenatal smoking and ADHD risk (D'Onofrio et al., 2008; Skoglund et al., 2014). However, after accounting for familial factors, this risk was completely mitigated, indicating a role for non-measured familial environmental factors (Skoglund et al., 2014).

Additionally, genetic predispositions and environmental influences can interact and affect family environment. That is, parents at genetic risk for using substances may not only be at

genetic risk for ADHD but also be more likely to have difficulty with mental health and may be more likely to provide a family environment high in risk factors associated with ADHD, such as conflict and stress, and lack of healthy routines (Lipari & Van Horn, 2017; Smith et al., 2016).

Parental substance use, especially when chronic and severe enough to represent a disorder, may also function as an indicator of the presence of other parenting and family characteristics that function as stressors for the developing child and are associated with later ADHD. Other papers in our series using the same methodology found relevant significant longitudinal associations between ADHD in children and parental stress, anxiety, depression, and antisocial personality disorder (Robinson et al., 2022) and between parenting factors such as maltreatment and quality of interaction (Claussen et al., 2022). Substance use and poor mental health commonly co-occur (Earls et al., 1988; Faraone et al., 2021) and both substance use and poor mental health are associated with parenting problems (Carbonneau et al., 1998; Earls et al., 1988; Smith et al., 2016; Lipari & Van Horn, 2017; Robinson et al., 2022).

In addition, substance use and use disorders are also associated with having lower socio-demographic status (Lipari & Van Horn, 2017; Office of Juvenile Justice and Delinquency Prevention, 2022; U.S. Department of Health & Human Services, 1999), which indicates lower access to resources and higher likelihood of exposure to structural inequities. The associated health disparities and lack of access to intervention resources compound the risks related to the impact of substance use on child outcomes. Moreover, there is evidence for an increased likelihood of substance use disorders occurring among partners of people with substance use disorders (Agrawal et al., 2006; Vanyukov et al., 1996), potentially increasing the child's postnatal exposure. Thus, parental substance use represents an increased presence of a range of risks affecting the parent–child relationship, home environment, and access to resources and support that negatively impact child development; any given factor such as prenatal exposure may be less salient than the cumulative impact of the associated risks (Smith et al., 2016).

Children's characteristics may also influence the parents (D'Onofrio et al., 2013). Children who are predisposed for ADHD symptoms may present unique challenges for parents. For example, coping with the child's ADHD symptoms may negatively impact the parent–child relationship (Darling Rasmussen et al., 2019). In some individuals, untreated stress and anxiety can lead to substance use as a way to self-medicate (Leyton & Stewart, 2014); therefore, parenting challenges may also contribute to parental substance use. Additional studies that address genetic risks and environmental risks could further explain the associations and advance information about possible causal pathways. However, the present data add to the literature that describe prenatal exposure and parental substance use as clear and consistent indicators of ADHD risk in children.

Strengths and Limitations

A major strength of the meta-analysis was the inclusion only of studies for which measurement of the risk factor preceded the measurement of ADHD. The review was also not limited to a single way to capture ADHD, such as relying on ADHD diagnosis, but

included ADHD symptoms as well (see Table 1), therefore decreasing the bias created by differential access to diagnosis. Patterns of findings emerged from a variety of studies using different methodologies, and the analysis was based on studies from multiple countries, such as the USA, Canada, Europe, South America, and Asia, and included males and females, which increases generalizability.

Our approach also has several limitations. In most studies, substance use was measured by parental report, which can be affected by disclosure bias. Many studies used retrospective report of prenatal exposure which is affected by recall bias. The studies were longitudinal or retrospective in design rather than randomized clinical trials, and therefore, causality could not be established. Both ADHD and risk factors varied in their definition and how they were measured, limiting the comparability of the data. ADHD outcomes included parent, teacher, and clinician ratings as well as tests of attention, structured clinical diagnostic assessments, and parent report of prior diagnosis. Findings may also have been affected by a potential bias to publish significant rather than non-significant findings.

Significant heterogeneity was evidenced for some of the effect sizes, especially for prenatal alcohol exposure, which had the largest number of eligible studies, and thus points to a potential need for subsequent analysis to examine the sources of variability in effect sizes. Measure of alcohol exposure included prospective and retrospective measures and varied whether they focused on alcohol use or on binge drinking. Heterogeneity was also found among some analyses of pre- and postnatal tobacco exposure, each based on a smaller number of studies, also mixing prospective and retrospective reports. Furthermore, our analyses did not account for amount of exposure to substances or severity of ADHD symptoms, which may have contributed to heterogeneity. As described, studies were conducted in multiple countries using a range of samples with varied sociocultural backgrounds which also may have contributed to heterogeneity. Caution may be warranted in interpreting those results. However, with the exception of the association of postnatal tobacco exposure with continuous overall ADHD, which was not significant, the effect sizes that were heterogeneous also showed statistically significant associations that were generally consistent in direction (positive or negative). Thus, while the heterogeneity limits the ability to interpret the accuracy of the magnitude of the pooled estimates for these factors in our study, the association may be present in future studies of these factors.

Gaps and Future Directions

There were multiple factors for which there were insufficient studies to calculate effect sizes, particularly when examining diagnosis, inattention, and hyperactivity-impulsivity. We noted that many of the non-significant results were among the smaller sample sizes and could be due to reduced power. Future studies with larger samples could also examine potentially important moderators of effect sizes, such as sex, age, co-occurring conditions, country in which research was conducted, or socio-economic factors so that more detailed conclusions can be drawn. Given the potential for risks occurring in clusters, such as health disparities, lack of resources, and mental health concerns occurring along with parental substance use, future studies could examine the relative contributions of these risks and identify which families may benefit most from which types of support and interventions.

Implications

The results of this study highlight potential risks associated with parental substance use that can be addressed in clinical practice and with public health promotion activities. Multiple factors associated with parental substance use were significant, with the largest effect size for substance use disorders. Treatment for unhealthy drug use has been found to be effective and can improve long-term health and outcomes (Chou et al., 2020). Further, population-level public health interventions and policies have shown to be effective to prevent or reduce tobacco use including second-hand smoke exposure[2] (King & Graffunder, 2018). Alcohol screening and brief interventions[3] may be used to address alcohol use in adolescents and adults, including those who are pregnant (US Preventive Services Task Force et al., 2018).

Risk for substance use itself is a developmental process, with early adversity, trauma, and stress increasing the risk for using substances and developing a substance use disorder starting in adolescence (Office of Juvenile Justice and Delinquency Prevention, 2022; Leyton & Stewart, 2014). Early intervention and support may be beneficial to break the intergenerational cycle of risk. For example, some school- or family-based interventions for adolescents have been found to be effective in preventing substance use (Office of Juvenile Justice and Delinquency Prevention, 2022). Enhancing parenting skills and promoting parents' own health and well-being can have positive effects on children's development (National Academies of Sciences Engineering & Medicine, 2019). Parent training may be beneficial to address both ADHD and substance use risk; parent training in behavior management is an effective treatment for ADHD (Wolraich et al., 2019), and parenting programs have been found to be effective in preventing substance use among adolescents (Office of Juvenile Justice and Delinquency Prevention, 2022). Parental substance use may involve the legal system, and absence of a parent due to incarceration may pose additional potential risk for developing ADHD (Claussen et al., 2022). Comprehensive programs such as family drug court that focus on family preservation, including targeted support such as parent training, have been found to be effective (Brook et al., 2015) and could be evaluated for effects on children's ADHD. Many families affected by multiple health concerns for which they need health care such as for parental substance use and other mental disorders, as well as for their child's ADHD, also experience other health disparities including difficulties with accessing mental health care. As parental substance use disorder is likely to occur with other mental disorders, child ADHD also is likely to occur with other mental, behavioral, and developmental disorders, thus warranting a comprehensive approach to family treatment. Therefore, improving family access to mental health care by addressing challenges associated with payment for healthcare, such as providing integrated family care, may be beneficial (Brundage & Shearer, 2019; So et al., 2019). Families affected by substance use and use disorder may benefit from a comprehensive public health approach to addressing risk and increasing support.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

[2]Tobacco Control Interventions | Health Impact in 5 Years | Health System Transformation | AD for Policy | CDC.
[3]CDC's Alcohol Screening and Brief Intervention Efforts | CDC.

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Data Availability

Data are all extracted from publicly available published research, with all studies referenced.

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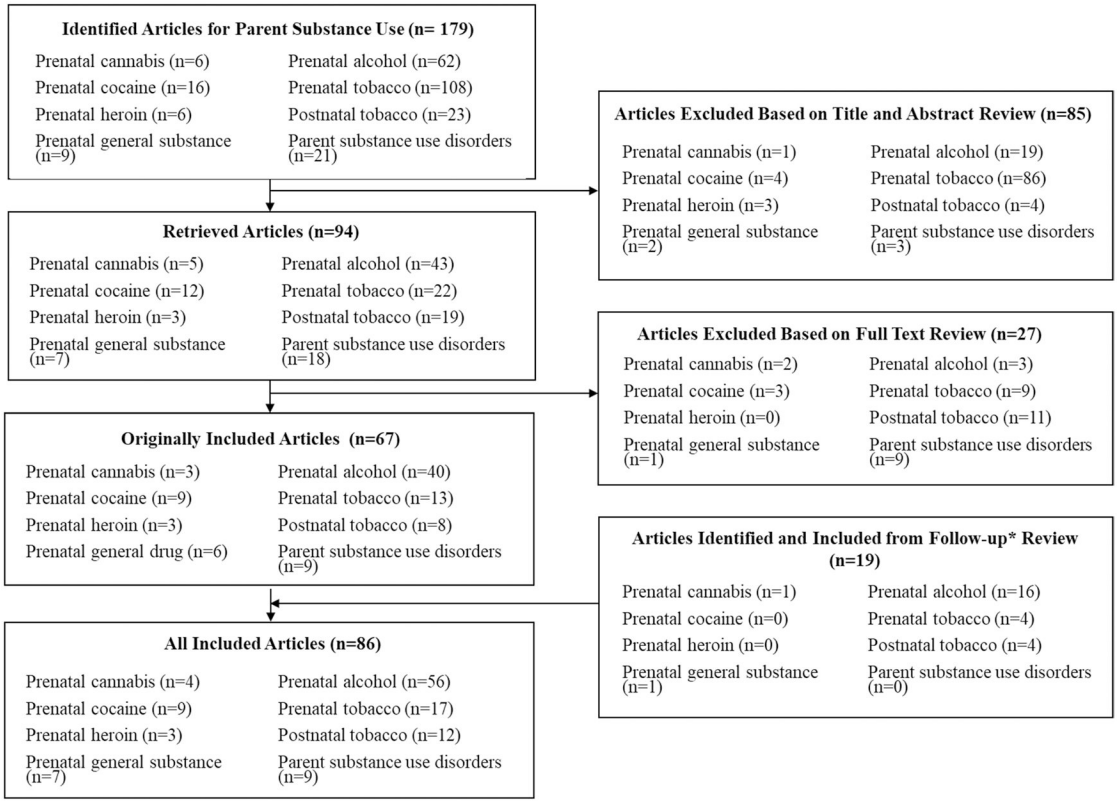

Fig. 1.

Flowchart of triage process for articles identified for meta-analyses of parental substance use and substance use disorder–related risk factors associated with child 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. For prenatal tobacco specifically, many articles that were excluded based on title and abstract review were included for other risk factors (and therefore, the number excluded at this step is higher than the total number excluded). Articles were identified through a comprehensive search of PubMed, Web of Science, and EMBASE in 2014; iterative reference mining; and an updated search of PubMed, Web of Science, and EMBASE in January 2021

Table 1

Characteristics of studies included in meta-analyses of parental substance use and substance use disorders as risk factors for child attention-deficit/hyperactivity disorder

Study	Risk factors (included)	Sample size	Age at outcome measurement (years)	Male (%)	ADHD outcome measurement (included)[a]	Sample (country)	Parental substance use risk factor measurement
Accornero et al. (2007)	Prenatal cocaine	401	7	49–50	Inattention (CPT)	Birth cohort (MPCS; USA)	Retrospective maternal self-report of cocaine use during pregnancy and maternal screening for cocaine metabolite
Alvik et al. (2013)	Prenatal alcohol	621	5.5	NR	ADHD Symptoms (SDQ)[P]	Population-based study of pregnant women (Norway)	Maternal self-report of binge drinking during weeks 0–6 of pregnancy
Anselmi et al. (2010)	Prenatal alcohol	4423	11.3	NR	ADHD Symptoms (SDQ)[P]	Birth cohort (1993 Pelotas Birth Cohort Study; Brazil)	Maternal self-report of alcohol use during pregnancy on perinatal visit
Arnold et al. (2005)	Prenatal tobacco, postnatal tobacco	714	7–9	78–82	Diagnosis (SNAP IV)[P,T]	Research study of children with ADHD from the MTA compared to a local normative comparison group (USA)	Maternal retrospective self-report of gestational smoking and postnatal smoke exposure as part of demographic form
Averdijk et al. (2011)	Prenatal alcohol	1095	7	52	Diagnosis (SBQ)[P,T,C]	Research study. School-based recruitment from The Zurich Project on the Social Development of Children and Youths (Switzerland)	Parent report of maternal alcohol use during pregnancy
Bada et al. (2011)	Prenatal cannabis, prenatal cocaine, prenatal heroin, prenatal alcohol; postnatal tobacco	962	7–13	51	Inattention (CBCL, TRF)[P,T]	Research study (MLS) of drug exposed and non-exposed children (USA)	Maternal self-report of alcohol, marijuana, cocaine, and opiate use during pregnancy on interview and/or positive meconium test for cocaine or opiate metabolites; caretaker report of postnatal tobacco exposure
Bandstra et al. (2001)	Prenatal cocaine	419	3–7	50–51	Inattention (puzzle task, TOVA, and CPT)	Birth cohort follow-up of exposed and non-exposed, comparison children (MPCS; USA)	Retrospective maternal self-report of cocaine use during pregnancy on postpartum interview and/or positive maternal or biological assay
Batstra et al. (2003)	Prenatal tobacco	1186	5–11	55	ADHD symptoms (behavioral questionnaire)[P, T]	Research study of birth cohort subsamples (GPP; the Netherlands)	Retrospective maternal self-report of smoking during pregnancy; obstetric/medical records
Bos-Veneman et al. (2010)	Prenatal alcohol	65	12.2	88	ADHD Symptoms (ADHD rating scale)[P]	Clinical, outpatient research survey/ interview of children identified in psychiatric clinic or tic disorder organization (The Netherlands)	Retrospective maternal self-report of alcohol use during pregnancy; self-completed questionnaire
Brown et al. (1991)	Prenatal alcohol	45	5.1	NR	Inattention (computer vigilance task similar to	Follow-up research study of children from differing prenatal alcohol exposures (USA)	Maternal self-report of alcohol use during pregnancy; self-completed questionnaire

Study	Risk factors (included)	Sample size	Age at outcome measurement (years)	Male (%)	ADHD outcome measurement (included)[a]	Sample (country)	Parental substance use risk factor measurement
					CPT) and hyperactivity (CBCL)[P]		
Day et al. (2000)	Prenatal tobacco, postnatal tobacco	672	3.2	49	ADHD symptoms (RAS, SNAP)[P]	Clinic-based research study (USA)	Maternal self-report of tobacco smoking during and after pregnancy; prenatal and postnatal interviews
Desrosiers et al. (2013)	Prenatal tobacco, postnatal tobacco	271	11.3	49	Diagnosis (DBD, TRF)[T]	Prospective birth-cohort study (Nunavik Child Development Study; Canada)	Retrospective maternal self-report of tobacco smoking during pregnancy and maternal self-report of postnatal environmental exposure to tobacco smoke; postpartum assessment data and/or maternal interview
Dodge et al. (2014)	Prenatal alcohol	112	14.4	59	ADHD Symptoms (DBD, TRF)[T]	Follow-up research study on protective factors of mother/child allele (Detroit Longitudinal Cohort; USA)	Retrospective maternal self-report of alcohol use during pregnancy; interview during prenatal clinic visits
D'Souza et al. (2019)	Prenatal alcohol	6246	2	NR	Inattention/hyperactivity (SDQ)[P]	Longitudinal prospective birth cohort (Growing Up in New Zealand; New Zealand)	Prospective maternal report
Earls et al. (1988)	Parental substance use disorders	37	6–17	62	Diagnosis (DICA)[P]	Research study of children born to alcoholic or non-alcoholic parent(s); parents were hospitalized alcoholics, convicted fellows, or hospitalized medical controls (USA)	Alcohol use disorder diagnosis obtained through structured diagnostic interview and confirmed through records and family history interviews
Eichler et al. (2018)	Prenatal alcohol	88	6–9 (mean 7.7)	52	German ADHD rating scale[P]	FRAMES and FRANCES research studies (Germany)	Level of ethyl glucuronide (EtG) in the meconium
Eiden et al. (2018)	Prenatal cannabis	247	2–3	53	CBCL[P]	Prospective research study recruited from prenatal clinics (USA)	Maternal report, maternal saliva levels of D9–tetrahydrocannabinol (THC)
El Marroun et al. (2011)	Prenatal cannabis	3357	1.5	50	Inattention (CBCL for toddlers)[P]	Birth cohort (Generation R) (the Netherlands)	Maternal self-report of cannabis use during pregnancy; self-completed questionnaire
Eskenazi and Trupin (1995)	Prenatal tobacco, postnatal tobacco	2124	5	50	Hyperactivity (active behavior)[P]	Research study (CHDS subsample; USA)	Maternal self-report of smoking during pregnancy verified by maternal serum cotinine level; maternal self-report of postnatal smoking during interview
Fryer et al. (2007)	Prenatal alcohol	69	11.2–12.1	53–54	Diagnosis (C-DISC-IV, K-SADS-PLP)[P]	Clinical research survey/interview of alcohol-exposed children who were referred or self-referred, and control children who were self-referred or recruited in community (USA)	Caregiver and parent reports, medical charts, and social services records indicating maternal alcohol use during pregnancy
Furtado and Roriz (2016)	Prenatal alcohol	56	11–12 (mean 11.9)	46	d2 Test of Attention (net result)	Gesta-Alcohol Study, longitudinal, prospective observational birth cohort from obstetrical clinic (Brazil)	Maternal report; a score of one point or above on the T-ACE screening tool; a diagnosis for alcohol harmful use or dependence

Study	Risk factors (included)	Sample size	Age at outcome measurement (years)	Male (%)	ADHD outcome measurement (included)[a]	Sample (country)	Parental substance use risk factor measurement
Galéra et al. (2011)	Prenatal general substance use, prenatal alcohol	2057	1–8	51	ADHD symptoms (Interviewer Computerized Questionnaire)[P]	Birth cohort (Quebec Longitudinal Study of Child Development; Canada)	Informant retrospective report of maternal alcohol and other substance use during pregnancy; home interview
Godel et al. (2000)	Prenatal alcohol	69	NR[b]	60	ADHD symptoms (ACTeRS)[T]	Research study of elementary school children (Canada)	Retrospective parent or other source report of maternal alcohol use during pregnancy; self-completed questionnaire
Goldschmidt et al (2000)	Prenatal cannabis	635	10.5	50	ADHD symptoms (SNAP)[P]	Research study (MHPCD; USA)	Maternal self-report of marijuana use during pregnancy; prenatal interviews
Grizenko et al. (2012)	Prenatal alcohol	142	9.0–9.9	51–89	Diagnosis (clinical evaluation, observation of child, school reports, and DISC-IV interview[P])	Research study of ADHD children referred by schools, social workers, and doctors; non-ADHD sibling served as control (Canada)	Report of maternal alcohol use during pregnancy
Ha et al. (2009)	Prenatal alcohol	1778	7.1	52	ADHD Symptoms (Conners scale for ADHD)[P]	Research study of children recruited from schools (CHEER; Republic of Korea)	Retrospective parent report of maternal alcohol use during pregnancy; self-completed questionnaire
Han et al. (2015)	Prenatal alcohol	19940	Elementary school age	49	ADHD symptoms (Korean version of the DuPaul Rating Scale, K-ARS)[P]	School-based survey of parents (South Korea)	Retrospective parent report of maternal alcohol use during pregnancy
Hill et al. (2000)	Prenatal alcohol	150	11	NR	Diagnosis (K-SADS)[P, C]	Research study of children with high or low risk of developing alcoholism (USA)	Retrospective maternal self-report of alcohol use during pregnancy; structured interview
Huang et al. (2019)	Prenatal alcohol	1732	6–18 (mean 8.0)	81	ADHD diagnosis (DSM-IV); Conners PSQ[P]	Case–control study with a clinical sample recruited from a hospital (China)	Retrospective report of maternal alcohol use during pregnancy
Jaspers et al. (2013)	Prenatal alcohol, prenatal tobacco	1664	11.1–16.3	48	Diagnosis (CBCL)[P]	Research study (TRAILS; the Netherlands)	Preventive Child Healthcare data or retrospective maternal self-report on TRAILS interview of alcohol and tobacco use during pregnancy
Kahn et al. (2003)	Prenatal tobacco	161	5.1	49	ADHD symptoms (CPRS R:L)[P]	Research study based on children with low-level lead exposure (USA)	Retrospective maternal self-report of smoking during pregnancy; home interview
Kelly et al. (2012)	Prenatal alcohol	7219	5	50	Hyperactivity (SDQ)[P]	Birth cohort (MCS; UK)	Retrospective maternal self-report of alcohol use during pregnancy; home interview
Kendler et al. (2013)	Prenatal alcohol	9069	3.5	NR	Hyperactivity (Rutter Scale)[P]	Population-based study (ALSPAC; UK)	Retrospective maternal self-report of alcohol use during pregnancy; self-completed questionnaire
Kesmodel et al. (2012)	Prenatal alcohol	1628	5	52	Inattention (TEACh-5)[C]	Research study (LDPS) (Denmark)	Retrospective maternal self-report of binge drinking during pregnancy; prenatal interview

Study	Risk factors (included)	Sample size	Age at outcome measurement (years)	Male (%)	ADHD outcome measurement (included)[a]	Sample (country)	Parental substance use risk factor measurement
Ketzer et al. (2012)	Prenatal alcohol, prenatal general substance use	248	11.7–11.8	69	Diagnosis (K-SADS-E[P,C] clinical committee, clinical evaluation)	Clinical, outpatient research study of children with ADHD-I and controls (Brazil)	Retrospective maternal self-report on telephone interview of substance use including alcohol during pregnancy; medical record supplementation
Keyes et al. (2014)	Prenatal alcohol, prenatal tobacco, postnatal tobacco	1752	9–10	50	Hyperactivity based on 100-item questionnaire[P]	CHDS; recruitment during pregnancy (USA)	Prospective maternal report of alcohol and tobacco use starting in pregnancy
Kim et al. (2009)	Prenatal alcohol	2419	10.0–11.2	49	Diagnosis (DISC-IV)[P]	Research study (2005 Seoul Child and Adolescent Mental Health Survey). School-based recruitment (Korea)	Retrospective parent report of maternal alcohol use during pregnancy; structured questionnaire
Knopik et al. (2005)	Prenatal alcohol, prenatal tobacco; Parental substance use disorders	3872	14.4	0	Parent report of diagnosis (DICA, C-SSAGA)[P]	Telephone interview of parents from Missouri Female Twin Study (USA)	Retrospective maternal self-report of alcohol and tobacco use during pregnancy and maternal assessment of alcohol use disorder
Knopik et al. (2006)	Prenatal alcohol, prenatal tobacco, postnatal tobacco, parental substance use disorders	403	16.5	45	Diagnosis (DICA, C-SSAGA)[C]	Telephone interview of female twins who previously participated in a diagnostic interview survey; at least one twin had a history of alcohol use disorder and at least one twin had children (Australia)	Retrospective maternal self-report of alcohol and tobacco use during pregnancy and of regular smoking not during pregnancy; assessment of alcohol use disorder
Kovess et al. (2015)	Prenatal tobacco	4463	6–11	NR	SDQ[P,T]; DAWBA	Cross-sectional school-based study (Turkey, Romania, Bulgaria, Lithuania, Germany, and the Netherlands)	Retrospective maternal report of tobacco use during pregnancy
Kristjansson et al. (1989)	Prenatal tobacco	76	5.5–5.6	48–57	Hyperactivity (level of activity during testing)[C]	Research study of subsample of mothers who smoked or did not smoke during pregnancy (OPPS: Canada)	Maternal self-report of cigarette smoking during pregnancy; prenatal interviews
Langley et al. (2012)	Prenatal alcohol, prenatal tobacco	5719	7.6	51	ADHD symptoms (DAWBA)[P, T]	Population-based study (ALSPAC; UK)	Maternal self-report of alcohol use and exposure to passive smoking during pregnancy; self-completed questionnaires
Leech et al. (1999)	Prenatal cocaine, prenatal alcohol	590	6.5	50	Inattention and impulsivity (CPT)[C]	Research study (MHPCD. Project; USA)	Retrospective maternal self-report of alcohol and cocaine use during pregnancy; interviews

Study	Risk factors (included)	Sample size	Age at outcome measurement (years)	Male (%)	ADHD outcome measurement (included)[a]	Sample (country)	Parental substance use risk factor measurement
Lewis et al. (2016)	Prenatal alcohol	89	11.1	50–59	ADHD diagnosis (using K-SADS[P]); DBD Scale[T]	Cape Town Longitudinal Cohort 10-year follow-up study (South Africa)	Maternal report of alcohol use during pregnancy
Liew et al. (2015)	Prenatal alcohol	770	~ 8–13	80–81	Medical record ICD-10 diagnosis from the Danish National Hospital Registry and the Danish Psychiatric Central Registry	Danish National Birth Cohort (Denmark)	Maternal self-report of alcohol use during pregnancy
Linares et al. (2006)	Prenatal cocaine	322	6	45–16	Diagnosis (Dominic Interactive)[C]	Research study of cocaine exposed and non-cocaine exposed children; hospital-based recruitment (USA)	Infant meconium or urine or maternal urine positive for cocaine, or retrospective maternal self-report on clinical interview of cocaine use during pregnancy
Linnet et al. (2006)	Prenatal alcohol	912	3.5	52	Hyperactivity (PBQ)[P]	Birth cohort (Denmark)	Maternal self-report of alcohol use during pregnancy; self-completed questionnaires. Denmark
Lynskey et al. (1994)	Parental substance use disorders	961	15	NR	Diagnosis (RBPC, DISC, SREDS)[P,C]	Birth cohort (CHDS; New Zealand)	Parental report of alcohol use disorder on interview
Marmorstein et al. (2009)	Parental substance use disorders	1100	17.5	46	Diagnosis (DICA-C)[C]	Community-based research study (Minnesota Twin Family Study; USA)	Structured interview assessing parental alcohol use disorder
Martel and Roberts (2014)	Prenatal alcohol	109	3–6	64	ADHD symptoms (DBRS)[P,T]	Community based research study (USA)	Retrospective parent report of maternal alcohol use during pregnancy
Melchior et al. (2015)	Prenatal alcohol, prenatal tobacco, postnatal tobacco	1113	5	51–53	ADHD symptoms (SDQ)[P]	DEN mother–child cohort study (France)	Prospective maternal report of alcohol and tobacco use starting in pregnancy
Mick et al. (2002)	Prenatal alcohol	522	11.2–12.2	51–55	Diagnosis (K-SADS-E, Structured Clinical Interview for DSM-III-R)[P]	Case–control family study of siblings with and without ADHD (USA)	Retrospective maternal self-report of alcohol use during pregnancy
Morrow et al. (2008)	Prenatal cocaine	400	5.5	49–51.6	Diagnosis (C-DISC, v2.3)[P]	Birth cohort (MPCS; USA)	Retrospective maternal self-report on postpartum interview of cocaine use during pregnancy, and/or positive toxicology assay for cocaine from mother and child
Murray et al. (2016)	Prenatal alcohol	6849	7	NR	ADHD symptoms (SDQ)[P]	ALSPAC Birth cohort (UK)	Maternal self-report of alcohol use during pregnancy
Murray et al. (2016)	Prenatal alcohol	3509	7	NR	ADHD symptoms (SDQ)[P]	Pelotas birth cohort (Brazil)	Maternal self-report of alcohol use at time of birth

Study	Risk factors (included)	Sample size	Age at outcome measurement (years)	Male (%)	ADHD outcome measurement (included)[a]	Sample (country)	Parental substance use risk factor measurement
Niclasen et al. (2014)	Prenatal alcohol	29435	7	NR	Hyperactivity (SDQ)[P]	Birth cohort sample of mothers who answered all binge drinking questions (DNBC; Denmark)	Mother self-report of binge drinking during pregnancy; prenatal interviews
Oades (2011)	Prenatal alcohol	54	10.6	82.1	Diagnosis (semi-structured interview: Parental Account of Children's Symptoms)[P]	Research study of children diagnosed with ADHD; controls recruited through advertisement (Germany)	Retrospective mother self-report of alcohol and recreational substance use during pregnancy; self-completed questionnaire
O'Callaghan et al. (2007)	Prenatal alcohol	4354	14	NR	Inattention (CBCL)[P]	Birth cohort (MUSP; Australia)	Mother self-report of alcohol use during pregnancy; prenatal interview and postpartum interview
O'Leary et al. (2010)	Prenatal alcohol	747	5–8	NR	Inattention (CBCL)[P]	Postal research survey of randomly sampled women who gave birth (RASCALS; Australia)	Retrospective mother self-report of alcohol use during pregnancy; postpartum survey
Ornoy (2003)	Prenatal heroin	60	6–12	NR	ADHD Symptoms (Conners Questionnaire)[P]	Research study of children born to and living with heroin-dependent mothers; controls from kindergartens and nurseries (Israel)	Children identified as born to heroin addicted mothers or heroin dependent fathers
Ornoy et al. (2010)	Prenatal heroin	52	12–16	54–55	ADHD symptoms (CRS)[P]	Research study of adolescents with and without prenatal heroin exposure who differed in SES and adoptive status; recruitment from substance use disorder treatment centers, public adoption agency, municipal welfare services, or schools (Israel)	Mothers in drug rehabilitation programs and evidence of heroin use during pregnancy
Park et al. (2014)	Prenatal alcohol	900	6–15	74–85.4	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)	Prospective maternal report of alcohol use starting in pregnancy
Pineda et al. (2007)	Prenatal general substance use, prenatal alcohol	486	7.9–8.3	47–75	Diagnosis (DSM-IV; ADHD checklist, BASC, DICA-PR, DSM-IV ADHD questionnaire)[P]	Clinic-based research study; controls recruited from schools (Colombia)	Retrospective parent report of perinatal factors as part of BASC
Pires et al. (2013)	Prenatal general substance use, prenatal alcohol	370	7.9	51	Diagnosis (CBCL[P], TRF[T])	School-based research study (Brazil)	Retrospective mother self-report of alcohol and other substance use during pregnancy
Pohlabeln et al. (2017)	Prenatal alcohol	15577	2–12	51	Diagnosis (parent report of ADHD)	European IDEFICS prospective multi-center cohort study (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, and Sweden)	Retrospective parent report of maternal alcohol use during pregnancy
Pringsheim et al. (2009)	Prenatal general substance use, prenatal alcohol	353	5–17 (mean 9.9)	77–83	Diagnosis (structured interview for DSM-IV-TR criteria)	Clinic-based case–control research study. Cases had ADHD+ Tourette	Retrospective parent report of maternal alcohol and other substance use during

Study	Risk factors (included)	Sample size	Age at outcome measurement (years)	Male (%)	ADHD outcome measurement (included)[a]	Sample (country)	Parental substance use risk factor measurement
						syndrome (TS); controls had TS only (Canada)	pregnancy as part of demographic form for all new patients
Richardson et al. (2011)	Prenatal cocaine	240	7.2	53	Inattention (CBCL)[P], impulsivity (SNAP)[P]	Follow-up research study of children with or without prenatal cocaine exposure (USA)	Retrospective mother self-report of cocaine use during pregnancy; prenatal interviews and postpartum interview
Rodriguez et al. (2009)	Prenatal alcohol	4968	10–12	51	ADHD symptoms (SDQ)[P,T]	Follow-up of birth cohort (ABC; Denmark)	Maternal self-report of alcohol use during pregnancy; prenatal questionnaire
Rodriguez et al. (2009)	Prenatal alcohol	7844	7–15	51	ADHD symptoms (SDQ)[P]	Follow-up of birth cohort (HHT; Denmark)	Maternal self-report of alcohol use during pregnancy; prenatal questionnaire
Rodriguez et al. (2009)	Prenatal alcohol	8525	7–8	51	ADHD symptoms (Rutter Scale)[T]	Follow-up of birth cohort (NFBC; Finland)	Maternal self-report of alcohol use during pregnancy; prenatal questionnaire
Romano et al. (2006)	Prenatal alcohol	15,468	0–1.9	51	Hyperactive symptoms (adapted from CBCL)[P]	National survey (NLSCY; Canada)	Retrospective maternal self-report of alcohol use during pregnancy; home interview
Rückinger et al. (2010)	Prenatal tobacco, postnatal tobacco	2862	10	51	ADHD symptoms (SDQ)[P]	Birth cohort (GINI; Germany)	Retrospective maternal self-report of smoking during pregnancy and parent report of tobacco smoke exposure in the home; at-birth and follow-up questionnaires
Sagiv et al. (2013)	Prenatal general substance use, prenatal alcohol	604	8.2	NR	Diagnosis (medical record), ADHD symptoms (CRS)[P,T]	Birth cohort (New Bedford Cohort; USA)	Retrospective maternal self-report of alcohol and illicit substance use; postnatal questionnaire
Savage et al. (2005)	Prenatal cocaine	80	10.2	42–18	Diagnosis (ASEBA)T, impulsivity (GDS Delay Task)[C]	Research study of cocaine-exposed and control children (USA)	Maternal self-report of cocaine use during pregnancy obtained from enrollment interview and medical record review; screening of maternal and infant urine for cocaine metabolites
Schmitz et al. (2006)	Prenatal alcohol	200	11.7–11.8	68	Diagnosis, inattentive type (K-SADS-E[P], SNAP-IV[T])	Case–control study; school-based recruitment (Brazil)	Retrospective maternal self-report of smoking during pregnancy; postnatal interview
Schuckit et al. (2000)	Parental substance use disorders	94	7–22	51	Diagnosis (CBCL)[P]	Research study of children born to fathers with or without alcohol use disorder (USA)	Parent history of alcoholism
Sciberras et al. (2011)	Prenatal alcohol	3781	6.8	51	Diagnosis (parent report of ADHD)[P]	Nationally representative population-based study (LSAC; Australia)	Primary caregiver report of maternal alcohol use during pregnancy; self-completed questionnaire
Sood et al. (2001)	Prenatal alcohol	501	6.9	51	Inattention (CBCL)[P]	Research study of children born to women with differing levels of alcohol consumption during pregnancy (USA)	Maternal self-report of alcohol use during pregnancy; prenatal interviews
Sood et al. (2005)	Prenatal cocaine	506	6.9	51	Inattention (CBCL)[P]	Research study of children born to women with differing levels of alcohol consumption during pregnancy (USA)	Maternal self-report of cocaine use during pregnancy on prenatal interviews or at follow up; prenatal or neonatal medical history of

Study	Risk factors (included)	Sample size	Age at outcome measurement (years)	Male (%)	ADHD outcome measurement (included)[a]	Sample (country)	Parental substance use risk factor measurement
							cocaine use; or positive biologic test during prenatal visit or at delivery
Stanger et al. (1999)	Parental substance use disorders	538	4–18	NR	Inattention (CBCL)[P]	Research study of children of drug abusing parents demographically matched to non-referred children (USA and Canada)	Clinical diagnosis of parental substance use disorders
Tanaka et al. (2016)	Postnatal tobacco	1200	5	NR	SDQ[P]	KOMCHS prospective prebirth cohort study (Japan)	Prospective maternal self-report of tobacco use
Tiesler et al. (2011)	Prenatal tobacco, postnatal tobacco	1654	10	52	ADHD symptoms (SDQ)[P]	Birth cohort (LISAplus; Germany)	Retrospective maternal self-report of smoking during pregnancy and of child's tobacco smoke exposure at home; at-birth and postnatal questionnaires
Vidal et al. (2012)	Parental substance use disorders	253	6.0–17.9	53	Diagnosis (K-SADS-E)[P,C]	Clinical research survey/interview of children born to lifetime alcohol- or heroin-dependent parents recruited from psychiatric inpatient or outpatient facilities and of control children recruited from orthopedic facilities (Switzerland)	Parents with DSM-IV lifetime alcohol dependence or heroin dependence were recruited from inpatient and outpatient psychiatric departments
Wang et al. (2019)	Prenatal alcohol, prenatal tobacco, postnatal tobacco	401	8.6	79–84	Diagnosis, (SNAP, clinical interview; DSM-IV)[P]	Community based case–control study (China)	Retrospective report by interview on prenatal and postnatal alcohol and tobacco use
Way and Rojahn (2012)	Prenatal alcohol	42	2.5–14.4	28–18	Diagnosis (CBRS-P)[P]	Research study of exposed children matched with neurotypical children recruited from preschools and after-school programs (USA)	Children with clinically confirmed prenatal alcohol exposure
Wiggs et al. (2016)	Prenatal general substance use, prenatal alcohol	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)	Retrospective parent report on maternal use of alcohol and other substances during pregnancy
Wilens et al. (2005)	Parental substance use disorders	99	11.6	57	Diagnosis (K-SADS-E)[P,C]	Clinical research survey/interview of children born to with a lifetime substance use disorder and of control children born to parents recruited from employee pool of teaching hospital (USA)	Parents recruited at outpatient methadone clinic or alcohol treatment center
Yoshimasu et al. (2009)	Prenatal alcohol	360	9.9–10.2	47–91	Diagnosis (clinical)	Case–control study; outpatient recruitment (Japan)	Retrospective maternal self-report of alcohol use during pregnancy
Yu et al. (2016)	Prenatal alcohol	207	4–15 (mean 8.9)	57–84	Diagnosis (DSM-IV)	Clinic-based research study (Taiwan)	Retrospective parent report of maternal alcohol use during pregnancy

ABC Aarhus Birth Cohort; *ACTeRS* ADD-H Comprehensive Teacher's Rating Scale; *ALSPAC* Avon Longitudinal Study of Parents and Children; A*SEBA* Achenbach System of Empirically Based Assessment; *BASC* Behavior Assessment System for Children; *C-DISC* computerized Diagnostic Interview Schedule for Children; *C-SSAGA* Semi-Structured Assessment of the Genetics of Alcoholism–Child Version; *CBCL* Child Behavior Checklist; *CBRS* Conners Comprehensive Behavior Rating Scales-parent report; *CHDS* Child Health and Development Studies; *CHEER* Children's Health and Environment Research; *CPRS* Conners Parent Rating Scale; *CPT* Continuous Performance Test; *CRS* Conners' Rating Scales; *DAWBA* The Development and Well-Being Assessment; *DBD* Disruptive Behavior Disorders Rating Scale; *DBRS* Disruptive Behavior Rating Scale; *DICA-C* Diagnostic Interview for Children and Adolescents; *DICA-PR* Diagnostic Interview for Children and Adolescents parent report; *DISC* Diagnostic Interview Schedule for Children; *DSM-III-R* Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, 4th edition; *DNBC* Danish National Birth Cohort, *GDS* Gordon Diagnostic System; *GINI* German Infant Nutrition Intervention; *GPP* Groningen Perinatal Project; *HHT* Healthy Habits for Two; *K-ARS* Korean ADHD rating scale; *K-SADS-E* Kiddie Schedule for Affective Disorders and Schizophrenia-Epidemiological version; *K-SADS-PL* Kiddie Schedule for Affective Disorders and Schizophrenia-present and lifetime version; *LDPS* Lifestyle During Pregnancy Study; *LSAC* The Longitudinal Study of Australian Children; *MCS* Millennium Cohort Study; *MHPCD* Maternal Health Practices and Child Development Study; *MLS* Maternal Lifestyle Study; *MPCS* The Miami Prenatal Cocaine Study; *MTA* Multimodal Treatment Study of Children; *MUSP* Mater-University of Queensland Study of Pregnancy; *NFBC* Northern Finland Birth Cohort; *NLSCY* National Longitudinal Survey of Children and Youth; *NR* not reported; *OPPS* Ottawa Prenatal Prospective Study; *PBQ* Preschool Behaviour Questionnaire; *PSQ* Conners Parent Symptom Questionnaire; *RASCALS* Randomly Ascertained Sample of Children born in Australia's Largest State; *RBPC* Revised Behaviour Problem Checklist; *SBQ* Social Behavior Questionnaire; *SDQ* Strengths and Difficulties Questionnaire; *SNAP* Swanson, Nolan, and Pelham Rating Scale; *SREDS* Self-Report Early Delinquency Scale; *TEACh-5* Test of Everyday Attention for Children at Five; *TRAILS* TRacking Adolescents' Individual Lives Survey; *TRF* Teacher Report Form

[a] Source of information: P parent or caregiver, C child, T teacher

[b] Age was reported as school grades (grades 11–13)

Table 2

Meta-analysis results of studies examining discrete child attention-deficit/hyperactivity disorder (ADHD) outcomes for selected parental substance use and substance use disorders risk factors

Risk factor	Outcome type	Overall		Diagnosis only		Inattention		Hyperactivity/ impulsivity	
		Sample size (studies)	ES[1] (95% CI)	Sample size (studies)	ES[1] (95% CI)	Sample size (studies)	ES[1] (95% CI)	Sample size (studies)	ES[1] (95% CI)
Prenatal cannabis exposure	Continuous	5201 (4)	0.04 (0.01; 0.07)[a]			5201 (4)	0.06 (0.02; 0.10)[a]		
Prenatal cocaine	Dichotomous	789 (3)	1.13 (0.50; 2.52)						
exposure	Continuous	2806 (7)	0.06 (0.02; 0.10)[a]			3848 (7)	0.09 (0.05; 0.13)[a]	1308 (4)	−0.03 (∓0.16; 0.10)[b]
Prenatal heroin exposure	Continuous	1074 (3)	0.07 (∓0.10; 0.24)						
Prenatal general substance use exposure	Dichotomous	4576 (7)	1.34 (0.75; 2.40)	2154 (5)	1.21 (0.60; 2.44)				
Prenatal alcohol	Dichotomous	135732 (42)	1.62 (1.33; 1.97)[a,b]	42,747 (25)	1.68 (1.23; 2.29)[a,b]	6868 (6)	1.41 (0.80; 2.48)	53,034 (4)	1.22 (0.87; 1.72)
exposure	Continuous	24,392 (20)	0.09 (0.05; 0.13)[a,b]			4313 (13)	0.21 (0.10; 0.32)[a,b]	11,995 (11)	0.18 (0.09; 0.27)[a,b]
Prenatal tobacco	Dichotomous	17593 (11)	1.67 (1.23; 2.26)[a]	7312 (6)	1.74 (1.15; 2.62)[a]				
exposure	Continuous	8965 (7)	0.11 (0.03; 0.19)[ab]					2661 (4)	0.17 (0.08; 0.26)[a,b]
Postnatal tobacco	Dichotomous	9208 (9)	1.45 (1.05; 2.00)[a]	1773 (4)	1.48 (0.88; 2.50)				
exposure	Continuous	3990 (5)	0.14 (∓0.01; 0.29)[b]			1887 (3)	0.09 (0.04; 0.14)[a]		
Parental substance use disorders	Dichotomous	7306 (9)	2.71 (1.68; 4.38)[a]	6768 (8)	2.90 (1.68; 5.00)[a]				

[1] *ES* effect size (odds ratio (OR) for dichotomous outcomes and correlation coefficient (CC) for continuous outcomes), *95% CI* 95% confidence interval

[a] Effect size significant at $p < 0.05$

[b] Cochran's *Q* tests of heterogeneity statistically significant at $p < 0.05$