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Update on Environmental Risk Factors for Attention-Deficit/ Hyperactivity Disorder

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurobehavioral disorder affecting 5% to 10% of children. Although considered to be a highly familial disorder, ADHD heritability estimates of 60% to 80% highlight the considerable role that environmental factors may still play in disorder susceptibility. Proposed ADHD environmental risk factors include prenatal substance exposures, heavy metal and chemical exposures, nutritional factors, and lifestyle/psychosocial factors. This paper reviews the literature published in 2010 investigating the association between environmental risk factors and ADHD or related symptomatology. Sources of risk factor exposure and the proposed mechanism by which each exposure is linked to ADHD-related neurobehavioral changes are also reported. Methodologic limitations of the current literature are discussed, and guidelines for future study are proposed. An improved understanding of the role that environmental factors play in ADHD etiology is critical to future ADHD prevention efforts.

Keywords

ADHD; Attention-deficit/hyperactivity disorder; Hyperactivity; Inattention; Environment; Environmental exposures; Adverse effects; Risk factors; Gene–environment interactions; Pregnancy; Prenatal; Nutrition; Diet; Psychosocial adversity; Lead; Heavy metals; Chemicals

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent psychiatric disorder characterized by difficulties with attention, impulsivity, and/or overactivity, and associated with impaired social, academic, adaptive, and occupational functioning [1]. Although evidence indicates that ADHD is a highly familial disorder, environmental and other modifiable risk factors also have been implicated [2]. These include prenatal substance exposures, heavy metal and chemical exposures, nutritional factors, and lifestyle/psychosocial factors. This paper reviews the literature published in 2010 investigating the association between ADHD or ADHD-related symptoms and environmental risk factors. For each risk factor, we review 1) the proposed mechanism by which the exposure is linked to ADHD-related neurobehavioral changes (Table 1) sources of risk factor exposure (Tables 2 and 3) the 2010 publications' design and findings and their contextualization within the earlier literature.

Substance and Medication Use During Pregnancy

Prenatal Tobacco Exposure

In 2010, four studies evaluated the association between prenatal tobacco exposure (PTE) and subsequent development of childhood ADHD. Utilizing a large, Swedish, population-based cohort (*N*=982,856), Lindblad and Hjern [3] found a dose-dependent relationship between PTE, assessed prospectively at prenatal medical visits, and risk of ADHD medication use in offspring (used as a proxy for ADHD diagnosis). However, when analyzing multiple births for the same mother with different smoking behaviors during each pregnancy, there was no longer a significant link between PTE and ADHD, suggesting that the observed association between smoking and ADHD may be a result of genetic confounding. The three other studies ascertained PTE retrospectively by maternal self-report, which is subject to possible recall and social desirability bias [4–6]. Nomura et al. [4] evaluated the association between both maternal and paternal smoking during pregnancy and ADHD-related behaviors in preschool children (*N*=209) in New York and found that maternal smoking during pregnancy was associated with an increased risk of offspring ADHD, but paternal smoking was not. In a case-control study, Motlagh et al. [5] (*N*=222) found that maternal smoking during pregnancy was associated with an increased odds of subsequent development of ADHD. In a Dutch cross-sectional study of children with tic disorders (*N*=75), Bos-Veneman et al. [6] found that the combination of exposure to prenatal smoking and having a first-degree relative with a mental disorder was associated with greater ADHD symptoms (particularly hyperactivity/impulsivity), but exposure to smoking alone was not, suggesting a gene–environment interaction. In summary, the findings of Nomura et al. [4] and Motlagh et al. [5] are consistent with the majority of published research indicating a positive association between PTE and ADHD [2]. However, the results from Lindblad and Hjern [3] and Bos-Veneman et al. [6] suggest that the relationship between PTE and ADHD may be influenced and/or confounded by familial factors, which is consistent with recent work by Thapar et al. [7] using a novel, genetically sensitive study design.

Additionally, two 2010 review articles examined the prior evidence regarding whether genetic makeup influences susceptibility to ADHD in the setting of PTE (ie, gene–PTE interactions) [8••, 9]. These articles by Nigg et al. [8••] and Wermter et al. [9] reviewed many of the same studies, and both concluded that findings have been inconsistent, with the notation that studies finding no gene–PTE effect relied on retrospective reports of maternal smoking, whereas prospective studies did identify significant gene–PTE interactions. Nigg et al. [8••] calculated small pooled effect sizes for dopamine receptor D4–PTE and dopamine transporter (DAT)–PTE effects on ADHD (0.14 and 0.27, respectively).

Prenatal Alcohol Exposure

One 2010 study evaluated the association between prenatal alcohol exposure (PAE) and later development of ADHD symptoms, while two review articles examined gene–PAE interactions [8••, 9]. In the Bos-Veneman et al. [6] Dutch sample of children with a tic disorder (*N*=75, see above), PAE was not associated with increased ADHD symptoms. This study's strengths included use of a standardized ADHD rating scale and adjustment for PTE, perinatal/delivery complications, and family mental health disorders. However, weaknesses included the small sample composed only of children with tic disorders, limiting both power and generalizability; retrospective assessment of PAE by parental report; and high use of psychotropic medications (53%), which may have affected ADHD symptom severity. The results from the Bos-Veneman et al. [6] study are not consistent with a prior body of literature documenting a positive association between PAE and ADHD, although similarly negative studies also have been reported [10]. As reported in review articles by Nigg et al. [8••] and Wermter and colleagues [9], results appear inconsistent for gene–PAE joint effects on ADHD susceptibility, with a small pooled effect size (*d*=0.16) for DAT–PAE interactions.

Prenatal Exposure to Illicit Drugs

Although some previous studies suggest that prenatal exposure to marijuana, cocaine, amphetamines, and heroin may be associated with an increased risk of childhood behavioral problems, including ADHD [11–14], we identified only one 2010 publication evaluating the relationship between fetal illicit drug exposure and ADHD. In a cross-sectional study of Israeli adolescents (*N*=191), Ornoy et al. [15] evaluated the impact of fetal heroin exposure and did not find a clear pattern of increased ADHD symptomatology in adolescents exposed to heroin in utero, although the study was unable to disentangle the effects of heroin from psychosocial and genetic confounders.

Prenatal Caffeine Exposure

Bekkhus et al. [16] examined the association between maternal-reported prenatal caffeine exposure (PCE) and inattentive and hyperactive symptoms in 18-month-old children. Study strengths included a large, population-based sample (*N*=25,343) and prospective data collection on caffeine exposure from two prenatal time points, while limitations included the inability to assess ADHD diagnostic status due to participants' young age. After controlling for confounders, they found a small adverse effect of PCE on overactivity at the 17th and 30th gestational weeks. These findings contrast with those of two prior studies on PCE and ADHD that found no significant associations [17, 18].

Prenatal Antihypertensive Exposure

In 2010, Pasker-de Jong et al. [19] published the first study investigating the association between prenatal exposure to labetalol and childhood ADHD. This Dutch historical cohort study (*N*=202) compared children exposed to labetalol, methyldopa, and bedrest for maternal hypertension and found that children exposed to labetalol had a significantly higher risk of ADHD (defined by meeting *DSM-III*–defined symptom thresholds on the Child Behavior Checklist) compared with those in the bedrest group. However, no differences were observed between the labetalol and methyldopa groups. The study had several limitations, including low follow-up rate (57%). Furthermore, failure to control for gestational age and level of hypertension despite treatment group differences in these factors make it difficult to disentangle the effects of medication from those of hypertension itself.

Prenatal Antidepressant Exposure

An observational study of antidepressant use during pregnancy and risk of offspring ADHD at age 5 years used medical claims data from 38,074 US children and families [20]. Prenatal exposure to bupropion was strongly associated with increased risk of ADHD, but selective serotonin reuptake inhibitor exposure was not. Study strengths included controlling for multiple demographic and perinatal factors. Limitations included identifying ADHD cases and covariates (ie, parental mental health diagnoses and smoking during pregnancy) using medical claims data, which may result in false positives and negatives; young participant age, as ADHD is often diagnosed after age 5 years; and lack of correction for multiple comparisons. In addition, because bupropion is used to facilitate smoking cessation, the apparent association between gestational bupropion exposure and ADHD may be due to confounding by PTE (which may not have been adequately controlled for in the analyses due to failure of medical claims data to identify smoking in some expectantmothers). In spite of these limitations, this is the first study to report an association between fetal bupropion exposure and childhood ADHD. Like Figueroa [20], prior studies of fetal selective serotonin reuptake inhibitor exposure have not shown effects on offspring cognition, temperament, or externalizing behaviors [21, 22].

Summary—The 2010 studies evaluating prenatal tobacco, alcohol, heroin, and caffeine exposure, in conjunction with previous studies, do not conclusively implicate them as ADHD risk factors, perhaps due in part to difficulties in accurately measuring exposure (as most studies depended on maternal report) and disentangling the independent effects of exposures from psychosocial and genetic confounders or interactions. Review articles suggest a possible small role for gene–PTE and gene–PAE interactions in ADHD etiology. In 2010, the first studies to identify associations between ADHD and prenatal exposure to labetalol and bupropion were published, but methodologic limitations highlight the need for further investigation.

Heavy Metal and Chemical Exposures

Lead

Three studies in 2010 investigated the link between lead exposure and ADHD. In a cross-sectional study of 667 Korean schoolchildren, Cho et al. [23] found that current blood lead levels were independently associated with teacher, but not parent ratings of inattention, hyperactivity, and ADHD total scores. Nicolescu et al. [24] conducted a cross-sectional study of 83 Romanian children and found that increasing blood lead levels had borderline or significant associations with parent ratings of hyperactivity, impulsivity, and ADHD total scores, as well as teacher ratings of impulsivity and ADHD total scores, even when adjusting for mercury and aluminum co-exposures. Nigg et al. [25] conducted a case-control study (N=236) and found that higher blood levels were associated with higher parent and teacher inattention and hyperactivity-impulsivity ratings, although findings varied depending on the rating scale used and whether children had a history of stimulant medication treatment. Strengths of these studies included adjustment for a range of potential confounders and investigation of the effects of low lead exposure levels, with mean levels in each sample well below the Centers for Disease Control and Prevention action level of 10 μg/dL [23–25]. However, study weaknesses included that each depended on a single concurrent blood lead level, making it difficult to disentangle the effects of earlier childhood levels from current levels. Nonetheless, the findings of these three studies are consistent with a confluence of earlier literature demonstrating an increased risk of ADHD with lead exposure [2].

Manganese

A case-control study by Farias et al. [26] (*N*=166) found that children with ADHD of both the inattentive and combined subtypes had higher serum manganese levels compared with controls, although the study did not control for potential confounders. The findings of Farias et al. [26] were consistent with those of four previous studies of more modest sample size that documented a link between manganese exposure and hyperactive behaviors [27].

Mercury

Nicolescu et al. [24] did not find a significant association between concurrent mercury levels and ADHD symptom scores in a cross-sectional study of Romanian children [28]. Study strengths included adjustment for a large number of possible confounders, including lead co-exposure. However, as no power calculations were presented, it is unclear whether this sample size (*N*=83) had adequate power to detect a significant effect. Nonetheless, the findings of Nicolescu et al. [24] are in agreement with several recent previous studies of more generous sample sizes that did not find a significant relationship between mercury exposure and ADHD-related outcomes [29, 30].

Organochlorines

In a prospective cohort of 607 US children, Sagiv et al. [31] assessed the association between Conners' Rating Scale for Teachers scores at ages 7–11 years and prenatal organo-chlorine exposure (POE). The authors reported that in comparison to children in the lowest quartile of prenatal polychlorinated biphenyl (PCB) and p,p'-dichlorodiphenyldichloroethylene exposure, children in the highest quartile were at 26% to 93% increased risk of displaying ADHD-like behaviors [31], with the exposure outcome estimates strengthened rather than weakened by adjustment for multiple prenatal, family, and child-related ADHD risk factors (including PTE and PAE). This study was the first to investigate the relationship between POE and ADHD symptomatology and is in agreement with prior studies documenting an association between POE and neuropsychological deficits as recently reviewed by Eubig et al. [32••]. An earlier study by Lee et al. [33] did not find a link between current child PCB levels and ADHD, but Lee et al. [33] did not evaluate effects of prenatal exposure, depended on parent reports of child ADHD diagnosis for outcome assessment, and evaluated the effects of only one PCB congener (rather the sum of multiple congeners, as per Sagiv et al. [31]).

Organophosphate Pesticides

In 2010, Marks et al. [34••] and Bouchard et al. [35] documented associations between organophosphate exposure and ADHD symptomatology. Although prenatal organophosphate metabolite (OPM) levels and attention ratings at age 2 years were not linked in a previous study the same Mexican-American prospective birth cohort [36], Marks et al. [34••] (*N*=331) found that prenatal OPM levels and to a lesser extent concurrent child OPM levels were adversely associated with attention at 3.5–5 years age as assessed by maternal report, psychometrician observation, and/or direct assessment, with associations stronger in boys than in girls. Study strengths included longitudinal assessment of prenatal and postnatal OPM levels, as well as multiple attention-related outcomes, while limitations included a possible lack of generalizability, as prenatal OPM levels were higher than average for US childbearing women [34••]. In a cross-sectional, nationally representative US sample of 8- to 15-year-olds (*N*=1,139), Bouchard and colleagues [35] found that for the most commonly detected OPM, children with detectable concurrent levels had twice the odds of developing ADHD—assessed using a standardized diagnostic instrument—compared with those with undetectable levels. Study strengths included generalizability to the US population and adjustment for many potential confounders (eg, PTE, current lead

exposure), while limitations included dependence on a single organophosphate measurement. These findings are consistent with those of earlier study that found an association between prenatal organophosphate levels and child attention/ADHD ratings 3 years of age [37].

Phthalates

In a prospective cohort of US children (*N*=404), Engel and colleagues found an association between third trimester, maternal, low molecular weight phthalate metabolite levels and poorer child scores at 4–9 years of age on the parent-rated Behavior Assessment System for Children attention problems and externalizing problems scales. A significant sex interaction was observed for externalizing behaviors: the adverse effects of phthalate exposure were stronger for boys compared with the full sample but diminished and no longer statistically significant for girls. The Engel et al. study is notable as the first study to investigate the relationship between prenatal phthalate exposure and ADHD-related behaviors. However, limitations included lack of adjustment for other ADHD-related risk factors such as PTE and PAE. Consistent with the findings of Engel et al., a previous study of Korean children found a strong positive association between higher current child phthalate metabolite levels and teachers' ADHD symptom ratings [38].

Polyfluoroalkyl Chemicals

Hoffman et al. [39] (*N*=571) found a dose–response relationship between current polyfluoroalkyl chemical (PFC) levels and parent-reported ADHD in a sample of 12- to 15-year-old participants in the National Health and Nutrition Examination Survey. Study strengths included the use of a nationally representative US sample and adjustment for a range of child, family, and other environmental exposure risk factors (eg, PTE and current lead levels), while limitations included the cross-sectional design—depending on a single, concurrent PFC measurement— and reliance on parent report for ADHD case identification. The findings of Hoffman et al. [39] are consistent with those of earlier animal studies showing neurobehavioral derangements after neonatal PFC exposure [40] but differ from those of the only prior study evaluating PFC exposure effects in children [41]. Fei et al. [41] did not find adverse effects of prenatal PFC exposure on attention and cognition in children at 6 and 18 months of age, but differences in the timing of PFC exposure measurement and participant age at assessment limit comparability to the findings of the Hoffman et al. [39] study.

Summary—Recent and earlier literature support a link between lead exposure and ADHD, and growing but more limited evidence suggests an increased ADHD risk with exposure to manganese, organophosphates, and phthalates. The year 2010 saw the first studies to identify a link between ADHD and prenatal organochlorine and postnatal polyfluoroalkyl exposures, while the available studies thus far do not suggest an association between mercury exposure and ADHD. Intriguingly, some 2010 studies suggest sex–toxicant interactions, indicating that organophosphate and phthalate exposures may pose a greater risk of ADHD-related behaviors in boys as compared with girls.

Nutritional Factors

Maternal Folate Levels

In the first epidemiologic study to assess the association between gestational folate levels and offspring behavior, Schlotz et al. [42] (*N*=100) investigated ADHD-related symptoms in children born to mothers who had measures of red blood cell folate at 14 weeks of gestation and total folate intake in early and late pregnancy. Lower maternal red blood cell folate and total folate intake in early pregnancy were significantly associated with higher child

hyperactivity and peer problem scores at a mean age of 8.75 years. Limitations included high cohort attrition and lack of information on child diet at the time of behavioral assessment, while study strengths included the prospective design and control for PTE and PAE, both of which have been associated with ADHD and low maternal folate levels.

Maternal Obesity

Rodriguez et al. [43] (*N*=1,714) examined the link between maternal obesity and ADHD symptoms in a sample of 5-year-old children from a Swedish, population-based, prospective, pregnancy–offspring cohort. After controlling for a range of child and family factors, maternal pre-pregnancy obesity was found to predict high child inattentive symptoms ratings on teacher, but not maternal questionnaires, with no significant associations observed for hyperactivity or ADHD total symptom scores across raters [43]. These results are consistent with an earlier finding by the same authors, who reported an association between high maternal pre-pregnancy body mass index and core ADHD symptoms in school-aged children in three Nordic prospective cohorts [44].

Iron

Two 2010 publications supported an association between iron deficiency and ADHD [45, 46], while two others did not [47, 48]. The longitudinal study by Corapci et al. [46] of 185 healthy Costa Rican children found that chronic iron deficiency in infancy predicted persistent externalizing problems at 5 and 11–14 years of age. The case-control study by Juneja et al. [45] (*N*=50) in India found that concurrent serum ferritin was significantly lower in children with ADHD compared with controls, although no significant correlation was found between ferritin levels and parent or teacher ratings of inattention or hyperactivity. In contrast to the above studies, a cross-sectional study by Menegassi et al. [47] of Brazilian children and a pilot study by Kiddie et al. [48] of children in Vancouver did not find an association between current iron status and ADHD or related symptoms, although both studies were limited by small sample sizes (*N*=62 and *N*=43, respectively). The mixed nature of the 2010 study findings reflects the prior literature, in which some studies documented a correlation between low iron/ferritin status and ADHD [49, 50], while others did not [51, 52].

Zinc

In a small pilot study (*N*=43), Kiddie et al. [48] showed that serum zinc levels in children with ADHD were lower than US population norms but failed to adjust for the contribution of other ADHD risk factors. Nonetheless, these findings are consistent with those of several earlier studies documenting a link between lower zinc levels and ADHD [53, 54].

Copper

Kiddie et al. [48] (*N*=43, see above) also found that serum copper levels of children with ADHD were significantly lower than US population norms but did not determine if low copper levels remained associated with ADHD if analyses were adjusted for other potential risk factors (eg, zinc levels, socioeconomic status). These findings are consistent with those of one prior study documenting a link between low copper levels and ADHD [55].

Omega-3 Fatty Acids

Kirby et al. [56] found that higher omega-3 fatty acid levels were associated with decreased levels of teacher, but not parent inattention/hyperactivity symptom ratings in a large study (*N*=411) of Welsh children that adjusted for a range of potential confounders. However, potential study weaknesses include lack of adjustment for multiple comparisons (as analyses investigated the relationship between 16 predictors and 15 behavioral rating outcomes),

although the high percentage of significant findings (18%) lends them credence. Many, but not all previous studies have similarly documented an association between ADHD and diminished omega-3 fatty acid levels [57].

"Western" Dietary Patterns

A cross-sectional study of 1,799 Australian adolescents by Howard et al. [58] was to our knowledge the first to investigate the relationship between "Western" dietary patterns and ADHD. The authors found an increased likelihood of an ADHD diagnosis in children who consumed more fat, refined sugars, and sodium and less fiber, folate, and omega-3 fatty acids. Study strengths included adjustment for many prospectively collected prenatal and concurrent covariates, while weaknesses included case identification by parent report of a prior ADHD diagnosis.

Food Additives

A double-blind, placebo-controlled, crossover trial in England conducted by Stevenson et al. [59] (*N*=297) found that food color additives and preservatives (sodium benzoate) were associated with more ADHD symptoms only in children with specific genetic polymorphisms, including those involving histamine degradation. Study limitations included the investigation of only short-term effects of food additive exposure (1 week). Results were mixed in the earlier literature assessing the association between ADHD symptomatology and consumption of color additives and sodium benzoate [60]. A recent US Food and Drug Administration review concluded that "exposure to … artificial food colors and preservatives may be associated with adverse behaviors … in certain susceptible children [60]," although evidence of risk to the general population was considered insufficient to place warnings on foods containing these ingredients.

Summary—Recent studies provide additional evidence for an association between ADHD and low child zinc and omega-3 fatty acid levels. The year 2010 saw the first studies to identify maternal folate levels during pregnancy and childhood "Western" dietary patterns, as well as the second studies to identify maternal obesity during pregnancy and child copper levels as risk factors for child ADHD, although methodologic limitations highlight the need for replication. A novel study suggested that genetic polymorphisms may mediate the effects of food additives on ADHD symptoms, possibly explaining why some prior studies found adverse effects of food additives, while others did not. The evidence linking low child iron levels to ADHD remains inconsistent.

Lifestyle and Psychosocial Factors

Electronic Media Exposure

Two studies evaluated the association between television and video game exposure and ADHD symptomatology. Cheng et al. [61] analyzed data from a longitudinal cohort study in Japan (*N*=316) and found that children with high levels of television viewing at 18 months of age had greater hyperactive and inattention symptoms at 30 months of age compared with those with low exposure. In a cross-sectional study, Swing et al. [62] evaluated the association between hours of television and video game use and attention problems in both school-aged children (*N*=1,323) and young adults (*N*=210) and found an association between higher total screen time (television plus video games) and increased attention problems. However, the study did not evaluate ADHD medication use as a possible confounder and did not assess ADHD symptoms in the school-aged group using a standardized scale [62]. The findings of Cheng et al. [61] and Swing and colleagues [62] are consistent with an earlier study that found an association between increased television viewing at ages 1 and 3 years and attention problems at age 7 years [63], although other

studies have not documented a significant link between television viewing and attention problems [64–66].

Maternal Stress

Two studies investigated the link between prenatal stress and ADHD. Using maternal bereavement as a proxy for stress in a population-based Danish birth cohort (*N*=1,015,912), Li et al. [67] found that boys born to mothers bereaved by the unexpected death of a child or spouse had a 72% increased risk of ADHD, but no increased risk was observed for female offspring. Study strengths included large sample size and adjustment for several perinatal and maternal factors, while limitations included ADHD case identification from medication and hospital records. Martini et al. [68] investigated the impact of maternal *DSM-IV* anxiety disorders and self-perceived distress (SPD) during pregnancy on ADHD in 992 mother–child pairs from a prospective, longitudinal German sample. They found that SPD during pregnancy, but not maternal anxiety disorders, was related to offspring ADHD. Study strengths included the prospective design in a large community sample, use of *DSM-IV*–based diagnostic interview for ADHD identification, exclusion of mothers with pre-pregnancy depression, and analytic adjustment for postpartum depression, while limitations included lack of a psychometrically established instrument to measure SPD and lack of control for additional potential confounders. The findings of Li et al. [67] and Martini et al. [68] are consistent with those of several prior studies that found an association between prenatal stress and increased childhood ADHD symptoms [69].

Early Institutional Care

Two studies compared ADHD symptomatology in children initially placed in institutional care with that of children never placed in an institution. Merz and McCall [70] (*N*=1,380) and McLaughlin et al. [71] (*N*=166) found an association between early institutional rearing and increased ADHD-related symptoms. Study strengths included use of standardized ADHD diagnostic instruments, inclusion of multiple institutional sites in each study, inclusion of different age ranges, and control for a wide array of possible confounders. The results are consistent with previous studies examining the link between early institutional care and ADHD [72].

Early Traumatic Events

Briggs-Gowan and colleagues [73] (*N*=213) found that 24- to 48-month-old children exposed to violence were more than three times more likely to have ADHD—assessed using a standardized diagnostic interview—than unexposed children. Study strengths included a large, ethnically diverse sample and adjustment for multiple contextual risk factors, while limitations included the young participant age at ADHD assessment. These findings are consistent with those of previous studies investigating externalizing problems in children with trauma exposure [74].

General Psychosocial Adversity

Although 2010 publications assessing the main effect of general psychosocial adversity on ADHD risk were not identified, review articles by Nigg et al. [8••] and Wermter et al. [9] evaluated the earlier evidence for interactive effects of genes and psychosocial adversity on ADHD susceptibility, with indicators of psychosocial adversity including low income, in-home discord, and adverse parenting practices. Both reviews indicate greater consistency in joint gene–psychosocial adversity effects on ADHD risk compared with gene–PTE or gene–PAE interactions [8••, 9]. Results suggest that children with certain genetic variations appear more vulnerable to ADHD, particularly with regard to inattentive symptoms, when

experiencing psychosocial stress, with effect sizes for interactions involving DAT and serotonin transporter polymorphisms ranging from d=0.54 to d=0.56 [8••].

Summary—The 2010 literature bolsters concerns that psychosocial adversity (eg, maternal stress during pregnancy, early traumatic experiences, and early institutional care) may increase ADHD risk. Of note, one study suggested that the increased ADHD susceptibility associated with maternal stress may be specific to boys, and reviews of gene–environment interaction studies suggest that those with certain genetic variations may have an increased vulnerability to ADHD in the setting of psychosocial adversity. Although two 2010 studies found a link between electronic media exposure and ADHD symptomatology, results of the earlier literature were mixed.

Conclusions

ADHD heritability estimates of 60% to 80% highlight the considerable role that environmental factors may play in disorder susceptibility [2]. The 2010 literature investigating the association between ADHD and environmental risk factors is substantial and implicates several exposures in ADHD susceptibility. However, these studies have many limitations, making it difficult to draw firm conclusions. For example, outcome assessment is often of concern: some studies assessed ADHD symptomatology in toddlers and preschoolers, which may not correlate with later diagnostic status [75], while others identified cases via caregiver report of a prior diagnosis or medical claims data, which may result in false positives and negatives. Exposure measurement is frequently problematic as well. Many studies do not utilize biomarkers but instead measure exposure by caregiver report, which may be subject to recall and/or social desirability bias. Studies often depend on a single exposure measurement, which may not reflect cumulative lifetime exposures or exposure at the most developmentally critical period. For studies based on concurrent exposure measurements, the temporal relationship with the outcome is unclear, leading to concerns that the exposure may not be independent of child behavior. In the absence of controlled trials, studies cannot definitively determine whether exposures contribute to disorder susceptibility or instead reflect preferences, dietary availability, or living conditions in children with ADHD. In addition, given that not all studies adequately assessed maternal mental health, there are concerns that the relationship between maternal substance use and ADHD may be explained by unmeasured genetic factors (as a propensity to use some substances may be associated with maternal ADHD that is transmitted genetically to the offspring). In addition, although most studies did adjust for some potential confounders, no study to date has considered a fully comprehensive set of environmental predictors. Furthermore, growing evidence suggests that the adverse effects of some ADHD risk factors may be accentuated in or limited to certain groups (ie, males or those with particular genetic variants), but few prior studies have investigated gene–environment or sex–environment interactions.

Given these limitations, further investigation of the relationship between environment risk factors and ADHD is critical. Ideal future studies would be based on prospective, longitudinal birth cohorts with exposure assessment, via biomarkers if applicable, beginning in pregnancy and continuing at intervals throughout childhood. A comprehensive assessment of possible risk factors would occur, as would diagnostic evaluation of parent and child mental health and ADHD status, in samples adequately powered to investigate gene-by-exposure, sex-by-exposure, and even exposure-by-exposure interactions. Although such studies would be monumental in scope and cost, efforts are currently under way. For example, the US National Children’s Study seeks to fulfill the above criteria and recently began to enroll children before birth, with plans to observe 100,000 children until age 21 years [76]. Ultimately, it is hoped that findings from large-scale, rigorous, prospective,

longitudinal cohorts such as the National Children's Study may form the basis for successful interventions that help prevent ADHD through reduction of environmental risk factors.

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Table 1

Proposed mechanism of action for ADHD environmental risk factors investigated in 2010

Risk factor	Proposed mechanism for ADHD-related neurobehavioral effects
Copper deficiency	Decreased availability of DA and NE, as copper is an essential co-factor in their production [48]
Electronic media exposure	Frequent stimulus changes in TV and video games may interfere with ability to stay focused on less attention-grabbing tasks [2]
Folate deficiency in pregnancy	Impaired cellular growth and replication, leading to net reduction in cells and loss of progenitor cells in fetal brain [77]
Food additives exposure	Sodium benzoate: downregulation of tyrosine hydoxylase and DA transporter expression in DA neurons [78]
	Food dyes: neuron membrane dysfunction preventing the uptake of DA and other neurotransmitters, although postmortem tissue analyses of animals fed a blend of all 7 food, drug, and cosmetic (FD & C) dyes showed no effect on brain levels of DA, NE, or Ser [79]
Psychosocial deprivation	Interference with cortical maturation (particularly in the frontal, temporal, and occipital areas) [80]
Iron deficiency	Changes in cortical fiber conduction, DA and Ser systems, and myelin formation [45, 47]
Lead exposure	Disruption of synapse formation; derangements to brain DA system, including reduction of DA neuron branching and length [81]
Manganese exposure	Accumulation of manganese in DA neurons; exposure associated with reduced striatal DA levels [81]
Mercury exposure	Disruption of synaptic transmission; decrease in Ach release and DA levels in striatum and hypothalamus [82]
Obesity during pregnancy	Maternal leptin derangements may affect maintenance and differentiation of neural stem cells in fetal cerebral cortex, including the cingulate cortex [83]; alterations in insulin and interleukin-6 levels may impair neurodevelopment [84]
Omega-3 fatty acid deficiency	Reduced neuronal size and branching; disruption of DA, Ser, and Ach neuronal release; altered membrane localization and activity for DA receptors and DA, NE, and Ser transporters [85]
Organochlorine exposure	Disruption of brain DA levels and function; possible reduction in circulating thyroid hormone levels [31]
Organophosphate exposure	Disruption of DNA replication and axonal and dendritic growth; perturbation of DA, NE, Ser, and Ach systems [35]
Phthalate exposure	Thyroid hormone derangements; suppression of nerve cell proliferation; downregulation of DA systems [86]
Polyfluoroalkyl chemical exposure	Changes in neuron cell differentiation, brain proteins tau and synaptophysin, thyroid hormone levels, and Ach system [39, 87]
Prenatal alcohol use	Reduction in neurons; reduced DA synthesis, uptake sites, and receptor-binding sites in mesolimbic/cortical areas [88, 89]
Prenatal antidepressant use	Inhibition of DA reuptake in fetal brain causing abnormalities in the DA system [20]
Prenatal antihypertensive use	Alteration of placental blood flow; increased risk of SGA birth and neonatal bradycardia, which may affect neurodevelopment [19]
Prenatal caffeine use	Upregulation of adenosine receptors; enhanced DA-induced changes in motor behavior [16]
Prenatal heroin use	Alteration of neuronal cell division/migration; increased fetal neuron apoptosis [90]; altered function of NE and opioid systems [91]
Prenatal tobacco use	Overexpression/desensitization of fetal brain nAChRs affecting the release of DA, Ach, NE, Ser, Glu, and GABA [10, 92]
Stress during pregnancy	Changes in offspring hypothalamo-pituitary-adrenal axis feedback, including altered hippocampus and locus coeruleus neuronal activation [93]
Trauma exposure	Altered development of frontal cortex, cerebellum, hippocampus, and amygdala [2]
Zinc deficiency	Increase in DA transporter activity, as zinc is a noncompetitive inhibitor of substrate (DA) translocation via the DA transporter [94]

Ach acetylcholine; *ADHD* attention-deficit/hyperactivity disorder; *DA* dopamine; *GABA* γ-aminobutyric acid; *Glu* glutamate; *nACHR* nicotinic acetylcholine receptor; *NE* norepinephrine; *Ser* serotonin; *SGA* small for gestational age

Table 2

Sources of exposure for ADHD environmental risk factors: elevated exposure associated with increased risk of ADHD

Risk factor	Sources of exposure
Caffeine	Coffee, tea, soft drinks, chocolate, energy drinks and supplements, and over the counter medications
Electronic media	Television, video games, computers, and hand-held electronic devices
Food additives	Foods preserved with sodium benzoate or colored with artificial dyes
Lead	A heavy metal used in many products–including building materials, paint, pipes, and gasoline–due to its high degree of malleability, ductility, and corrosion resistance. Although U.S. efforts to ban the use of lead in paint and gasoline began in the 1970's, contamination persists in soil, dust, and water. Contamination of children's toys, jewelry, imported candies/foods, folk medicines, cosmetics, and some ceramic glazes also occurs
Manganese	A heavy metal used industrially to prevent rust and corrosion of steel, in iron production, and in power plants. Excess manganese levels have been found in soil, air, water, and plants (particularly soybean and rice)
Mercury	A heavy metal with many industrial uses due to its lack of reactivity with non-oxidizing acids, high electrical conductivity, ability to emit ultraviolet light when excited, and ability to easily form amalgams with other metals. Current primary sources of exposure include emissions from waste incinerators, power plants, and manufacturing, leading to water and food contamination (particularly fish)
Organochlorines/Polychlorinated Biphenyls (PCB)	Synthetic compounds used for their insulating and nonflammable properties in electrical transformers and capacitors, paints, hydraulic fluids, plastics, adhesives, and flame retardants. Although the U.S. banned their production in 1979, PCBs are highly persistent in soil, sediment, and water. The current primary exposure route is consumption of contaminated fish, meat, and poultry
Organophosphates	Synthetic compounds used as the basis of many insecticides, herbicides, and nerve gases, as well as solvents and plasticizers. Current primary exposure routes include direct pesticide exposure or ingestion of contaminated food or drinking water
Phthalates	Synthetic compounds used as plasticizers (substances added to plastics to increase their flexibility, transparency, durability, and longevity); found in plastics, solvents, anti-foam agents, alcohol denaturants, pesticides, tubing, vinyl products, and personal care products such as fragrances, shampoos, cosmetics, and nail polish
Polyfluoroalkyl chemicals (PFC)	Synthetic compounds used for their water repellant, oil repellent and stain resistant properties in food packaging, nonstick pans, paper/textile coatings, carpets, personal care products, industrial surfactants/emulsifiers, and firefighting foams. Due to their extreme resistance to environmental and metabolic degradation, PFC contamination can be found in water, indoor air, and house dust

Table 3

Sources of exposure for ADHD environmental risk factors: insufficient exposure associated with increased risk of ADHD

Risk factor	Dietary sources of exposure
Copper	Liver, turnip greens, crimini mushrooms, molasses, sesame seeds, nuts (cashews, sunflower seeds), legumes, soybeans, and barley
Folate/Folic Acid	Spinach, legumes, fruits (i.e., citrus fruits and juices), broccoli, liver, and fortified grain products
Iron	Red meats, poultry, fish, legumes, soybeans, molasses, spinach, and iron-fortified foods
Omega-3 fatty acid	Fish and fish oils, shellfish, walnuts, flaxseed, soybeans, and canola oil
Zinc	Meat, shellfish, whole grains, legumes, yogurt, and cheese