International Journal of Occupational Medicine and Environmental Health 2012;25(4):330–355
DOI 10.2478/S13382-012-0048-0

EXPOSURE TO ENVIRONMENTAL AND LIFESTYLE FACTORS AND ATTENTION-DEFICIT / HYPERACTIVITY DISORDER IN CHILDREN – A REVIEW OF EPIDEMIOLOGICAL STUDIES

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Abstract
Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children. Although the mechanisms that lead to the development of ADHD remain unclear, genetic and environmental factors have been implicated. These include heavy metals and chemical exposures, nutritional and lifestyle/psychosocial factors. The aim of this review was to investigate the association between ADHD or ADHD-related symptoms and widespread environmental factors such as phthalates, bisphenol A (BPA), tobacco smoke, polycyclic aromatic hydrocarbons (PAHs), polyfluoroalkyl chemicals (PFCs) and alcohol. Medline, PubMed and Ebsco search was performed to identify the studies which analyze the association of prenatal and postnatal child exposure to environmental toxicants and lifestyle factors and ADHD or ADHD-related symptoms. The review is restricted to human studies published since 2000 in English in peer reviewed journals. Despite much research has been done on the association between environmental risk factors and ADHD or ADHD symptoms, results are not consistent. Most studies in this field, focused on exposure to tobacco smoke, found an association between that exposure and ADHD and ADHD symptoms. On the other hand, the impact of phthalates, BPA, PFCs, PAHs and alcohol is less frequently investigated and does not allow a firm conclusion regarding the association with the outcomes of interest.

Key words:
Children, Environmental toxicants, Attention–deficit/hyperactivity disorder, Inattention, Impulsivity

INTRODUCTION

Attention–deficit / hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children, with an estimated pooled worldwide prevalence in children and adolescents of 5.3% (95% CI: 5.0–5.6) [1]. When the children are considered alone, the range for prevalence is about 5–10%, whereas when adolescents are considered by themselves, the range is lower (about 2.5–4%) [1,2]. Like many other childhood–onset behavioural disorders, ADHD is diagnosed more frequently in boys than girls [3,4]. Children diagnosed with ADHD are a heterogeneous population sharing common symptoms, including inattention, impulsivity, and, in some cases, hyperactivity, or a combination of

This study was performed under the project "Prenatal and postnatal exposure to tobacco smoke, PAHs and heavy metals and the risk of respiratory diseases, allergy and poor mental and physical development" supported by the grant PNRF-218-AI-1/07 from Norway through the Norwegian Financial Mechanism within the Polish-Norwegian Research Fund and project "Phthalate exposure and birth outcome and child neurodevelopment" supported by the grant UMO-2011/01/B/NZ7/06462 from National Science Centre.
Received: May 8, 2012. Accepted: July 6, 2012.
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the symptoms. Inattention is identified when child is easily distracted and unable to keep his/her mind on single task for extended periods of time. Impulsivity can be recognized by lack of control or restraint and hyperactivity by child's constant restlessness. Children with ADHD are at increased risk for conduct disorder, antisocial behaviour and drug abuse later in life [3,5,6]. Although the mechanisms that lead to the development of ADHD remain unclear, genetic and environmental factors have been implicated. These include heavy metals and chemical exposures, nutritional and lifestyle/psychosocial factors.

This paper reviews the literature published since 2000 investigating the association between ADHD or ADHD-related symptoms and widespread environmental factors such as phthalates, bisphenol A (BPA), tobacco smoke, polycyclic aromatic hydrocarbons (PAHs), polyfluoroalkyl chemicals (PFCs) and alcohol.

Criteria for inclusion of studies into the review

Medline, PubMed and Ebsco search was performed to identify the studies which analyze the association of prenatal and postnatal child exposure to widespread environmental toxicants and ADHD or ADHD-related symptoms. Relevant studies were also identified via review of references cited in all published studies. The review is restricted to human studies published since 2000 in English in peer reviewed journals. The following keywords were used to identify relevant papers: ADHD, hyperactivity, inattention, impulsivity, pregnancy, prenatal period, child, environment, environmental exposures, chemicals, lifestyle factors, maternal smoking, passive smoking, PAHs, phthalates, BPA, PFCs and alcohol. For each factor we reviewed:

- study design and population,
- sources of exposure and methods used for its assessment,
- assessment of ADHD or ADHD-related symptoms,
- confounding factors included in analysis,
- the proposed mechanism by which the exposure is linked with ADHD-related neurobehavioural changes.

Out of total 72 articles identified, 40 meet eligibility criteria and have been included in the present review.

PHTHALATES AND ADHD OR ADHD SYMPTOMS

Phthalates are a family of industrial chemicals that have been used for a variety of purposes. They are added to plastics applied in the manufacture of children's toys and medical devices to make them soft and flexible as well as added to cosmetics as a vehicle for fragrance. Because phthalates are ubiquitous in daily life, the potential consequences of human exposure to phthalates have raised concerns in the general population. Animal studies have also reported that some phthalates might cause hyperactivity similar to the clinical syndrome of ADHD found in children [7].

Several mechanisms of adverse neurodevelopmental outcomes in humans exposed to phthalates are postulated. Phthalates may interfere with the thyroid hormone system [8,9], lipid signal transduction pathways [10], decrease the number of midbrain dopaminergic neurons, reduce tyrosine hydroxylase biosynthetic activity [11] and tyrosine hydroxylase immunoreactivity [12], and exhibit antiandrogenic activity [13]. Phthalates have been shown to cause hyperactivity in rats, possibly through effects on the dopamine system [12,14].

The first studies investigating the relationship between prenatal phthalate exposure and ADHD-related behaviours and ADHD were published by Engel et al. [15,16] and Kim et al. [17] (Table 1). In the study performed among neonates enrolled into a multiethnic birth cohort at the Mount Sinai School of Medicine in New York City, maternal urinary concentrations of phthalate metabolites and neonatal behaviour measured within 5 days of birth were evaluated. There were strong, inverse associations

between increasing levels of high molecular weight phthalate metabolites (monobenzyl phthalate (MBzP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-(2-ethyl-5-hydroxylhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethylhexyl) phthalate (MEHP), mono-(3-carboxypropyl) phthalate (MCPP)) and attention and orientation scores among girls. Similarly, there was an inverse association between high molecular weight metabolite concentrations and quality of alertness scores among girls [15]. The association of prenatal phthalate exposure with behaviour and executive functioning at 4–9 years of age in the same cohort of children was examined. However, in multivariate adjusted models, increasing $\log_e$ concentrations of low molecular weight phthalate metabolites (monobutyl phthalate (MBP), monoethyl phthalate (MEP), monoisobutyl phthalate (MiBP), monomethyl phthalate (MMP)) were significantly associated only with conduct problems [16].

In childhood, exposures to DEHP metabolites were associated with ADHD in a cross-sectional study of South Korean children between the ages of 8 and 11 years. Significant relationship was also observed between the urine concentrations of metabolites of dibutyl phthalate (DBP) and the number of omission and commission errors in continuous performance tests [17].

As there are only three studies which suggest that exposure to phthalates is associated with ADHD [17] and ADHD behaviours: conduct problems [16] and concentration or orientation [15], it is very difficult to arrive at a conclusion and additional research is necessary.

BISPHENOL A AND ADHD OR ADHD SYMPTOMS

Bisphenol A (BPA) is produced in large quantities and used primarily to manufacture polycarbonate plastics and epoxy resins; it is considered to show weak oestrogen-like properties.

BPA might disrupt the endocrine system [18]. Experimental studies with animals indicated that gestational BPA exposure disrupts normal neurodevelopment, affecting sexually dimorphic behaviours such as aggression, anxiety, exploration, and spatial memory [19–21]. BPA may alter the course of normal neurodevelopment by the impact on neuronal connectivity, distribution of serotonergic fibres, synaptic function, and dendritic length [22].

The effect of exposure to BPA and ADHD behaviours were examined only in two studies performed in the United States [23,24] (Table 1). In the study in Cincinnati, Ohio, among 249 mothers and their children, maternal urine was collected around 16 and 26 weeks of gestation and at birth to measure the level of bisphenol A. An association between mean prenatal BPA concentrations and externalizing scores in females was observed. The strongest association was found between early (below 16 weeks of gestation) urinary BPA concentrations and externalizing scores [23]. The same author continued the study and examined the children at 3 years of age [24]. Gestational BPA exposure was associated with higher scores for measures of anxiety, hyperactivity, emotional control, and behavioural inhibition. Similar to previous findings [23], the effects of gestational BPA exposure on these behavioural domains were larger among girls than boys [24].

Summing up, in the reported studies the exposure to BPA was associated with ADHD behaviours like externalizing problems [24] and anxiety, hyperactivity, weaker emotional control, and impaired behavioural inhibition [24].

However, as noted by Longnecker [25], the results need careful consideration as the hyperactivity and aggression are externalizing behaviours more frequent in boys than in girls [26,27]. Sexually dimorphic behaviours in female rodents have been shown to be masculinized by exogenous estrogens [28], and BPA is weakly estrogenic in most experimental systems [29].

Table 1. Exposure to phthalates and bisphenol A and ADHD or ADHD symptoms

Study population	Type of study	Definition of exposure	Test used	Confounding	Results	References
Exposure to phthalates						
US, New York City: 295 children at 1–5 days	Cohort	Third-trimester maternal urines analyzed for 10 phthalate metabolites (MECPP, MEHHP, MEOHP, MEHP, MBzP, MCPP, MiBP, MBP, MEP, MMP)	BNBAS to children within 5 days of delivery	Race, drug use and smoking during pregnancy, maternal education, age, marital status, prenatal dialkylphosphate pesticide level, caesarian delivery, delivery anaesthesia, examiner	Among girls, there was a significant linear decline in mean Orientation score ($p = 0.02$) and Quality of Alertness score ($p < 0.01$) with increasing urinary concentrations of high molecular weight (HMW) phthalate metabolites	Engel 2009 [15]
US, New York City: 404 women; 188 children at 4–9 years of age	Cohort	Third-trimester maternal urines analyzed for 10 phthalate metabolites (MECPP, MEHHP, MEOHP, MEHP, MBzP, MCPP, MiBP, MBP, MEP, MMP)	Parent-report forms of the BRIEF and BASC-PRS	Race, gender, education and marital status of the primary caretaker, urinary creatinine	Increased $\log_e$ concentrations of low molecular weight (LMW) phthalate metabolites were associated with poorer scores on the: Clinical scale: – aggression: 1.24; 95% CI: 0.15–2.34 – conduct problems: 2.40; 95% CI: 1.34–3.46 – attention problems: 1.29; 95% CI: 0.16–2.41 – depression: 1.18; 95% CI: 0.11–2.24 Composite scale: – externalizing problems: 1.75; 95% CI: 0.61–2.88 – behavioural symptom index: 1.55; 95% CI: 0.39–2.71 – global executive composite index: 1.23; 95% CI: 0.09–2.36 Emotional control scale: 1.33; 95% CI: 0.18–2.49	Engel 2010 [16]
South Korea, Seoul, Seongnam, Ulsan, Yeoncheon: 261 Korean children, at 8–11 years of age	Cross-sectional	4 urine phthalate metabolites concentrations (MEHP, MEOP, MEHP+ MEOP, MNBP)	Teacher-Rated ADHD Rating Scale; Computerized Measurements of Inattention and Impulsivity; IQ Measurement	Children's IQ, age, gender, parental education, SES	Teacher-rated ADHD scores were significantly associated with DEHP metabolites but not with DBP metabolites. Significant relationships were found between the urine concentrations of metabolites for DBP and the number of omission and commission errors in continuous performance tests	Kim 2009 [17]

Exposure to Bisphenol-A						
US, Cincinnati, Ohio: 249 mothers and their children at 2 years of age	Cohort	BPA concentration in urine collected 16 and 26 weeks of gestation and at birth	BASC-2 Parent Rating Scale for preschoolers	Child gender, race, maternal age, education, marital status, depression during pregnancy household income, HOME	Mean prenatal BPA concentrations were associated with externalizing scores, but only among females. Among all children, measurements done at ≤ 16 weeks showed a stronger association with externalizing scores than did measurements taken at 17–21 weeks	Braun 2009 [23]
US, Cincinnati, Ohio: 244 mothers and their children at 3 years of age	Cohort	BPA concentration in urine collected 16 and 26 weeks of gestation and at birth and child (1, 2, 3 years of age) urine samples	BASC-2, BRIEF-Preschool	Race, household income, education, marital status, depressive symptoms during pregnancy, HOME	Each 10-fold increase in gestational BPA concentration was associated with more anxious and depressed behaviour on the BASC-2 and poorer emotional control and inhibition on the BRIEF-P	Braun 2011 [24]

BRIEF – Behaviour Rating Inventory of Executive Function; BASC-PRS – Behaviour Assessment System for Children-Parent Rating Scales; BNBAS – Brazelton Neonatal Behavioural Assessment Scale; HOME – Home Observation for Measurement of the Environment scores; SES – socioeconomic status.
MCPP – mono-3-carboxypropyl phthalate; MEHHP – mono-(2-ethyl-5-hydroxylhexyl) phthalate; MEOHP – mono-(2-ethyl-5-oxo hexyl) phthalate; MiBP – monoisobutyl phthalate; MEP – monoethyl phthalate; MBzP – monobenzyl phthalate; MBP – monobutyl phthalate; MECPP – mono-2-ethyl-5-carboxypentyl phthalate; MEHP – mono-(2-ethylhexyl) phthalate; MMP – monomethyl phtalate; DEHP – di-(2-ethylhexyl) phthalate; DBP – dibutyl phthalate; MEOP – mono-2-ethyl-5-oxohexylphthalate; MMP – monomethyl phthalate; MnBP – mono-n-butyl phthalate; BPA – bisphenol A.

POLYFLUOROALKYL CHEMICALS AND ADHD OR ADHD SYMPTOMS

Polyfluoroalkyl chemicals (PFCs) have been widely used in consumer products and in industrial applications as surfactants and emulsifiers, food packaging, non-stick pan coatings, fire-fighting foams, paper and textile coatings, and personal care products [30,31]. Preliminary data suggest that PFCs may be potential developmental neurotoxicants [32]. Animal studies have indicated that polyfluoroalkyl chemicals may interfere with normal neuromuscular development by inhibiting choline acetyltransferase (ChAT) activity [33,34] or by disturbing lipid metabolism [35].

Hoffman et al. [36] have noticed an association between exposure to PFCs (Perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS)) measured in serum samples in children aged 12–15 years in the United States (Boston, Massachusetts) and ADHD diagnosed by a doctor or health care professional. Exposure to PFOS, PFOA, PFHxS was associated with ADHD. On the other hand, Fei et al. [37] did not find adverse effects of prenatal PFC exposure on attention and cognition in children at 6 and 18 months of age (Table 2).

As there are only two studies on exposure to polyfluoroalkyl chemicals and ADHD and ADHD symptoms (attention problems) and their results are inconsistent, it is difficult to reach the right conclusion. The age of individuals in the study populations may explain the difference in the results. Fei et al. [37] assess the exposure to PFCs and ADHD among children around 6 months and 18 months of age whereas Hoffman et al. [36] assess only children 12–15 years of age. Further investigation into the impact of PFC exposure on ADHD and children's neurodevelopment is needed.

Table 2. Exposure to PFCs and ADHD or ADHD symptoms

Study population	Type of study	Definition of exposure	Test used	Confounding	Results	References
Denmark: 1400 pairs of mothers and children at 6 and 18 months of age	Cohort	Maternal blood level of PFOS and PFOA	Motor and mental development of infants assessed based on mothers' self-report	Maternal age, education, prepregnancy BMI, alcohol consumption during pregnancy	Higher PFOS levels dose not impair children attention	Fei 2008 [37]
US, Boston, Massachusetts: 571 children at 12–15 years of age, within this group 48 children with ADHD	Cross-sectional	PFCs: PFOS, PFOA, PFNA, and PFHxS measured in children's serum	Parental report of a previous diagnosis by a doctor or health care professional of ADHD in the child	Age, gender, race, ETS and maternal smoking during pregnancy	Parentally reported ADHD was significantly associated with exposure to a PFOS, PFOA and PFHxS. Nonsignificant positive association between exposure to PFNA and ADHD	Hoffman 2010 [36]

PFCs – polyfluoroalkyl chemicals; PFOS – perfluorooctanesulfonate; PFOA – perfluorooctanoate; PFNA – perfluorononanoic acid; PFHxS – perfluorohexane sulfonic acid; ETS – environmental tobacco smoke.

Table 3. Exposure to PAHs and ADHD or ADHD symptoms

Study population	Type of study	Definition of exposure	Test used	Confounding	Results	References
US, New York City: 215 mother-child pairs followed from *in utero* to 7–8 years of age	Cohort	PAH–DNA and other bulky aromatic adducts measured in umbilical cord	CBCL	Gender, gestational age, parental ETS, maternal IQ, education, ethnicity, parental demoralization, age at assessment, heating season, HOME	Higher cord adducts were associated with higher symptom scores of anxious/depressed at 4.8 years and attention problems at 4.8 and 7 years, and with anxiety problems at 4.8 years	Perera 2011 [38]

PAHs – polycyclic aromatic hydrocarbons; HOME – Home Observation for Measurement of the Environment; CBCL – Child Behaviour Check List.

POLYCYCLIC AROMATIC HYDROCARBONS AND ADHD OR ADHD SYMPTOMS

Polycyclic aromatic hydrocarbons (PAHs) are one of the most widespread organic pollutants. In addition to their presence in fossil fuels they are also formed by incomplete combustion of carbon-containing fuels such as wood, coal, diesel oil, and tobacco [38]. PAHs have been shown to be neurodevelopmental toxicants in experimental studies [39,40]. Suggested mechanisms include endocrine disruption [41–43], binding to receptors for placental growth factors resulting in decreased exchange of oxygen and nutrients [44], binding to the human Ah receptor to induce P450 enzymes, DNA damage resulting in activation of apoptotic pathways [45–47], epigenetic effects [48], or oxidative stress due to inhibition of the brain antioxidant scavenging system [49]. Only one study on exposure to polycyclic aromatic hydrocarbons and children's ADHD symptoms was performed [38]. In the birth cohort of children born to non-smoking women, the neurodevelopment was assessed at 4–8 years of age. The PAH–DNA and other bulky aromatic adducts were measured in umbilical cord. Higher cord adducts were associated with higher symptom scores of anxious/depressed at 4.8 years, attention problems at 4.8 and 7 years, and with anxiety problems at 4.8 years as defined in Diagnostic and Statistical Manual of Mental Disorders, 4th edition [38] (Table 3).

TOBACCO SMOKE EXPOSURE AND ADHD OR ADHD SYMPTOMS

The association between the exposure to tobacco smoke constituents and behaviour problems in children has been studied from the 1970s [50]. Since then, a lot of original papers and several review articles [2,51–55] have been published on the associations of prenatal maternal active or passive smoking and/or postnatal child environmental tobacco smoke exposure with ADHD or ADHD-related disorders in children of different ages.

The physiological explanation for possible adverse effects of intrauterine exposure is that metabolites from tobacco smoke cross the placenta and the foetus is exposed to a 15% higher nicotine concentration than the smoking mother [56]. The possible mechanism may be modulation of dopaminergic system and increased number of nicotine receptors [57]. Studies on rats demonstrated long-lasting alterations in the structure of hippocampus associated with prenatal exposure to nicotine [57].

Table 4 presents 30 papers, published since 2000, analyzing the association between tobacco smoke exposure and ADHD or ADHD symptoms in children, including 7 papers published in 2010 [6,27,58–85]. The strength of association does differ slightly between studies, although generally it appears that the children of smokers are approximately 1.5–3 times more likely to have ADHD or ADHD symptoms than the children of non-smokers. Some studies which analyzed ADHD symptoms based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or DuPaul Rating Scale indicate the statistically significant association with the exposure to tobacco smoke [58,60–64]. In opposite, the results from Hill et al. [65], Nigg et al. [66], Thapar et al. [67] and Lavigne et al. [68] were not statistically significant. Other studies focusing on the specific symptoms such as hyperactivity and/or impulsivity [69–74], aggressive behaviour [69,72,75,84], attention problems [74,75,77] and externalizing problems [27,75,77–79] generally reported consistent positive association.

Some studies analyzing the impact of tobacco smoke exposure on child ADHD-related symptoms have found independent effects of both pre- and postnatal exposure, but most researchers state that the correlation between maternal smoking in pre- and postnatal period is so high that it is difficult to separate the effects. The results for postnatal exposure are less consistent than for prenatal maternal smoking. Since nicotine is transmitted through breast milk, the effect of maternal smoking during the few months after delivery may be more pronounced than

Table 4. Exposure to tobacco smoke and ADHD or ADHD symptoms

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
US: 99 children at 2 years of age	Cohort	Retrospective assessment of smoking during pregnancy	Three subscales of toddlers' troublesome behaviours: impulsivity, risk taking, and rebelliousness	Maternal age at child birth, maternal alcohol use during pregnancy, marital status, SES, maternal personality attitudes, mother-child relationship	Maternal smoking during pregnancy was related to negativity in the child (OR = 4.2; 95% CI: 1.4–12.5)	Brook 2000 [83]
US, Pittsburgh: 109 children at 8–18 years of age	Cohort	Retrospective report on smoking in pregnancy	ADHD diagnosis based on DSM-III-R and K-SADS-E	Maternal alcohol use, maternal delinquency, parental psychiatric disorder	No statistically significant association between maternal smoking during pregnancy and ADHD (OR = 1.4; 95% CI: 0.5–4.1)	Hill 2000 [65]
US: 672 children at 3 years of age	Cohort	Interview at the end of each trimester of pregnancy and at 3 years postpartum	Oppositional Behaviour, Immaturity, Emotional Instability, Physical Aggression, Activity scale and CBCL	Age, gender, number of siblings, maternal race, age, education, marital status, work status, income, home environment, depression, hostility, self-esteem, current maternal intake of substance of abuse	Impulsivity and peer problems were associated with both prenatal and current tobacco exposure. Current tobacco exposure predicted attention problems	Day 2000 [74]
US, Boston: 522 children at 6–17 years of age (280 cases and 242 controls)	Case-control	Maternal interview	ADHD diagnosis based on DSM-III-R, K-SADS-E	Maternal alcohol use, illicit drugs, SES, parental ADHD, parental IQ, birth weight	ADHD cases were 2.1 times more likely to have been exposed to cigarettes *in utero* than were the non-ADHD control subjects (p = 0.02)	Mick 2002 [61]
US: 4704 children at 4–15 years of age	Cross-sectional	Prenatal and postnatal tobacco exposure based on parent report	Parent report of diagnosis of ADHD and stimulant medication use	Age, gender, race, postnatal ETS exposure, blood lead levels, preschool or child care attendance, health insurance coverage, ferritin level	Prenatal tobacco exposure was significantly associated with ADHD (OR = 2.5; 95% CI: 1.2–5.2) Postnatal ETS exposure was not associated with ADHD (OR = 0.6; 95% CI: 0.3–1.3). The difference in risk by sex was not statistically significant (p = 0.1)	Braun 2006 [6]

US, New York: 203 children at 8–13 years of age	Cohort	Interview with mothers	Aggressive behaviour scale which consists of six items	Demographic factors, maternal unconventional behaviour, low maternal warmth	Maternal smoking during pregnancy was associated with having offspring who were aggressive ($\beta = 0.2$; $p < 0.01$)	Brook 2006 [84]
US, Michigan: 713 children at 6 to 17 years of age	Cohort	Interview with mothers when the child was 6 years of age	Parent and teacher report for ADHD (DSM-III-R)	Birth weight, place of residence, alcohol and drug, maternal education	The association of prenatal smoking exposure with ADHD was highly confounded by family variables (OR = 1.3; 95% CI: 0.9–1.9)	Nigg 2007 [66]
US: 8889 children at 4–10 years of age	National Longitudinal Survey of Youth	Maternal interview about the smoking 12 months prior and during pregnancy	Behaviour Problem Index	Intellectual ability, years of education, income, delinquency, age at first birth	There was a slight association between smoking during pregnancy and ADHD, but the magnitude of the association was greatly reduced by methodological and statistical controls. Unmeasured environmental variables account for the observed associations	D'Onofrio 2008 [78]
US: 2588 children at 8–15 years of age	Cross-sectional	Report of maternal cigarette use during pregnancy	DSM-IV	Age, gender of the child, race, income, preschool attendance, mother's age at childbirth, birth weight	Prenatal tobacco exposure was associated with ADHD (OR = 2.4, 95% CI: 1.5–3.7). Compared with children with neither exposure, children exposed prenatally to tobacco and lead had greater risk of ADHD than would be expected if the independent risks were multiplied (OR = 8.1; 95% CI: 3.5–18.7; tobacco-lead exposure interaction $p < 0.001$)	Froehlich 2009 [58]
US, New York: 209 children at 3–4 years of age	Cohort	Retrospective assessment by questionnaire	ADHD-Rating Scale –IV filled by parents and teachers, K-SADS-PL	Age, gender, race, birth weight, alcohol during pregnancy, SES, mother's and father's ADHD symptoms	Maternal smoking during pregnancy was associated with ADHD (OR = 4.0; 95% CI: 1.4–11.1) and combined ADHD and oppositional defiant disorder (OR = 5.0; 95% CI: 1.5–12.5); for paternal smoking the associations were not statistically significant (OR = 0.3; 95% CI: 0.1–1.9 and OR = 0.9; 95% CI: 0.1–5.6 respectively)	Nomura 2010 [63]

Table 4. Exposure to tobacco smoke and ADHD or ADHD symptoms – cont.

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
US, Yale: 222 children at 7–18 years of age	Case-control	Retrospective report of smoking during pregnancy	Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version, parental report using DuPaul-Barkley ADHD Rating Scale	Gender	Maternal smoking during pregnancy was associated with increased odds of subsequent development of ADHD (OR = 13.5; 95% CI: 1.6–113.2)	Motlagh 2010 [64]
US, Illinois: 679 children at 4 years of age	Cohort	Retrospective report of smoking during pregnancy	Diagnostic Interview Schedule for Children-Parent Scale -Young Child Version, Child Symptom Inventory, DuPaul ADHD Rating Scales, Eyberg Child Behaviour Inventory	SES, life stress, family conflict, maternal depression, maternal scaffolding skills, mother–child attachment, child negative affect and effortful control	Smoking during pregnancy was not associated with child behaviour or emotional problems	Lavigne 2011 [68]
Canada, Quebec: 504 children at 5–42 months of age	Cross-sectional	Interview with mothers after child birth	Physical aggression based on 3 items from rating scale	Gender, siblings, income, marital status, maternal age, education, alcohol, social behaviour, maternal postpartum depression, parent background and family characteristics	Smoking during pregnancy was associated with increased risk of physical aggression (OR = 2.2; 95% CI: 1.1–4.1)	Tremblay 2004 [76]

Canada: 4 data-collection cycles (children at 0–23 months at first cycle and 6–7 years at IV cycle)	Cross-sectional	Interview with mothers after child birth	CBCL	Age at birth of the child, family status and composition, educational level, employment status, household income, maternal depression, child age, child gender, child birth weight, child temperament, alcohol during pregnancy, family dysfunction, parenting practices	Prenatal maternal smoking was associated with the increased risk of hyperactive symptoms in children (OR = 2.8; 95% CI: 1.6–4.6)	Romano 2006 [73]
Canada: 1745 children at 17–42 months of age	Cohort	Questionnaire when the child was 5 months of age	Maternal ratings of child behaviour based on items from the CBCL, the Ontario Child Health Study Scales, and the Preschool Behaviour Questionnaire	Age at birth of first child, family status, presence of siblings, family income, maternal education, alcohol and drug exposure during pregnancy, birth weight, family functioning and parenting, parental background and mental health	Maternal prenatal smoking was associated with physical aggression (PA) but not with hyperactivity-impulsivity (HI) in covariate regression analysis when they were examined separately. Maternal prenatal smoking independently predicted co-occurring elevated levels of PA and HI compared to low levels of both behaviours, to high PA alone, and to high HI alone	Huijbregts 2007 [72]
Denmark: 1355 children at 3.5 years of age	Cohort	Self-administrated questionnaire at 16 and 30 weeks of pregnancy and 3.5 years after delivery	Preschool Behaviour Questionnaire	Maternal age, marital status, parity, educational level at follow-up, caffeine and alcohol intake, parental psychiatric hospitalization, gender of child, birth weight, gestational age, Apgar	Smokers ≥10 cigarettes/day vs. non-smokers: – hyperactive-distractible (OR = 1.7, 95% CI: 1.1–2.6) – hostile-aggressive (OR = 1.3; 95% CI: 0.6–2.8); – anxious-fearful (OR = 1.4; 95% CI: 0.7–2.7)	Markussen Linnet 2006 [69]
Finland and Denmark: 20 936 children at school age	Cohort	Self-reported data on pre-pregnancy and pregnancy smoking habits	Rutter B2 questionnaire, Strength and Difficulties Questionnaire	Gender, alcohol intake during pregnancy, parental education, family structure, SES	Children, whose mothers smoked during pregnancy had an increased prevalence of a high hyperactivity-inattention score compared with children of non-smokers	Obel 2009 [71]

Table 4. Exposure to tobacco smoke and ADHD or ADHD symptoms – cont.

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
Finland: 9357 children at 8 years of age	Cohort	Questionnaire data	Children's Behaviour Questionnaire	Gender, family structure, SES, maternal age, maternal alcohol use	Maternal smoking was associated with hyperactivity (OR = 1.3; 95% CI: 1.1–1.6). The association was particularly notable among children of young mothers with low social standing. The positive dose-response relationship was found	Kotimaa 2003 [70]
Sweden: 290 children at 7 years of age	Cohort	Assessment of smoking and stress at gestational weeks 10, 12, 20, 28, 32 and 36	18 symptoms given in DSM-IV criteria for ADHD reported by mother and teachers	Gender, education, income, maternal age, marital status, birth outcomes	Prenatal exposure to smoking ($\beta = 0.2$, $p < 0.01$) and stress ($\beta = 0.2$, $p < 0.01$) were independently associated with symptoms of ADHD	Rodriguez 2005 [60]
Sweden: 1428 children at 3 years of age; 677 children at 5.5 years of age	Cohort	Questionnaire during pregnancy and when the child was 3 months	Achenbach CBCL	Gender, age of mother, immigrants, life stress score, postnatal depression scale, personality of the mothers	Maternal smoking was associated with externalizing problems, aggressive behaviour, destructive/ delinquent behaviour ($p < 0.05$) but not with internalizing syndromes or attention problems ($p > 0.05$)	Höök 2006 [75]
Sweden: 982 856 children at 6–19 years of age	Cohort	Routine collection by midwife at 8–12 weeks of pregnancy	ADHD medications from Swedish Prescribed Drug Register	Age, year of birth, child gender, country of residence, maternal age, birth order, maternal education, single parent, social assistance, maternal/ paternal psychiatric/ addictive disorders, small for gestational age, low Apgar score	Smoking during pregnancy was associated with ADHD in the offspring but this risk is explained by genetic and socioeconomic confounding. (OR = 1.9; 95% CI: 1.8–2.04 for children of mothers who smoked ≥10 cigarettes/ day during pregnancy in the entire study population; OR = 1.3; 95% CI: 0.95–1.58 when two pregnancies of the same mother were analyzed)	Lindblad 2010 [80]

Norway: 22 545 mothers and their 18-month-old children	Cohort	Questionnaire during 17th week of pregnancy and when the child was 18 months old	8 items from CBCL	Gender, mother's depressed mood, alcohol use during pregnancy, education, marital status, gestational age, birth weight	Threshold effect of smoking ≥10 cigarettes per day during pregnancy on subsequent externalizing behaviours (OR = 1.32, 95% CI: 1.03–1.70). The child's gender did not moderate these effects (OR = 0.98, 95% CI: 0.83–1.16)	Stene-Larsen 2009 [27]
UK: 1452 twin pairs at 5–16 years of age	Population-based sample of twins	Questionnaire about smoking during pregnancy	ADHD symptoms rating by teacher and parents	Social adversity, birth weight, antisocial symptom score	Maternal smoking during pregnancy shows significant association with offspring ADHD symptoms that is additional to the influence of addictive genetic factors and non-shared environmental influences	Thapar 2003 [82]
England: 2082 twin pairs at 5–18 years of age	Population-based twin register	Mother's retrospective report of smoking during pregnancy	Rutter A scale, DuPaul ADHD Rating Scale	Age, gender	Maternal prenatal smoking contributed significant amounts to the variance of ADHD and had a specific influence on each phenotype independent of the effect on the other phenotype	Button 2005 [62]
UK and Massachusetts: 815 families of the children at 4–11 years of age (231 mother-child pairs unrelated, 584 mother-child related pairs)	Natural experiment	Questionnaire with mothers	DuPaul ADHD Rating Scale	Alcohol use in pregnancy, prematurity, current maternal smoking and paternal smoking in pregnancy, income, parent ADHD symptoms	The magnitude of association between smoking during pregnancy and ADHD symptoms was significantly higher in the related pairs ($\beta = 0.1$; $p < 0.02$) than in unrelated pairs ($\beta = -0.05$; $p > 0.1$)	Thapar 2009 [67]
UK and Brazil: 7244 children at 4 years of age	Cohort	Questionnaire during pregnancy collected at perinatal visit	ALSPAC cohort – Strengths and Difficulties Questionnaire; Pelotas cohort – CBCL	Maternal and paternal education, social class, family income, parental psychopathology, birth weight, gestational age, breastfeeding	Significant impact of maternal smoking during pregnancy on conduct/externalizing problems (ALSPAC cohort: OR = 1.2; 95% CI: 1.1–1.5; Pelotas cohort: OR = 1.8; 95% CI: 1.2–2.8)	Brion 2010 [79]

The Netherlands: 1186 children at 5.5–11 years of age	Cohort	Questionnaire during pregnancy and after delivery	Parents' and teachers' assessment of behavioural problems; reading, spelling, and arithmetic performance levels were assessed with short standardised Dutch tests.	Socio-economic civil state of parents, age of mothers during first clinical visit, use of medication during pregnancy, neonatal neurological condition, gestation, birth weight, type of feeding, infectious diseases in the first years of life, child gender	Children of mothers who smoked during pregnancy showed more signs of attention deficit and displayed higher levels of externalizing behaviour ($p < 0.05$)	Batstra 2003 [77]
The Netherlands: 396 children at ages 5, 10 to 11, and 18 years	Cohort	Self-reported prenatal smoking	CBCL, parent-reported internalizing and externalizing problems	Co-occurrence of internalizing and externalizing problems and co-occurrence of pre- and perinatal risk factors, demographic characteristics, maternal mental health, and child social and attention problems	Children whose mothers smoked during pregnancy had increased levels of both internalizing and externalizing problems over the period of ages 5 to 18 years	Ashford 2008 [85]
The Netherlands: 75 children (with a tic disorder) at 6-18 years of age	Cross-sectional	Retrospective report of smoking during pregnancy	DuPaul ADHD Rating Scale	Pregnancy and delivery complications	Combination of exposure to prenatal smoking and having a first-degree relative with mental disorder was associated with a higher hyperactive-impulsive score ($p < 0.01$); exposure to smoking alone was not associated with higher score ($p = 0.5$)	Bos-Veneman 2010 [81]
South Korea 667 children at 8–11 years of age	Cross-sectional	Urinary cotinine level	The teachers and parents completed the Korean version of the ADHD Rating Scales (K-ARS)	Age, gender, birth weight, educational level of the father, maternal IQ, child IQ, residential area, blood lead	There was no statistically significant association between urinary cotinine level and ADHD symptom ($\beta = 0.05$; $p = 0.4$)	Cho 2010 [59]

ADHD – attention-deficit/hyperactivity disorder, SES – socioeconomic status; DSM— Diagnostic and Statistical Manual of Mental Disorders; K-SADS – Kiddie SADS; CBCL – Child Behaviour Checklist.

environmental passive smoking during later postnatal periods and during childhood [75]. For example Day et al. [74] indicated that postnatal (not prenatal) exposure predicted attention problems in 3 years old children. On the other hand, Braun et al. [6] did not find statistically significant association between postnatal ETS exposure and ADHD in 4–15 years old children (OR = 0.6; 95% CI: 0.3–1.3).

Recently, the possibility of genetic factors confounding the study of the effects of smoking during pregnancy on child behaviour outcomes has been raised [86]. Genetic confounding can occur, for example, if mothers with ADHD who are more likely to smoke also transmit genes that predispose the child to developing ADHD. To address genetic confounds, genetically-sensitive designs are needed to estimate the relative contributions of genetic factors and smoking during pregnancy. The results from D'Onofrio et al. [78], Lindblad and Hjern [80], Bos-Veneman et al. [81] suggest that the relationship between prenatal tobacco smoke exposure and ADHD may be influenced and/or confounded by familial factors, such as family history of mental disorders. As the example, the analysis based on large Swedish population-based cohort indicated dose-dependent relationship between foetal exposure to tobacco constituents assessed prospectively at prenatal visit and the risk of ADHD medications use in children at 6–19 years of age (OR = 1.9; 95% CI: 1.8–2.0 for the children of mothers who smoked ≥ 10 cigarettes per day during pregnancy in the entire study population) [80]. However, when the authors analyzed multiple births for the same mothers with different smoking status during each pregnancy, there was no longer statistically significant association between such exposure and ADHD (OR = 1.3; 95% CI: 0.95–1.58). Such results are consistent with a paper published by Thapar et al. [82]. The authors used novel, genetically sensitive study design based on offspring conceived with assisted reproductive technologies recruited from fertility clinics (231 unrelated mother-child pairs and 584 mothers related to their children). They concluded that magnitude of the association between smoking during pregnancy and ADHD symptoms was significantly higher in related pairs ($\beta = 0.1$; $p < 0.02$) than in unrelated pairs ($\beta = -0.05$; $p > 0.1$) which confirmed the inherited effect.

In summary, most of published studies indicated statistically significant association between exposure to tobacco smoke constituents and ADHD or ADHD symptoms, although some of the recent studies have indicated that part of this association can result from genetic and/or socio-demographic and lifestyle factors.

ALCOHOL AND ADHD OR ADHD SYMPTOMS

Maternal alcohol use during pregnancy contributes to a range of effects in exposed children, including hyperactivity and attention problems, learning and memory deficits and problems with social and emotional development [87, 88]. Evidence from animal studies suggests that even a single binge exposure is sufficient to produce neurotoxic effects [89–91]. Ethanol enhances migration of nerve cells, which is hypothesized to be involved in behavioural difficulties in childhood. It also interferes with the production of neuroendocrine hormones, which may perturb brain growth [92].

Six studies examined the association between exposure to alcohol and ADHD and ADHD related symptoms (Table 5). Most of them were performed in the United States: Detroit, Michigan [93,94], Pennsylvania [65], Boston, Massachusetts [61] and one in Canada [73]. A case-control study of prenatal exposure to alcohol found that cases of ADHD were 2.5 times more likely to have been exposed to alcohol *in utero* than were the non-ADHD control subjects; however, when adjusted for confounders, the results were not significant [61]. In addition, adverse effects of prenatal alcohol exposure on aggressive and externalizing behaviour in particular, at age 6–7 years were found evident even at low levels of exposure (one

alcoholic beverage a week), and showed dose–response effects after control for confounding factors [93]. Also in the study performed by Delaney-Black V et al. [94] prenatal exposure to alcohol was associated with higher total score for externalizing problem (aggressive, delinquent), increased attention problems, and more delinquent behaviours. However, in the study of 150 children/adolescents, prenatal alcohol exposure had no impact on ADHD after adjustment for familial risk of alcoholism, intrauterine exposure to smoking, maternal current alcohol intake, or information on alcohol and parental psychopathology [65]. Also in the study performed in Canada, prenatal maternal drinking was not associated with increased risk of hyperactive symptoms in children [73].

The results of the studies on alcohol exposure and ADHD and ADHD symptoms are inconsistent. Whereas some of them suggest the link between exposure and externalizing and aggressive behaviours [93,94], increased attention problems, more delinquent behaviours [94] and ADHD [116], others [65,73] do not find association between alcohol exposure and hyperactive symptoms in children.

SUMMARY OF THE STUDY RESULTS

ADHD is a complex disorder with great heterogeneity in the behavioural symptoms presented and brain functions and structures affected [2]. ADHD heritability, estimated at 60% to 80%, highlights the considerable role of environmental factors in disorder susceptibility [55,95]. Despite much research has been done on the association between environmental risk factors and ADHD or ADHD symptoms, results are not consistent. Most studies in this field focused on exposure to tobacco smoke and mostly indicated positive association with ADHD and most of its symptoms. On the other hand the impact of phthalates, BPA, PFCs, PAHs and alcohol is less frequently investigated and does not allow for firm conclusion regarding the association with outcomes of interest. Table 6 presents the summary of the impact of different environmental toxicants on ADHD or ADHD symptoms. The increased risk of ADHD was noticed in some studies on the exposure to tobacco constituents [6,58,60–64,82], although a few of them did not give statistically significant results [65–68,80,81]. Statistically significant association was noted between ADHD and phthalates [17] and PFCs [36] exposure. Regarding the exposure to alcohol, the results are not consistent. The attention problems were identified among children exposed to PAHs [38] and alcohol [94] and in two studies on tobacco exposure [74,77]. Results of most studies on the impact of exposure to tobacco smoke on impulsivity and hyperactivity were positive [69–71,73,74]. Additionally most studies focusing on the prenatal exposure to tobacco smoke or alcohol indicated higher risk of aggressive behaviour [72,75,76,84,93,94] or externalizing problems [27,75,77,79,85,93,94]. Individual difference in vulnerability to chemical contaminants is one potential source of variability in the observed dose-effect relationship. Also genetic polymorphisms can contribute to individual risk from contaminant by affecting toxicokinetic or toxicodynamic variability [96].

Because the studies used different instruments and measured behaviour problems rather than ADHD (some lacking validation), a clear picture does not emerge concerning the link between exposure to environmental factors and symptoms specifically related to ADHD. ADHD terminology has undergone significant changes over the past decades [1]. The ICD-10 and DSM-IV criteria provide very similar list of symptoms but recommend different ways of establishing diagnosis. The ICD-10 requires a minimum number of symptoms in all three dimensions (inattention, overactivity, and impulsivity), additionally it requires that all criteria are met in at least two different situational contexts and includes mood, anxiety, and developmental disorders as exclusion diagnoses. The DSM-IV defines only two dimensions (with hyperactivity and

Table 5. Exposure to alcohol and ADHD or ADHD symptoms

Study population	Type of study	Definition of exposure	Test used	Confounding	Results	References
US, Detroit: 665 children at 6–7 years of age and their families	Cohort	Prenatal alcohol exposure was computed as the average absolute alcohol per day across pregnancy	Wechsler Preschool and Primary scale of Intelligenc – Revised Achenbach CBCL	Maternal age; education; cigarette, cocaine, and other substances of abuse; and the gestational age of the infant. Postnatal factors studied included maternal psychopathology, continuing alcohol and drug use, family structure, SES, children's lead level, and exposure to violence	Higher mean scores on externalizing and aggressive behaviours were observed at low levels of prenatal alcohol exposure, whereas for delinquent and total problem behaviours, higher mean scores were observed at moderate/ heavy levels of exposure	Sood 2001 [93]
US, Detroit: 474 parent-child dyads at 6 years of age (201 exposed)	Case-control	Drinking during pregnancy: ounces of alcohol intake/day	Achenbach CBCL	Gender, other prenatal exposures; home-environment variables	Prenatal exposure to alcohol was associated with higher total score for externalizing problem (aggressive, delinquent) increased attention problems, and more delinquent behaviours	Delaney-Black 2000 [94]
US, Pittsburg: 150 children with high or low risk for developing alcohol dependence because of their familial burden of alcoholism	Cohort	No assessment	Annual assessment of offspring: in-depth psychiatric interview	Maternal smoking during pregnancy, familial risk of alcoholism, maternal current alcohol intake, information on alcohol, parental psychopathology	Prenatal alcohol exposure had no impact on ADHD	Hill 2000 [65]

Table 5. Exposure to alcohol and ADHD or ADHD symptoms – cont.

Study population	Type of study	Definition of exposure	Test used	Confounding	Results	References
US, Boston: 280 ADHD cases and 242 non-ADHD controls of both genders	Case-control	Maternal interview	ADHD diagnosis based on a structured diagnostic interview DSM-III-R, K-SADS-E	Familial psychopathology, Rutter's indicators of social adversity, comorbid conduct disorder	ADHD cases were 2.5 times (95% CI: 1.1–5.5) more likely to have been exposed to alcohol *in utero* than were the non-ADHD controls. After controlling for confounders the effect of prenatal exposure to alcohol was not statistically significant	Mick 2002 [61]
Canada, Ottawa: four data-collection cycles (children at 0–23 months at first cycle and 6–7 years at IV cycle)	Cross-sectional	Interview with mothers after child birth	CBCL	Age at birth of the child, family status and composition, education, employment, income, maternal depression, child age, gender, birth weight, temperament, alcohol during pregnancy, family dysfunction, parenting practices	Prenatal maternal drinking was not associated with the increased risk of hyperactive symptoms in children	Romano 2006 [73]

ADHD – attention-deficit/hyperactivity disorder, SES – socioeconomic status; DSM-III-R – Diagnostic and Statistical Manual of Mental Disorders; K-SADS – Kiddie SADS; CBCL – Child Behaviour Checklist.

Table 6. Summary of the impact of environmental toxicants on ADHD or ADHD symptoms

ADHD or ADHD symptoms	Phthalates	BPA	PFCs	PAHs	Tobacco	Alcohol
ADHD	+ Kim, 2009 [17]		+ Hoffman 2010 [36]	+ Perera 2011 [38]	+ Mick 2002 [61], Thapar 2003 [82], Button 2005 [62], Rodriguez 2005 [60], Braun 2006 [6] for prenatal exposure, Froehlich 2009 [58], Nomura 2010 [63], Motlagh 2010 [64] – Hill 2000 [65], Braun 2006 [6] for postnatal exposure, Nigg 2007 [66], Thapar 2009 [67], Lindblad 2010 [80], Bos-Veneman 2010 [81], Lavigne 2011 [68]	+ Mick 2002 [61] – Hill 2000 [65]
Attention problems	– Engel 2010 [16]		– Fei 2008 [37]	+ Perera 2011 [38]	+ Day 2000 [74] for postnatal exposure, Bastra 2003 [77] – Höök 2006 [75]	+ Delaney-Black 2000 [94]
Impulsivity and/or hyperactivity					+ Day 2000 [74], Kotimaa 2003 [70], Marcussen Linnet 2006 [69], Romano 2006 [73], Obel 2009 [71] – Huijbregts 2007 [72]	– Romano 2006 [73]
Anxious and depressed behaviour	– Engel 2010 [16]	+ Braun 2011 [24]		+ Perera 2011 [38]	– Marcussen Linnet [69]	
Aggressive behaviours	– Engel 2010 [16]				+ Thremblay 2004 [76], Brook 2006 [84], Höök 2006 [75], Huijbregts 2007 [72] – Marcussen Linnet 2006 [69]	+ Sood 2001 [93] + Delaney-Black 2000 [94]
Externalizing problems	– Engel 2010 [16]	+ Braun 2009 [23]			+ Bastra 2003 [77], Höök 2006 [75], Ashford 2008 [85], Brion 2010 [79], Stene-Larsen 2009 [27] – D'Onofrio 2008 [78]	+ Sood 2001 [93] + Delaney-Black 2000 [94]

Table 6. Summary of the impact of environmental toxicants on ADHD or ADHD symptoms – cont.

ADHD or ADHD symptoms	Phthalates	BPA	PFCs	PAHs	Tobacco	Alcohol
Delinquent behaviour				+ Höök 2006 [75]		+ Delaney-Black 2000 [94]
Orientation and Quality of alertness	+ Engel 2009 [15]					
Conduct problems	+ Engel 2010 [16]					
Omission and commission errors	+ Kim, 2009 [17]					

"+" – statistically significant association between the exposure to environmental toxicants and ADHD or ADHD symptoms.
"–" – no statistically significant association between the exposure to environmental toxicants and ADHD or ADHD symptoms.

impulsivity symptoms included in the same dimension), and a diagnosis can be made if there is a minimum number of symptoms in only one dimension, it requires the presence of some impairment in more than one setting and the diagnoses may be classified as comorbid conditions [1].

It is important to notice that some studies identified the ADHD or ADHD symptoms in toddlers and preschoolers which may not correlate with later diagnostic status, whereas others identified cases via caregiver report of a prior diagnosis or medical claims. Both situations may result in false positives and negatives [55]. However, previous research indicates that parental reports of ADHD are highly reliable [97].

One key difficulty in identifying the aetiology of the association between variety of environmental risk factors and adverse neurobehavioural outcomes in human studies is the presence of numerous confounders. For appropriate risk assessment it is crucial to have valid assessment of the exposures. In the studies in which exposure status is evaluated from questionnaire data, recall bias can significantly influence the results, especially if evaluated retrospectively. It is also important to note that for some exposures, such as smoking or alcohol consumption, for which detrimental health impacts are well established, the reported exposure levels may be underestimated. Besides the obvious methodological inadequacy of assessing exposure level retrospectively, other limitations include assessing some exposure as dichotomized variable (such as smoking).

Additionally in most studies a single exposure measurement was performed which may not reflect cumulative exposure or exposure at the most developmentally crucial periods [55]. For example mothers who smoke during pregnancy are also more likely to smoke after delivery, so the judgment which exposure period is crucial is difficult. Also most studies continue to focus on one contaminant at a time despite widespread co-exposure to other chemicals which can be potential effect modifiers. Co-exposure could exacerbate, mitigate or mask the toxicity of the exposure

of interest [96]. Few studies have investigated prevalence of child behaviour problems related to ADHD as the function of prenatal stress [56,60]. Those studies indicated that the role of stress should be taken into account. As the example, smokers tend to smoke more under stress and perceived stress increases the likelihood of continued smoking during pregnancy, so it is reasonable to study smoking and stress together [60]. Increased stress, along with reduced resources for coping with stress, is thought to contribute to the increased risk of a variety of physical health problems among individuals [98,99]. Accumulating evidences suggest that stress exacerbates the toxicity of contaminants such as retinoids, sodium arsenate, cadmium sulphate and ethanol [100]. In addition, given that not all studies adequately assess parental mental health, there are concerns that the relationship between analysed environmental factors and ADHD may be explained by non-measured genetic factors. Potentially confounding effects of genetic influences could not be completely ruled out. Recent studies suggest that genetic influences might not be a confounder but might function to increase the susceptibility of the brain to environmental factors [96].

Gender differences have been recently highlighted in research primarily because boys are overrepresented in clinical samples, which may be due to a more manifest clinical presentation in boys [101] and less impairment is seen in girls [102]. It may be possible that both males and females are affected but in different ways [60,103]. The clinical presentation of attention deficit disorder may be manifested in girls as more inattentive-type problems and in boys as more hyperactive and impulsive behaviours [101,104]. A recent meta-analysis reported that differences in brain morphology between youth with ADHD and controls varied by child sex [105].

Some but not all of the limitations stated above have been addressed in prospective studies more frequently conducted in recent years. Ideal future studies would be based on prospective, longitudinal birth cohorts (with the possibility of combined analysis of data from different cohorts) with the exposure assessment via biomarkers, if applicable, beginning in pregnancy and continuing 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 sample adequately powered to investigate gene-by-exposure, sex-by-exposure and exposure-by-exposure interaction.

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