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REVIEW ARTICLE

Prenatal risk factors and genetic causes of ADHD in children

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Abstract

Background Attention deficit/hyperactivity disorder (ADHD) is a common disease among children; it affected 5–7% of the population in 2015. ADHD is a multifactorial disease, and its etiology is still not clearly understood.

Data Sources This narrative review has been done by searching the PubMed and Embase databases using attention deficit/hyperactivity disorder, ADHD, risk factors; genetics; pediatrics; psychiatrics as keywords.

Results ADHD is considered to be a hereditary disorder in which genes play the fundamental role in the pathogenesis; however, findings from genetic–environmental studies support the hypothesis that genetic factors can exert effects on an individual's condition by determining his/her responses to environmental exposures, especially those during the prenatal stage.

Conclusion ADHD is considered as a hereditary disorder in which genes and prenatal risk factors play fundamental roles in the pathogenesis.

Keywords Attention deficit/hyperactivity disorder genetics · Risk factors · Pediatrics · Psychiatrics

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a multifactorial disease that is attributed to a variety of causes which are not yet fully understood. Although a large body of studies have focused on exploring the etiology of ADHD, a definite answer to the mechanism of this disease's development is not available. In 2015, ADHD affected 5–7% of the population [1]; this number increased in recent years, since the update of ADHD's definition in the latest edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2].

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ADHD is classified as a familial neurodevelopmental disorder that is most commonly seen in school children and is characterized by difficulty in problem-solving, paying attention and hyperactivity [3]. Multiple studies have largely investigated the underlying causes leading to ADHD phenotypes. Most of these studies have focused on the environmental, prenatal or postnatal risk factors, which comprise the smaller proportion of ADHD etiology (10–40%) [3].

Despite being responsible for about 70% of ADHD causes, the research on genetic risk factors has been limited and has been growing slowly [4]. Interestingly, the international twin studies on children with ADHD found a hereditary rate ranging from 71% to 90%. The likelihood of having ADHD in first degree relatives of ADHD patients is estimated to be 2 to 8 folds higher than normal individuals [5].

The early investigations on genetic and molecular basis of ADHD were limited to a number of candidate gene studies involved in ADHD pathology [5]. Despite the discovery of specific candidate genes, such as *DRD4*, *DRD5*, *DAT1*, *HTR1B*, *SLC6A4*, *SNAP25*, they were not confirmed as major predictors of ADHD. Genomic wide association studies (GWAS) on common genetic variants were not accompanied with promising findings either [6]. Furthermore, researches on rare genetic variant abnormalities have suggested an overlap between ADHD and other neurological disorders, namely, autism and schizophrenia in terms

of high number of copy number variants (CNVs) in certain chromosomal regions [5].

Environmental risk factors predisposing to ADHD pathogenesis have been widely explored either generally or distinctively. Among them, prenatal risk factors and maternal exposures before birth gained a lot of attention, because they were thought to be involved in completion of the ADHD puzzle. Environmental factors are not independent of genetic ones; in fact, their interaction is commonly referred to as ADHD pathogenesis. Formation of de novo mutations, in addition to epigenetic alterations, has been suggested as a possible role of environmental risk factors but researches are still insufficient [5].

The most commonly cited prenatal risk factors linked to ADHD were maternal smoking during pregnancy, maternal substance and alcohol use, maternal stresses, birth complications (namely, low birth weight and prematurity), and being exposed to chemical substances, such as lead, toxins, pesticides, and drugs [4]; yet these findings are inconclusive.

Generally speaking, ADHD is more a hereditary disorder than an acquired one. Having said that, authors have firmly proposed the concept of "genetic–environmental interaction" in the literature, shedding the light on the interplay between pre- and post-natal risk factors and genetic predisposition.

In spite of the recent reduction in the research rate of ADHD pathogenesis field, some new clinical trials and review studies have yielded important findings that call for a general review of the literature. The present study aims to review the recent literature on genetic and prenatal risk factors of ADHD with an eye on genetic–environmental interplay and the role of genetic predisposition in children who have been exposed to environmental risk factors before birth.

Genetic risk factors of ADHD

Studies have reported different numbers for the role of heritability in ADHD that range from 54% to more than 70% of the causes [7], making ADHD one of the neurodevelopmental disorders with the highest heritability rate [8]. Overall, ADHD is more prevalent in males, but different studies have reported different male to female ratios. Ujjwal et al. reported a male to female ratio of 2.28:1, which is relatively lower than the results of other similar studies; authors have suggested that under-diagnosing female ADHD cases in previous studies was the underlying reason [9].

One study compared the severity of ADHD between offspring of parents who had ADHD and those without; the results were supportive of the inheritable nature of this condition, showing that offspring of parents with ADHD were more likely to develop severe forms. Interestingly, this study did not provide any evidence for a synergistic effect of bi-parental ADHD; in fact, the results suggest that paternal and maternal ADHD status would have different effects on the severity of hyperactive–impulsive and inattentive symptoms in their children [10].

Separate family, twin and adoption studies have concluded that ADHD is more likely to be inherited by children who have a genetic connection. Twin and adoption studies have shown a high heritability rate of 60–90% for ADHD. Siblings and parents of ADHD patients are two to eight folds more affected by ADHD than relatives of healthy individuals. The results from twin studies have shown that monozygotic twins are more concordant in having ADHD than dizygotic twins. In line with these studies, comparing biological parents of ADHD children with their adoptive parents and parents of controlled children without ADHD revealed that the rate of ADHD is highest in biological parents of ADHD children [11]. A 4-year follow-up of siblings of ADHD children was also indicative of ADHD's high heritability rate, because the rate of school failure, as well as neuropsychological and psychosocial dysfunction, was higher in those siblings [12].

Investigating the genome of children and adults with ADHD, Bovicini et al. reported that the genes involved in ADHD pathology, differed in the two age groups [13]. Children who had participated in this study shared some genetic polymorphisms in certain regions of their genome, including genes involved in dopaminergic pathway (*SLC6A3*, *DRD4* and *MAOA*) and neurodevelopmental (*LPHN3* and *DIRAS2*) systems and *OPRM1*. The study also concluded that adults and kids share some genetic abnormalities in terms of oxidative stress proteins (*MAD*, *SOD*, *PON1*, *ARES*, *TOS*, *TAS* and *OSI*), *DISC1*, *DBH*, *DDC*, microRNA and adiponectin genes [13].

Now, it is well known that ADHD is a multifactorial disorder, which occurs mostly due to genetic abnormalities rather than pure environmental factors. However, the exact genetic defects are not fully established. Previous studies tried to find the best gene–trait correlation, using candidate gene studies, genome-wide association studies, copy number variants and more recently epigenetics.

Epigenetic modification during a key developmental period during pregnancy has shown a significant association with environmental insults during or around this period [14]. Mitotic activity is higher in the developmental stages, and therefore, the neurons are more prone to epigenetic modifications after exposure to environmental triggers [15]. Examples of these epigenetic changes include, cytosine methylation in CpG islands that leads to silencing of gene and to compaction of chromatin; histone acetylation, methylation, and phosphorylation; and RNA-mediated modifications with an example being small interfering RNAs that can suppress the activity of specific genes through targeted RNA interference and micro-RNA (miRNA) [14].

Studies have suggested a significant association between severity of behavioral abnormalities of ADHD children with differential methylation patterns in dopaminergic and serotonergic genes [16]. For example, Park et al. reported an increased methylation of the pro-motor region of the serotonin–transporter gene (*5HTT*) associated with more severe ADHD signs and changes in the thickness of occipitofrontal cortex [17]. Similarly, another study found an association between severity of mental disorders, such as ADHD, bipolar disorder and borderline personality disorder and methylation of *5-HT3A* gene [18]. Ding et al. also found an effect of *DAT1* methylation on the responsiveness of ADHD patients to methylphenidate [19].

Candidate gene studies failed to establish certain genetic abnormalities, except for some valuable findings that will be discussed later. The findings from GWAS—which examined the whole genome of ADHD patients and healthy individuals to point out gene polymorphisms—were inconsistent. In the last decades, scientists have accomplished ten GWAS searching for ADHD etiology [20]. The first locus that had been discovered by GWAS was located near genetic regions that were involved in neurodevelopmental processes related to ADHD, including *FOXP2*, *SORCS3*, and *DUSP6* [21]. The most recent GWAS found 12 independent loci of genes that were known to be involved in brain function regulation [22].

Copy number variants (CNV) studies were established recently to find rare (i.e., less frequent than 1% in the general population) genetic variants for ADHD. Although CNV studies were accompanied by new findings on ADHD pathogenesis, they only contributed to 0.2% of ADHD heritability [22]. Most CNVs found to be associated with ADHD, also were linked to the pathogenesis of other psychiatric disorders (namely, autism and schizophrenia), suggesting an overlap in the impaired mechanisms involved in them, such as cell–cell communication, neuronal plasticity and regulation of extracellular matrix [23]. Scientists also found an association between fragile X syndrome, tuberous sclerosis and other microdeletion syndromes, such as Smith Magenis and Velocardiofacial (VCFS; 22q11 microdeletion) syndromes with ADHD, especially the inattentive form [11].

As is typical in multifactorial disorders, the results from different studies do not always come to identical conclusions. Some studies have investigated chromosomal regions expected to exert an effect in ADHD pathology through disrupted neurotransmission, while others have considered genes involved in cell functions, such as cell division, adhesion, and synaptic plasticity. It seems that scientists are more eager to find an association between neurotransmitter signaling pathways defects and ADHD, because most studies have reported dopaminergic, serotonergic, noradrenergic or glutamatergic genes, at least as one of the most common genetic variations seen in ADHD patients. As a matter of fact, most medications used for ADHD would deliberately affect those systems. For example, dopaminergic agonists can improve impulsivity, hyperactivity and inattention. Norepinephrine agonists have the same effects in treating this condition, as well. The impairment of neurotransmitter's pathway disrupts attention, inhibitory control and working memory [24].

Recently, Hayman and Fernandez completed an analysis of the 105 genes that were pooled from the literature and were thought to be most robustly associated with ADHD. Following this analysis, the authors found 14 core genes that showed the most prominent connection with ADHD. These genes were separated into two groups, including nitric oxide synthase and α-1 adrenergic pathways and had enriched expression in the cerebellum and the cortex. They also supported the role of dysfunctional neurotransmission in ADHD. Investigating candidate genes, this study reports that nicotine signaling pathway, *N*-methyl-D-aspartate receptor (*NMDAR*) and cannabinoid pathway were correlated with ADHD pathology, but yet it requires further studies [25].

One study investigated the possible role of dopamine, norepinephrine and serotonin pathways as well as neurite outgrowth genes in ADHD development. The authors concluded that hyperactive/impulsive component of ADHD is affected by the genes involved in these neurohormonal pathways, whereas inattentive traits do not seem to be relevant to them [26].

Scientists found multiple gene associations with ADHD through different approaches. The most robust predisposing genes are: dopamine transporter *DAT1*, *SLC6A3*, dopamine receptors *DRD4* and *DRD5*, neuronal isoform of the nitric oxide synthase (*NOS1*), synaptosomal-associated protein (*SNAP25*), G-protein-coupled receptor kinase interacting ArfGAP 1 (*GIT1*), and cannabinoid receptor gene 1 (*CNR1*) [20].

One study summarized the gene polymorphisms found in ADHD in comparison to a control group. The findings were variants including the *TaqIA* polymorphism of *DRD2* gene, the *A1* allele of the *DRD2* gene in the hyperkinetic patients, abnormal genotypes of the *DAT1* gene in boys with ADHD, and polymorphism of *IL-6* gene. The study discovered a correlation between certain genes involved in the immunological pathways, such as *IL-2*, *IL-6*, *TNF-alpha* and *BDNF,* and the risk of ADHD [27].

Dopamine alteration is one of the first and most studied genes in ADHD neurobiology. Some variants of *DRD4* gene, which are located on the chromosome 11p15.5, have been widely reported to play a role in ADHD [6]. DRD is a dopamine receptor that can bind to dopamine and norepinephrine. The polymorphism in the 3rd exon of this gene has been extensively studied and linked to ADHD. A rare 7 repeat (7R) variant of *DRD4* gene is another risk factor associated with this condition, but both common and rare polymorphisms of this gene can play a role in the condition.

DRD5, another dopamine receptor, has also been implicated in ADHD studies [11].

Dopamine transporter (*DAT1*)—also known as *SLC6A3*—is one of the most replicated genes in ADHD. *DAT1* is responsible for dopamine reuptake at the site of neuronal communication. Methylphenidate, the most common ADHD medication, targets this receptor and leads to accumulation of dopamine in the site of synapses [6]. This gene is one of the most robust genetic factors that have been related to ADHD, as seen in animal and human studies. In fact, *DAT1* knocked-out mice have shown hyperactive symptoms. 480-bp allele of the most common studied polymorphism—which is a variable number of tandem repeat (VNTR) in the 3' untranslated region (UTR) region of the gene—is shown to be significantly correlated with ADHD. The 3' UTR VNTR polymorphism of *DAT1* gene also may predispose an individual to ADHD through an interaction between genetic and prenatal risk factors, such as mother's smoking or alcohol use [11].

A recent GWAS supported the role of *CDH13* and *LPHN3* in ADHD pathology. *CDH13* gene, which is involved in neurodevelopment was found to be associated with ADHD etiology. *CDH13* expresses the protein cadherin-13, which is responsible for neuronal growth and cell adhesion. Two independent samples found the association of *CDH13* and ADHD [20].

A common haplotype of *LPHN3* has also been suggested to raise the risk of ADHD and the response to stimulant drugs. This gene is predominantly expressed in the brain regions that are found to be associated with ADHD, such as amygdala. *LPHN3* is involved in axon signaling, the development of glutaminergic synapses, and plasticity of synapses [20]. Acosta et al. found an interesting interaction between SNPs of *LPHN3* and specific genes in the 11q region, namely, *DRD2* and *NCAM1*. The interaction would probably increase the risk of ADHD and its severity as well [28].

Studies also reported a possible role for *SPOCK3* and glutamate receptor (*GRM5*) genes in ADHD development. *SPOCK3* is known for coding a proteoglycan called Ca^{2+}-binding extracellular heparan/chondroitin–sulfate–proteoglycan, which exerts inhibitory effects on neurite growth by matrix-metalloproteinases [20]. Many studies focused on the polymorphisms of catechol *O* methyl transferase (*COMT*) gene, a dopamine degrading enzyme. They found a valine–methionine transition that can affect the enzyme's function and may be related to ADHD through dopamine changes [11].

Several microRNAs have been shown to play a role in regulation of ADHD-associated genes, such as *BDNF*, *DAT1*, *HTR2C*, *HTR1B*, and *SNAP25* [20]. MicroRNAs are short, noncoding RNAs responsible for gene regulation after transcriptional stage. Among the few studies that have investigated the role of microRNAs in the ADHD etio-pathology, one study found the altered expression levels of microRNA 5692b and microRNA let-7d in the blood of ADHD affected children and adults, supporting the possible role of them in this condition [29].

The genetic findings have supported several possible genes that are involved in ADHD pathology; yet they also show a considerable inconsistency and uncertainty. Although genetic risk factors appear to be the most determining causes of ADHD, these risk factors have not been firmly established and require further investigations with higher sample sizes.

Prenatal environmental risk factors

Despite being the less contributing factor in developing ADHD, environmental risk factors have been investigated considerably. Prenatal exposures consist of an important proportion of ADHD risk factors, because multiple studies have focused on their contribution to offsprings' ADHD. The literature on ADHD prenatal risk factors lacks consistency; in fact, it has been suggested that a single risk factor is not capable of developing ADHD symptoms in a child. Rather, it is the combination of multiple environmental exposures and genetic predisposition that might lead to the condition.

A study has supported evidence for different environmental factors that can influence inattentive or hyperactive–impulsive symptoms. Inattentive symptoms seem to be significantly influenced by psychosocial risk factors, whereas hyperactive–impulsive symptoms are more likely to be the result of biological risk factors [30].

A recent meta-analysis that integrated the results of previous studies on environmental risk factors, protective factors, and peripheral biomarkers for ADHD found nine specific associations between environmental risk factors and ADHD. The most prominence of these associations is acetaminophen use during pregnancy, maternal smoking, pre-pregnancy obesity and overweightness [31].

Reviewing the extended literature around prenatal risk factors of ADHD, multiple exposures and complications during pregnancy or during labor come into play. Most clinical trials have focused only on one or two of these variables, but it's not yet known whether their convolution can add further risk for having ADHD. Many studies have suggested an association between different prenatal risk factors and ADHD in children. This review has classified them into three groups that will be discussed further: chemical exposures during pregnancy, pregnancy or birth complications and maternal health status.

Chemical exposures during pregnancy

Exposure to smoking

Maternal cigarette smoking is a key risk factor that has been significantly associated with ADHD in offspring. Milberger et al. reported a higher rate (2.7-fold) of ADHD risk in children with mothers who smoke [32]. Similarly, another study has found a twofold greater risk of ADHD in offspring who had been exposed to tobacco during pregnancy [33]. Prenatal exposure to nicotine also was associated with a significant cognitive impairment in animals [34]. Nicotine exposures during brain development window can affect catecholaminergic (i.e., dopaminergic and noradrenergic) systems in certain parts of the brain, resulting in their hypo-responsiveness to stimulants and eventually developing ADHD [35]. Cigarette smoking can have multiple adverse effects on the embryonic development: interfering with placental function, disrupting fetal blood flow, depriving the fetus of oxygen and nutrients, and finally causing fetal retardation [3]. Carbon monoxide and other ingredients within the cigarette can also have direct harmful effects on brain development [36].

Maternal and paternal smoking is associated with ADHD in offspring, but maternal smoking seems to have a greater influence than father's. One study supported this finding by comparing the risk of ADHD in children who were born from smoker mothers and non-smoker fathers with children with complete opposite parents; the results displayed a higher risk of ADHD in the offspring of smoker mothers and mothers who received nicotine replacement during pregnancy [37]. Similarly, another study supported a significant association between offspring's ADHD and maternal and paternal smoking but also suggested that maternal smoking doesn't seem to have intrauterine effects on the fetus and that the effects might be confounded with genetic or household-level factors [37]. The same result was concluded by Gustavson et al. who ruled out intrauterine effects of smoking during pregnancy on a child's ADHD risk, because the association between maternal active or passive smoking disappeared after adjusting the same experiments for sibling-control analyses [38].

As suggested by another study, the risk of ADHD is higher in children of mothers who were heavy smokers than in those whose mothers were light smokers [39]. In addition, one study has reported higher levels of severe psychosocial stress and higher rates of heavy smoking (> 10 cigarettes per day) during pregnancy in mothers who had ADHD children compared to those who had unaffected kids [40]. There are heterogeneous results pertaining to maternal passive smoking through father's smoking habit as well, but the correlation needs further investigations. Minatoya et al. suggested an increased risk of hyperactivity/inattention symptoms in pre-school children whose mothers have experienced low and high passive smoking during pregnancy, but the correlation lacked statistical significance in contrast to what was observed for maternal active smoking [41].

Interestingly, Dong et al. found a strong correlation between maternal smoking during pregnancy and maternal smoking cessation during the first trimester, with the risk of developing ADHD in their offspring. This study recommended early smoking cessation for smoker women who aim to be pregnant soon, because they reported a much lower risk of ADHD among mothers that quit cigarette smoking before getting pregnant [42].

Simultaneous exposure to tobacco and alcohol during pregnancy might add a double risk for developing ADHD. Han et al. reported 1.55, 2.64 and 1.17 folds greater risks of ADHD in offspring who were prenatally exposed to alcohol, maternal smoking and paternal smoking, respectively [43].

Exposure to diet components

Prenatal exposure to alcohol is one of the most studied risk factors related to ADHD pathogenesis. Ikonomidou et al. have demonstrated that ethanol-treated rats had higher rates of neurodegeneration in the forebrain, a key brain region involved in ADHD, than their saline-treated counterparts [44]. It has also been shown that human brain is sensitive to alcohol during neurodevelopmental period and is prone to anomalies or disrupted development especially in the cerebellum [45]. Apart from maternal exposures before birth, paternal alcohol use has been explored as an ADHD risk factor. One study showed no definite correlation between these two variables and further suggested that the possible influence of paternal alcohol consumption on kids' risk of ADHD might be a result of interactions of different pathways rather than direct influence [46].

A systematic review has shown that diet components have no significant impact on ADHD risk. However, there are some evidences of a pathologic effect of eating heavy metals by mothers during pregnancy. The offspring of mothers who had consumed mercury-contaminated fish during pregnancy in New Zealand and the Faroe Islands had higher rates of memory and attention disruption and had lower IQ than the normal kids and affected motor skills [3].

Konikowska et al. carried out a study to investigate the influence of diet during pregnancy and lactation period in developing ADHD [47]. The findings supported a fundamental role for long-chain polyunsaturated fatty acids and minerals, such as zinc, iron, magnesium and iodine, in the brain development of the fetus. The authors suggested an

increased risk of ADHD in children whose mothers were chronically deficient from polyunsaturated omega-3 fatty acids—especially DHA—which is essential for normal development and activity of brain [47]. Children diagnosed with ADHD and autism spectrum disease are reported to have lower DHA levels. One study has found controversial evidence on prenatal supplementation with DHA and unexpected neurodevelopmental disorders. This study suggested that this association might be confounded by socio-economic background and life-style [48]. Manganese exposure before birth is associated with ADHD development. Animal models exposed to manganese have also shown hyperactive traits [3].

The impact of polychlorinated biphenyls (PCB) has also been investigated in multiple cohort studies. All of them concluded that prenatal PCB exposure is associated with ADHD symptoms, such as lower concentration, lack of accuracy in the performance and longer reaction time [3].

Exposure to certain drugs

Consuming acetaminophen, as an antipyretic drug, by pregnant mothers is a concern for multiple teratogenic effects that it might provoke. Masarwa et al. recently found an increased risk of ADHD and hyperactivity in the offspring of mothers who consumed acetaminophen during gestation. The study has suggested a mechanism for acetaminophen's adverse effect, which is its interference with endogenous hormones and signaling pathways of the developing fetus [49]. A previous study had concluded that short-term acetaminophen use had a negative correlation with ADHD in the born child, whereas long-term consumption was significantly associated with greater risk of developing ADHD [50]. Another study also supported the association between using acetaminophen during gestation and greater odds of ADHD-like symptoms at 7 years of age. The authors proposed a greater association when mother had consumed acetaminophen in more than 1 trimester in pregnancy [51].

Prenatal exposure to anti-depressant medication and the risk of ADHD has also gained some attention. Despite multiple studies done in this field, a unique conclusion is absent due to heterogeneity of the study results possibly due to the existence of some confounding factors [52].

The studies on the risk of consuming anti-seizure drugs during pregnancy were not consistent as well. For example, maternal use of lamotrigine was not associated with elevated risk of ADHD or autism spectrum disorder, whereas valproic acid consumption raised the risk of these two conditions. A recent cohort study reported a higher likelihood of ADHD (48%) in children who were exposed to valproate during gestation compared to children without this history [53]. In addition, carbamazepine association with ADHD lacked significance [54].

Prenatal antibiotic exposures are under investigation for finding a possible association with offspring's ADHD but a recent study has shown no significant correlation between these two variables [55].

Consuming anti-ADHD medications during pregnancy is another hypothetical risk factor for offspring's ADHD. A recent study reviewed existing evidences for this risk factor and concluded that prenatal exposure to ADHD medications is not directly linked to ADHD development. The authors suggested that this association might be the result of genetic factors or familial environmental factors [56].

Exposure to toxins

Interestingly, the study by Nilsen et al. showed that the association between chemical exposures and ADHD development in children can be explained by the monoamine oxidase A (*MAOA*) pathway that is involved in serotonin uptake. It has been suggested that *MAOA* activity can be altered when it is exposed to chemicals, such as naphthylamine, nicotine, bisphenol A (a plasticizer), organophosphate pesticides and Pb (lead), hence leading to higher likelihood of ADHD. It was further explained that some metals, including Pb, manganese (Mn), arsenic (As) and mercury (Hg) can inhibit *N*-methyl-D-aspartate receptor (*NMDAR*) by interfering with the calcium channels involved in *NMDAR* regulation and can alter *MAOA* activity. NMDAR is an ionotropic channel composed of different subunits including NR1 and four subtypes of NR2 family (A–D) [57]. Notably, monoamine neurotransmitters, such as dopamine and serotonin, can influence the composition of NMDAR and its function which is passage of cations; hence, it is suggested that the function of MAOA, the catalyzer of monoamine degradation, is in part regulated by NMDAR function [58, 59]. However, the evidence for Pb is conflicting, because the authors have ruled out Pb as an agonist for *NMDAR* [60]. This is consistent with some studies that have shown lead exposure before birth is not significantly associated with ADHD pathogenesis [3].

The correlation between children's low level pesticide exposure and onset of ADHD symptoms also was supported by another study by Roberts et al. This finding is consistent with animal studies that treated animals with a controlled concentration of pesticides and found correlation with ADHD and autistic symptoms [61].

Prenatal exposure to air pollutants is an interesting concept in the context of ADHD etiology. However, the study by Oudin et al. did not find a significant association between prenatal exposure to theses toxic substances and the risk of developing ADHD in the offspring [62].

In line with maternal exposure to chemicals during pregnancy, one large, cohort study has investigated the influence

of amalgam, a chemical used for filling teethes in dentistry, on the offspring's ADHD risk. The authors failed to find any significant correlation between mother's amalgam fillings during pregnancy and children's risk of ADHD [63].

Inborn errors of metabolism

According to the literature, a number of inborn errors of metabolism are associated with attention deficit and hyperactive behavior. The characteristic symptoms of ADHD as mentioned earlier, were observed in 28% of cases born with succinic semialdehyde dehydrogenase deficiency [64]. Interestingly, Antshel et al. revealed that prenatal exposure to elevated levels of phenylalanine as in phenylketonuria is correlated with expressing hyperactive/impulsive behavior, while postnatal exposure to this metabolite is associated with inattentive symptoms [65, 66]. According to Arnold et al. 26% of 38 children with phenylketonuria consumed anti-inattentive medications [67].

In line with metabolic defects, different case reports have reported 3-methylcrotonyl-CoA carboxylase deficiency [68], argininosuccinate lyase deficiency [69] and succinyl-CoA: 3-oxoacid CoA transferase deficiency in pediatric cases of ADHD [70]. Moreover, ADHD is also thought to be associated with mitochondrial dysfunction [71]. ADHD is one of the conditions that is suggested to be linked to a hyperammonemic crisis [72].

Pregnancy birth complications

Maternal age

The association between maternal age and the risk of ADHD in the offspring was the subject of many investigations. Presumably, the mother's age at first birth can predict the ADHD risk in their kids. The results of one study had shown that mothers who have started childbearing early in their lives have children that are more likely to show ADHD symptoms. The study further suggested that this association is probably due to genetic confounding, which makes the mothers more likely to have children at an early age and predisposes their children to ADHD [73].

Prematurity and low birth weight

Prematurity is a possible risk factor for ADHD. One study suggested an association between prematurity and risk of ADHD based on the results of three studies exploring the effect of prematurity. The study suggested a negative correlation between the risk and the gestational age of the children [4]. Another study showed that children who were born prematurely (less than 26 weeks of gestational age) and thus had lower birth weight were four times more prone to have ADHD [74]. However, the results did not show whether prematurity or the lower birth weight increases the risk; so, another study was done by Heinonen et al. that controlled the effects of both variables; the authors reported no association between pre-maturity and later clinical manifestations of ADHD. However, being small for gestational age was correlated with a threefold higher likelihood of reaching clinical cutoff criteria for ADHD in comparison with children who were born with an average normal weight [75]. Despite gaining a significant odds ratio of 2.6 in a meta-analysis study, low birth weight and prematurity, which are frequently mentioned in the list of possible ADHD causes, need further investigation, because only a small number of ADHD patients present with these complications [76].

Gestational problems

Gestational bleeding can increase the risk of ADHD or specific ADHD symptoms. As one study suggested, bleeding during pregnancy was linked to higher risks for inattentive traits. The study concluded that fetal hypoxia could be the linkage between gestational bleeding and elevated inattentive symptoms in ADHD, as was previously demonstrated for autism [30]. The role of neuro-inflammation in the development of ADHD is not yet stablished but is proposed to interfere with development of gray matter volume, especially in certain cortical areas relevant to ADHD. Animal studies have added further evidence for the role of neuro-inflammation in terms of disrupting the development and function of dopaminergic, serotonergic and glutamatergic systems [77]. Hypoxia and ischemia during fetal life can have irreversible effects on the development of different body organs, especially in brain tissue. One study has explained the mechanisms by which it can produce ADHD in the fetus. First, hypoxemia and ischemia are known to cause lower birth weight in the offspring, which itself is a prominent risk factor for ADHD. Second, the activity of ischemia–hypoxia response pathway is altered through epigenetic modification to promote the vitality of hypoxic tissue. If ischemia–hypoxia response modifications last for a long time in the brain tissue, the occurrence of ADHD will be more probable in the child [78]. Pre-eclampsia, which is characterized by high blood pressure, proteinuria and swelling in the limbs during pregnancy, has been under investigation as another prenatal risk factor of ADHD. One study firmly suggested that children who were born of mothers with pre-eclampsia have an increased risk of ADHD [79].

Maternal health status

Maternal health during pregnancy is effective on the child's normal development. Several studies have investigated the influence of mother's sickness on developing ADHD.

One example is maternal anemia during pregnancy. Wiegersma et al. have demonstrated that maternal anemia that is diagnosed early during gestation is correlated with higher rates of diagnosing neurodevelopmental disorders in the offspring, including ADHD, while such correlation was absent with later anemia diagnosis [80].

Maternal obesity and overweightness is among multiple factors that are strongly associated with ADHD development in the offspring. However, the effect of genetic and familial confounding factors should not be neglected in this context [31].

Parental asthma also has been linked to greeter risks of ADHD in children, but no significant correlation was observed between using asthmatic medications during pregnancy and offspring's ADHD [81].

Psychological status of parents, and more importantly of mothers before birth, is also thought to play roles in ADHD development in their children. Joelsson et al. reported a significant association between parental diagnosis with psychological disorders before birth and higher probability of ADHD in their born childs. Maternal diagnosis was more significantly correlated with her offspring's condition [82]. In addition, a Swedish study has shown that maternal stress during the 3rd gestational trimester increases the risk of ADHD in their offspring [83]. As supported by Clement et al. maternal history of major depressive disorder is also correlated with increased risk of ADHD [84].

Gene–environment interaction

It has become clear that ADHD develops when an individual with underlying genetic predispositions faces some stresses, either prenatally or postnatally. The studies are supportive of a combination of factors, both genetically and environmentally, to be involved in ADHD pathogenesis.

The role of gene–environment interaction gained a lot of attention in the last decade. A considerable number of studies have tried to clarify the possible association between genetic variants and environmental exposures. Some have even taken a step further and suggested that genetic variations are even responsible for higher risk of being exposed to some environmental factors. For example, one study has shown a strong correlation between the likelihood of early life exposure to environmental risks and the maternal neurodevelopmental risk alleles, suggesting a possible mechanism for those alleles in elevating the risk of neurodevelopmental disorders in the offspring [85].

One study has proposed an interaction between genetic variation in *DRD4* region and exposure to organophosphates and oxidative stresses. The authors reported a higher likelihood of ADHD in children who had *DRD4 GG* genotype than in whom a *DRD4 GA/AA* genotypes (rs752306) was present. They also emphasized the importance of *DRD4* polymorphism in terms of susceptibility to chemicals, such as organophosphate, because the levels of dimethyl phosphate and 4-hydroxy-2-nonenal-mercapturic acid also were higher in ADHD kids, which might predispose them to ADHD, possibly through the mechanism of lipid peroxidation [86].

Kahn et al. have shown an interaction between *DAT1 VNTR* genotype and prenatal smoking exposure, which predisposes the child to oppositional and hyperactive–impulsive symptoms [87]. A later study found a different interaction between *DAT1 VNTR* alleles and maternal alcohol use with a greater risk of ADHD in childhood; the interaction between maternal alcohol use and *DAT1* haplotype showed an increased risk of ADHD in children from southeast England and Taipei, Taiwan [88].

However, not all studies were supportive of gene–environment interaction. Altink et al. have reported no significant interaction between *DRD4* 7-repeat allele and maternal smoking as a risk factor for ADHD [89]. In contrast, another study has found a robust interconnection between prenatal smoking exposure and the *ADRA2A* rs553668 variant for ADHD. The authors concluded that the risk of having genetic variant indicative of ADHD is higher in children who were exposed to tobacco smoking before birth [90]. Another study has reported a significant correlation between maternal smoking during pregnancy and a genetic predisposition of the child to have ADHD further in life. The authors further reported that twins who were exposed to prenatal maternal smoking and who had inherited *DAT1* 440 allele had a greater odds ratio (2.9) for having ADHD than twins who had none of these genetic or environmental risk factors [91].

A 2016 study done on opiate-dependent parents and their offspring has reported valuable findings by exploring six risk alleles of four different gene regions—*DAT1*, *5HTTLPR*, *D4DR4* and *MAO-A*, which mostly are ADHD risk factors. They concluded that opiate-dependent parents were more likely to carry almost all of those risk alleles (except for *DRD4EX3*) indicating that these risk alleles can predispose a person to opioid-dependence and possibly to ADHD. Children of opiate-dependent mothers were also more diagnosed with ADHD than the children of opiate-dependent fathers. Although the study did not directly mention the interaction between opioid exposure and ADHD risk alleles, it could be understood that the same gene polymorphisms that have been frequently referred to as ADHD risk alleles, might also play a role in opioid-dependence of parents and possibly predispose their children to ADHD, either through those risk alleles or opioid effects during pregnancy [92].

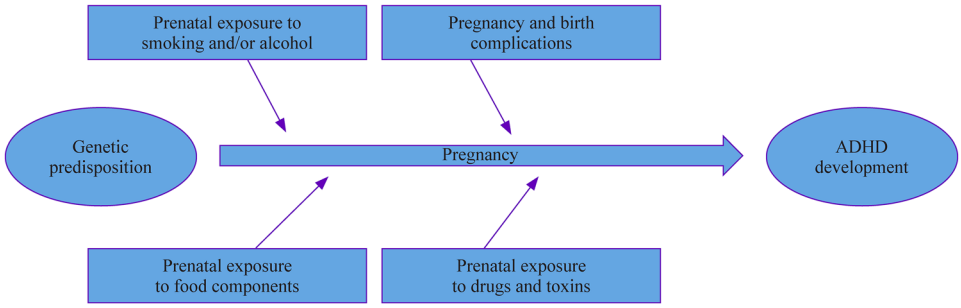

Fig. 1 Gene–environment interaction in the course of ADHD. ADHD development in a child is the result of an interaction between genetic risk factors and environmental assaults. Children who have been exposed to environmental risk factors and also have genetic predisposition are at greater risk of having ADHD

Conversely, another study looking for gene–environment interaction in the population of female twins showed no significant interaction between genetic risk factors and prenatal substance or alcohol use of mothers. The authors concluded that this lack of interaction might be the result of indirect association that might be present between those distinct variables [93]. Interestingly, one study found that the maternal alcohol use and inheriting genetic risk factors will lead to development of ADHD in an additive way rather than an interactive way. This result means that children who have inherited the genetic polymorphisms from their mothers are more susceptible to experience environmental harms, such as maternal alcohol use, as well [94]. Genetic–environment interaction—the most probable etiology for ADHD—is summarized in Fig. 1.

Conclusions

This narrative review aimed to provide an overview of the most studied risk factors of ADHD, both genetically and environmentally. The literature on genetic findings of this condition is vast and scattered. Given the polygenic nature of ADHD, each study has focused on only a small fraction of genetic abnormalities. Apart from genetic causes, prenatal risk factors of ADHD are also the place of controversy. Various study designs have investigated their contribution to ADHD development in the offspring, but the results are not always consistent. In addition, potential prenatal risk factors that can be correlated with ADHD are varied and need separate and comprehensive trials to be established as ADHD risk factors.

ADHD etiology is still the place of many discussions. Despite the great evidences that have covered the pathogenesis of ADHD, there is still a vague understanding about the exact causes that lead to the development of ADHD in children. Altogether, ADHD is considered as a hereditary disorder in which genes play the fundamental role in the pathogenesis. However, the findings from genetic–environmental studies support the hypothesis that genetic factors can exert their effects on the condition by determining the individual's responses to the environmental exposures, especially those at the prenatal stage.

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References

1. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Pediatrics. 2015;135:e994–1001.
2. Tannock R. Rethinking ADHD and LD in DSM-5: Proposed changes in diagnostic criteria. J Learn Disabil. 2013;46:5–25.
3. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. Acta Paediatr. 2007;96:1269–74.
4. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal risk factors and the etiology of ADHD—review of existing evidence. Curr Psychiatry Rep. 2017;19:1.
5. Thapar A, Cooper M, Eyre O, Langley K. Practitioner review: what have we learnt about the causes of ADHD? J Child Psychol Psychiatry. 2013;54:3–16.
6. Akutagava-Martins GC, Salatino-Oliveira A, Kieling CC, Rohde LA, Hutz MH. Genetics of attention-deficit/hyperactivity disorder: current findings and future directions. Expert Rev Neurother. 2013;13:435–45.
7. Eilertsen EM, Gjerde LC, Kendler KS, Røysamb E, Aggen SH, Gustavson K, et al. Development of ADHD symptoms in preschool children: genetic and environmental contributions. Dev Psychopathol. 2019;31:1299–305.
8. Tarver J, Daley D, Sayal K. Attention-deficit hyperactivity disorder (ADHD): an updated review of the essential facts. Child Care Health Dev. 2014;40:762–74.

9. Ramtekkar UP, Reiersen AM, Todorov AA, Todd RD. Sex and age differences in attention-deficit/hyperactivity disorder symptoms and diagnoses: implications for DSM-V and ICD-11. J Am Acad Child Adoles Psychiatry. 2010;49:217-28.e1-3.
10. Takeda T, Stotesbery K, Power T, Ambrosini PJ, Berrettini W, Hakonarson H, et al. Parental ADHD status and its association with proband ADHD subtype and severity. J Pediatr. 2010;157:995–1000.
11. Thapar A, Cooper M, Jefferies R, Stergiakouli E. What causes attention deficit hyperactivity disorder? Arch Dis Child. 2012;97:260–5.
12. Faraone SV, Biederman J, Mennin D, Gershon J, Tsuang MT. A prospective four-year follow-up study of children at risk for ADHD: psychiatric, neuropsychological, and psychosocial outcome. J Am Acad Child Adolesc Psychiatry. 1996;35:1449–59.
13. Bonvicini C, Faraone SV, Scassellati C. Common and specific genes and peripheral biomarkers in children and adults with attention-deficit/hyperactivity disorder. World J Biol Psychiatry. 2018;19:80–100.
14. Mill J, Petronis A. Pre-and peri-natal environmental risks for attention-deficit hyperactivity disorder (ADHD): the potential role of epigenetic processes in mediating susceptibility. J Child Psychol Psychiatry. 2008;49:1020–30.
15. Spiers H, Hannon E, Schalkwyk LC, Smith R, Wong CC, O'Donovan MC, et al. Methylomic trajectories across human fetal brain development. Genome Res. 2015;25:338–52.
16. van Mil NH, Steegers-Theunissen RP, Bouwland-Both MI, Verbiest MM, Rijlaarsdam J, Hofman A, et al. DNA methylation profiles at birth and child ADHD symptoms. J Psychiatr Res. 2014;49:51–9.
17. Park S, Lee JM, Kim JW, Cho DY, Yun H, Han D, et al. Associations between serotonin transporter gene (SLC6A4) methylation and clinical characteristics and cortical thickness in children with ADHD. Psychol Med. 2015;45:3009–17.
18. Perroud N, Zewdie S, Stenz L, Adouan W, Bavamian S, Prada P, et al. Methylation of serotonin receptor 3A in ADHD, borderline personality, and bipolar disorders: link with severity of the disorders and childhood maltreatment. Depress Anxiety. 2016;33:45–55.
19. Ding K, Yang J, Reynolds GP, Chen B, Shao J, Liu R, et al. DAT1 methylation is associated with methylphenidate response on oppositional and hyperactive-impulsive symptoms in children and adolescents with ADHD. World J Biol Psychiatry. 2017;18:291–9.
20. Palladino VS, McNeill R, Reif A, Kittel-Schneider S. Genetic risk factors and gene–environment interactions in adult and childhood attention-deficit/hyperactivity disorder. Psychiatr Genet. 2019;29:63–78.
21. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019;51:63–75.
22. Cortese S, Coghill D. Twenty years of research on attention-deficit/hyperactivity disorder (ADHD): looking back, looking forward. Evid Based Ment Health. 2018;21:173–6.
23. Genro JP, Kieling C, Rohde LA, Hutz MH. Attention-deficit/hyperactivity disorder and the dopaminergic hypotheses. Expert Rev Neurother. 2010;10:587–601.
24. Purper-Ouakil D, Ramoz N, Lepagnol-Bestel AM, Gorwood P, Simonneau M. Neurobiology of attention deficit/hyperactivity disorder. Pediatr Res. 2011;69:69–76.
25. Hayman V, Fernandez TV. Genetic insights into ADHD biology. Front Psych. 2018;9:251.
26. Bralten J, Franke B, Waldman I, Rommelse N, Hartman C, Asherson P, et al. Candidate genetic pathways for attention-deficit/hyperactivity disorder (ADHD) show association to hyperactive/impulsive symptoms in children with ADHD. 2013;52:1204–1212.e1.
27. Drtilkova I, Sery O, Theiner P, Uhrova A, Zackova M, Balastikova B, et al. Clinical and molecular-genetic markers of ADHD in children. Neuroendocrinol Lett. 2008;29:320–7.
28. Acosta M, Velez J, Bustamante M, Balog J, Arcos-Burgos M, Muenke M. A two-locus genetic interaction between LPHN3 and 11q predicts ADHD severity and long-term outcome. Transl Psychiatry. 2011;1:17.
29. Aydin SU, Basay BK, Cetin GO, Aydin AG, Tepeli E. Altered microRNA 5692b and microRNA let-7d expression levels in children and adolescents with attention deficit hyperactivity disorder. J Psychiatr Res. 2019;115:158–64.
30. Freitag CM, Haenig S, Schneider A, Seitz C, Palmason H, Retz W, et al. Biological and psychosocial environmental risk factors influence symptom severity and psychiatric comorbidity in children with ADHD. J Neural Transm. 2012;119:81–94.
31. Kim JH, Kim JY, Lee J, Jeong GH, Lee E, Lee S, et al. Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: an umbrella review. Lancet Psychiatry. 2020;7:955–70.
32. Milberger S, Biederman J, Faraone SV, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children? Am J Psychiatry. 1996;153:1138–42.
33. Weissman MM, Warner V, Wickramaratne PJ, Kandel DB. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. J Am Acad Child Adolesc Psychiatry. 1999;38:892–9.
34. Levin ED, Briggs SJ, Christopher NC, Rose JE. Prenatal nicotine exposure and cognitive performance in rats. Neurotoxicol Teratol. 1993;15:251–60.
35. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? J Pharmacol Exp Ther. 1998;285:931–45.
36. Ernst M, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. J Am Acad Child Adolesc Psychiatry. 2001;40:630–41.
37. Zhu JL, Olsen J, Liew Z, Li J, Niclasen J, Obel C. Parental smoking during pregnancy and ADHD in children: the Danish national birth cohort. Pediatrics. 2014;134:382–8.
38. Gustavson K, Ystrom E, Stoltenberg C, Susser E, Surén P, Magnus P, et al. Smoking in pregnancy and child ADHD. Pediatrics. 2017;139:20162509.
39. Huang L, Wang Y, Zhang L, Zheng Z, Zhu T, Qu Y, et al. Maternal smoking and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. Pediatrics. 2018;141:20172465.
40. Motlagh MG, Katsovich L, Thompson N, Lin H, Kim YS, Scahill L, et al. Severe psychosocial stress and heavy cigarette smoking during pregnancy: an examination of the pre-and perinatal risk factors associated with ADHD and Tourette syndrome. Eur Child Adolesc Psychiatry. 2010;19:755–64.
41. Minatoya M, Araki A, Itoh S, Yamazaki K, Kobayashi S, Miyashita C, et al. Prenatal tobacco exposure and ADHD symptoms at pre-school age: the Hokkaido Study on Environment and Children's Health. Environ Health Prev Med. 2019;24:1–9.
42. Dong T, Hu W, Zhou X, Lin H, Lan L, Hang B, et al. Prenatal exposure to maternal smoking during pregnancy and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. Reprod Toxicol. 2018;76:63–70.
43. Han JY, Kwon HJ, Ha M, Paik KC, Lim MH, Lee SG, et al. The effects of prenatal exposure to alcohol and environmental tobacco smoke on risk for ADHD: a large population-based study. Psychiatry Res. 2015;225:164–8.
44. Ikonomidou C, Bittigau P, Ishimaru MJ, Wozniak DF, Koch C, Genz K, et al. Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. Science. 2000;287:1056–60.

45. Sowell ER, Jernigan TL, Mattson SN, Riley EP, Sobel DF, Jones KL. Abnormal development of the cerebellar vermis in children prenatally exposed to alcohol: size reduction in lobules I–V. Alcohol Clin Exp Res. 1996;20:31–4.
46. Knopik VS, Jacob T, Haber JR, Swenson LP, Howell DN. Paternal alcoholism and offspring ADHD problems: a children of twins design. Twin Res Hum Genet. 2009;12:53–62.
47. Konikowska K, Regulska-Ilow B, Rozanska D. The influence of components of diet on the symptoms of ADHD in children. Roczniki Państwowego Zakładu Higieny. 2012;63:127–34.
48. Martins BP, Bandarra NM, Figueiredo-Braga M. The role of marine omega-3 in human neurodevelopment, including autism spectrum disorders and attention-deficit/hyperactivity disorder—a review. Crit Rev Food Sci Nutr. 2020;60:1431–46.
49. Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I. Prenatal exposure to acetaminophen and risk for attention deficit hyperactivity disorder and autistic spectrum disorder: a systematic review, meta-analysis, and meta-regression analysis of cohort studies. Am J Epidemiol. 2018;187:1817–27.
50. Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, et al. Prenatal exposure to acetaminophen and risk of ADHD. Pediatrics. 2017;140: e20163840.
51. Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014;168:313–20.
52. Morales DR, Slattery J, Evans S, Kurz X. Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations. BMC Med. 2018;16:1–14.
53. Christensen J, Pedersen L, Sun Y, Dreier JW, Brikell I, Dalsgaard S. Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring. JAMA Netw Open. 2019;2:e186606.
54. Wiggs KK, Rickert ME, Sujan AC, Quinn PD, Larsson H, Lichtenstein P, et al. Antiseizure medication use during pregnancy and risk of ASD and ADHD in children. Neurology. 2020;95(24):e3232–40.
55. Hamad AF, Alessi-Severini S, Mahmud S, Brownell M, Fan Kuo I. Prenatal antibiotic exposure and risk of attention-deficit/hyperactivity disorder: a population-based cohort study. CMAJ. 2020;192:E527–35.
56. Lemelin M, Sheehy O, Zhao JP, Bérard A. Maternal ADHD medication use during pregnancy and the risk of ADHD in children: importance of genetic predispositions and impact of using a sibling analysis. Eur Neuropsychopharmacol. 2021;44:66–78.
57. Cull-Candy S, Brickley S, Farrant M. NMDA receptor subunits: diversity, development and disease. Curr Opin Neurobiol. 2001;11:327–35.
58. Yuen EY, Jiang Q, Chen P, Gu Z, Feng J, Yan Z. Serotonin 5-HT1A receptors regulate NMDA receptor channels through a microtubule-dependent mechanism. J Neurosci. 2005;25:5488–501.
59. Masuko T, Suzuki I, Kizawa Y, Kusama-Eguchi K, Watanabe K, Kashiwagi K, et al. Monoamines directly inhibit *N*-methyl-D-aspartate receptors expressed in *Xenopus oocytes* in a voltage-dependent manner. Neurosci Lett. 2004;371:30–3.
60. Nilsen FM, Tulve NS. A systematic review and meta-analysis examining the interrelationships between chemical and non-chemical stressors and inherent characteristics in children with ADHD. Environ Res. 2020;180:108884.
61. Roberts JR, Dawley EH, Reigart JR. Children's low-level pesticide exposure and associations with autism and ADHD: a review. Pediatr Res. 2019;85:234–41.
62. Oudin A, Frondelius K, Haglund N, Källén K, Forsberg B, Gustafsson P, et al. Prenatal exposure to air pollution as a potential risk factor for autism and ADHD. Environ Int. 2019;133: 105149.
63. Lygre GB, Aase H, Haug K, Lie SA, Björkman L. Prenatal exposure to dental amalgam and risk of symptoms of attention-deficit and hyperactivity disorder (ADHD). Commun Dent Oral Epidemiol. 2018;46:472–81.
64. Jurecka A, Zikanova M, Tylki-Szymanska A, Krijt J, Bogdanska A, Gradowska W, et al. Clinical, biochemical and molecular findings in seven Polish patients with adenylosuccinate lyase deficiency. Mol Genet Metab. 2008;94:435–42.
65. Antshel KM. ADHD, learning, and academic performance in phenylketonuria. Mol Genet Metab. 2010;99:S52–8.
66. Antshel KM, Waisbren SE. Developmental timing of exposure to elevated levels of phenylalanine is associated with ADHD symptom expression. J Abnorm Child Psychol. 2003;31:565–74.
67. Arnold G, Vladutiu CJ, Orlowski C, Blakely E, DeLuca J. Prevalence of stimulant use for attentional dysfunction in children with phenylketonuria. J Inherit Metab Dis. 2004;27:137–43.
68. Darin N, Andersen O, Wiklund LM, Holmgren D, Holme E. 3-methylcrotonyl-CoA carboxylase deficiency and severe multiple sclerosis. Pediatr Neurol. 2007;36:132–4.
69. Nagamani SC, Erez A, Lee B. Argininosuccinate lyase deficiency. Genet Med. 2012;14:501–7.
70. Berry G, Fukao T, Mitchell G, Mazur A, Ciafre M, Gibson J, et al. Neonatal hypoglycaemia in severe succinyl-CoA: 3-oxoacid CoA-transferase deficiency. J Inherit Metab Dis. 2001;24:587–95.
71. Marazziti D, Baroni S, Picchetti M, Landi P, Silvestri S, Vatteroni E, et al. Psychiatric disorders and mitochondrial dysfunctions. Eur Rev Med Pharmacol Sci. 2012;16:270–5.
72. Simons A, Eyskens F, Glazemakers I, Van West D. Can psychiatric childhood disorders be due to inborn errors of metabolism? Eur Child Adolesc Psychiatry. 2017;26:143–54.
73. Chang Z, Lichtenstein P, D'Onofrio BM, Almqvist C, Kuja-Halkola R, Sjölander A, et al. Maternal age at childbirth and risk for ADHD in offspring: a population-based cohort study. Int J Epidemiol. 2014;43:1815–24.
74. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. 2010;49:453-63.e1.
75. Heinonen K, Räikkönen K, Pesonen AK, Andersson S, Kajantie E, Eriksson JG, et al. Behavioural symptoms of attention deficit/hyperactivity disorder in preterm and term children born small and appropriate for gestational age: a longitudinal study. BMC Pediatr. 2010.
76. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA. 2002;288:728–37.
77. Dunn GA, Nigg JT, Sullivan EL. Neuroinflammation as a risk factor for attention deficit hyperactivity disorder. Pharmacol Biochem Behav. 2019;182:22–34.
78. Smith TF, Schmidt-Kastner R, McGeary JE, Kaczorowski JA, Knopik VS. Pre-and perinatal ischemia-hypoxia, the ischemia-hypoxia response pathway, and ADHD risk. Behav Genet. 2016;46:467–77.
79. Dachew BA, Scott JG, Mamun A, Alati R. Pre-eclampsia and the risk of attention-deficit/hyperactivity disorder in offspring: findings from the ALSPAC birth cohort study. Psychiatry Res. 2019;272:392–7.
80. Wiegersma AM, Dalman C, Lee BK, Karlsson H, Gardner RM. Association of prenatal maternal anemia with neurodevelopmental disorders. JAMA Psychiat. 2019;76:1294–304.
81. Liu X, Dalsgaard S, Munk-Olsen T, Li J, Wright RJ, Momen NC. Parental asthma occurrence, exacerbations and risk of attention-deficit/hyperactivity disorder. Brain Behav Immun. 2019;82:302–8.
82. Joelsson P, Chudal R, Uotila J, Suominen A, Sucksdorff D, Gyllenberg D, et al. Parental psychopathology and offspring attention-deficit/hyperactivity disorder in a nationwide sample. J Psychiatr Res. 2017;94:124–30.

83. Class QA, Abel KM, Khashan AS, Rickert ME, Dalman C, Larsson H, et al. Offspring psychopathology following preconception, prenatal, and postnatal maternal bereavement stress. Psychol Med. 2014;44:71–84.
84. Clements CC, Castro VM, Blumenthal SR, Rosenfield HR, Murphy SN, Fava M, et al. Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. Mol Psychiatry. 2015;20:727–34.
85. Leppert B, Havdahl A, Riglin L, Jones HJ, Zheng J, Smith GD, et al. Association of maternal neurodevelopmental risk alleles with early-life exposures. JAMA Psychiat. 2019;76:834–42.
86. Chang CH, Yu CJ, Du JC, Chiou HC, Chen HC, Yang W, et al. The interactions among organophosphate pesticide exposure, oxidative stress, and genetic polymorphisms of dopamine receptor D4 increase the risk of attention deficit/hyperactivity disorder in children. Environ Res. 2018;160:339–46.
87. Kahn RS, Khoury J, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. J Pediatr. 2003;143:104–10.
88. Brookes KJ, Mill J, Guindalini C, Curran S, Xu X, Knight J, et al. A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. Arch Gen Psychiatry. 2006;63:74–81.
89. Altink ME, Arias-Vásquez A, Franke B, Slaats-Willemse DI, Buschgens CJ, Rommelse NN, et al. The dopamine receptor D4 7-repeat allele and prenatal smoking in ADHD-affected children and their unaffected siblings: no gene–environment interaction. J Child Psychol Psychiatry. 2008;49:1053–60.
90. Wang Y, Hu D, Chen W, Xue H, Du Y. Prenatal tobacco exposure modulated the association of genetic variants with diagnosed ADHD and its symptom domain in children: a community based case–control study. Sci Rep. 2019;9:1–9.
91. Neuman RJ, Lobos E, Reich W, Henderson CA, Sun L-W, Todd RD. Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. Biol Psychiatry. 2007;61:1320–8.
92. Ornoy A, Finkel-Pekarsky V, Peles E, Adelson M, Schreiber S, Ebstein PR. ADHD risk alleles associated with opiate addiction: study of addicted parents and their children. Pediatr Res. 2016;80:228–36.
93. Knopik VS, Sparrow EP, Madden PA, Bucholz KK, Huziak JJ, Reich W, et al. Contributions of parental alcoholism, prenatal substance exposure, and genetic transmission to child ADHD risk: a female twin study. 2005;35:625–35.
94. Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA, et al. Maternal alcohol use disorder and offspring ADHD: disentangling genetic and environmental effects using a children-of-twins design. 2006;36:1461–71.