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Review Article

# The Influence of Prenatal Environmental Factors on the Risk and Development of ADHD: Insights from Epidemiological and Neurodevelopmental Research - Review

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***Motto:*** *Living with ADHD is like being locked in a room with 100 televisions and 100 radios all playing. None of them have power buttons so you can turn them off and the door is locked from the outside – Sarah Young [1].*

## Abstract

Recent research on Attention-Deficit/Hyperactivity Disorder (ADHD) underscores the significance of prenatal environmental factors alongside the well-documented genetic influences in the disorder's development. Studies have shown that approximately 5% of children and 2.5% of adults globally are affected by ADHD, with symptoms that severely impact various aspects of life. While genetics play a crucial role, accounting for 70% to 80% of ADHD's heritability, factors such as maternal diet, exposure to pollutants and teratogens, psychological stress, and prenatal inflammation are gaining attention for their potential impact on fetal brain development. These environmental factors could increase the risk of ADHD by altering critical developmental pathways, as evidenced by the association between maternal stress, dietary patterns during pregnancy, and increased ADHD symptoms in offspring. Furthermore, exposure to substances like alcohol and tobacco, as well as maternal inflammation, are linked to a higher risk of developing ADHD, highlighting the complex interplay between genetic predisposition and environmental exposures. This growing body of evidence calls for a comprehensive approach to prenatal care, emphasizing the importance of mitigating environmental and nutritional risks to prevent the development of ADHD and improve long-term outcomes for children.

**Keywords:** ADHD (Attention-Deficit/Hyperactivity Disorder); Prenatal environmental factors; Maternal diet and nutrition; Teratogens; Psychological stress; Prenatal inflammation; Maternal medication use

## Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that begins in childhood, characterized by inattention, hyperactivity, and impulsiveness. Being the most common psychiatric disorder in children, ADHD often persists into adulthood and is estimated to affect approximately 5% of children under 18 and 2.5% of adults worldwide [2,3]. ADHD is associated with a wide range of other mental health problems, including mood disorders, personality disorders, antisocial behavior, self-harm, and substance abuse [4]. In children, ADHD can disrupt social life and sometimes lead to poor educational performance and integration difficulties [2].

During fetal development, the brain undergoes rapid growth and development. Early environmental exposures during this vulnerable phase may have long-term consequences, including an increased risk of common neurodevelopmental disorders such as ADHD [5].

The etiology of ADHD has not yet been well-defined, but it is suggested that is an inherited disorder, with an estimated heritability of 70% to 80% [4]. The increasing prevalence of ADHD in recent decades has led to the hypothesis that environmental factors may also contribute to the development of ADHD. Some studies have shown that ADHD is associated with factors such as maternal obesity, prenatal exposure to alcohol, smoking, stress, as well as perinatal factors like prematurity and low birth weight, exposure to pollutants, psychosocial factors (parental neglect, aggressive maternal behavior), excessive exposure to social media/television, and certain nutritional deficiencies and unhealthy eating habits [1,4].

In the prenatal environment, exposures such as nutritional imbalances, smoking, alcohol consumption, pharmacological interventions, maternal immune activation (MIA), and psychological stress are recognized as critical environmental determinants that substantially shape offspring health trajectories (Figure 1).

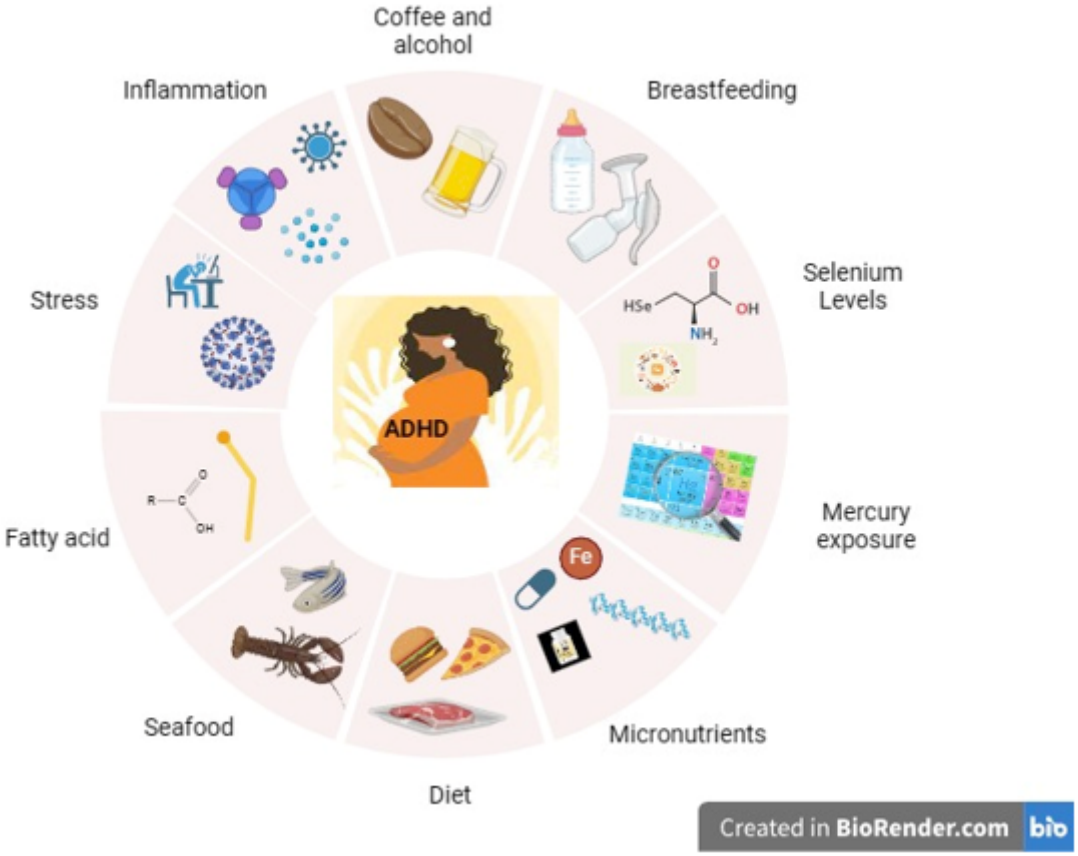


**Figure 1:** Prenatal Environmental Factors implicated in the development of ADHD.

These factors are implicated in the etiology of a spectrum of neurodevelopmental disorders (NDDs) and psychiatric pathologies, including ADHD, Autism Spectrum Disorder (ASD), schizophrenia, and depressive disorders [6,7]. The elucidation and modification of these prenatal environmental determinants offer a pivotal opportunity for the primary prevention of a diverse array of diseases, thereby underscoring the profound influence of early developmental conditions on health outcomes across an individual's lifetime. This framework underscores the interplay between early life exposures and subsequent health, advocating for the enhancement of public health outcomes through anticipatory preventive measures.

### The Impact of Maternal Diet on ADHD Risk in Offspring

Current epidemiological data highlights the limited understanding of the relationship between a pregnant woman's diet and her child's subsequent health challenges, including ADHD [8]. Recent research has identified a link between a poor-quality diet during pregnancy and an increased risk of ADHD in offspring. Specifically, diets high in carbohydrates and fats have been associated with ADHD through IGF2 DNA methylation, suggesting a potential developmental risk pathway, particularly for individuals with an early onset of the condition [9]. Alterations in the development of the cerebellum and hippocampus, crucial for ADHD development, have been linked to genetic and epigenetic modifications of the IGF2 gene and the levels of IGF2 [8, 9]. Additionally, the French EDEN study [8], involving 1,242 mother-child pairs, found significant correlations between a maternal diet low in healthful components or high in Western-style foods and children's hyperactivity/inattention problems, though not with behavioral issues.

Moreover, the Moba study (The Norwegian Mother, Father and Child Cohort Study) [10] observed an inverse relationship between the quality of the pregnant woman's diet and the symptom score and the diagnosis of ADHD in children. This study also noted a positive association between the proportion of ultra-processed products in the maternal diet and the incidence of ADHD symptoms in offspring [10].

These findings underscore the importance of targeting the dietary habits of pregnant women in early ADHD prevention measures. Emphasizing a nutritious diet rich in fruits, vegetables, fish, and whole grains and reducing or eliminating processed and snack-type foods are key strategies [8,10].

It has been shown that maternal deficiencies in iron, zinc, vitamin D, and polyunsaturated omega-3 fatty acids can affect fetal brain development. Nutrition during the preconception and prenatal periods is essential for fetal development and, by extension, fetal brain development. However, its associations with neurodevelopmental disorders, including ADHD, in offspring are not yet well understood.

## The Connection between Micronutrients and ADHD

### The Impact of Maternal Iron Deficiency on ADHD Development in Children

Iron deficiency (ID) has been positively associated with ADHD, with the common underlying pathophysiology arising from iron's central role in the brain. Iron serves as a cofactor in the synthesis of neurotransmitters (such as dopamine and serotonin) and is crucial for ATP production and myelination [11]. The impact of ID varies depending on the developmental stage during which the brain is exposed to iron depletion. Intrauterine/maternal and early postnatal ID is likely to adversely affect the development of brain structures, leading to irreversible neurocognitive and behavioral deficits [11,12]. The hippocampus, in particular, seems especially vulnerable, resulting in persistent hippocampus-based cognitive deficits in adulthood, despite iron supplementation [11,12].

Low maternal iron levels during pregnancy can cause iron deficiency in the brain of offspring, leading to neurocognitive disturbances related to neurodevelopmental disorders [13]. Unfortunately, the neurocognitive alterations caused by iron deficiency during the critical prenatal period of brain development are difficult to reverse and persist later in life [14]. In this context, low Serum Ferritin (SF) levels in the umbilical cord have been associated with poorer auditory recognition memory in newborns [15] and impaired cognitive and psychomotor development in early childhood [16].

To date, only a few studies have evaluated prenatal iron status and ADHD in children of different ages, giving mixed results [12,13]. In a large cohort of Swedish women and their offspring aged 6 to 29 years, Wiegersma, et al. [12] discovered that iron deficiency anemia in early pregnancy (at ≤ 30 weeks of gestation) was associated with a higher risk of ADHD co-occurring with autism spectrum disorder and/or intellectual disability disorder. However, these associations did not reach statistical significance with anemia diagnosed later in pregnancy (at >30 weeks of gestation) or when considering only ADHD as the outcome. Similarly, the Spanish INMA (Environment and Childhood) Birth Cohort Study [13] reported an inverse association between maternal serum ferritin in early pregnancy and inattention and total ADHD symptoms in boys at preschool age (4 years). However, SF levels were not predictive of hyperactivity/impulsivity symptoms [13].

The limited evidence and inconsistent findings in this area highlight the need for further research. Additionally, evidence suggests that maternal iron status during pregnancy affects child neurodevelopment differently depending on the trimester of pregnancy. However, it is still unclear which trimester the fetus is most susceptible to prenatal iron status or how this might influence ADHD symptomatology in children.

A deeper understanding of the critical times when iron deficiency most affects brain development and how this may contribute to ADHD symptomatology is needed.

## The Role of Zinc in Fetal Development and its Implications for ADHD

Zinc, an essential cofactor for over 100 enzymes, including various metalloenzymes and metalloenzyme complexes, plays a critical role in the metabolism of carbohydrates, fatty acids, proteins, and nucleic acids. Its significance extends to the metabolism of neurotransmitters and prostaglandins, as well as the maintenance of brain structure and function. Notably, zinc is implicated in the pathophysiology of Attention Deficit and Hyperactivity Disorder (ADHD), given its necessity for melatonin metabolism - an essential hormone for regulating dopamine, a key factor in ADHD [17].

Furthermore, zinc's role in fetal development is underscored by its involvement in carbohydrate and protein metabolism, nucleic acid synthesis, cell division, and differentiation [18]. Research in rodents has shown that gestational zinc deficiency leads to decreased cell counts and reduced brain mass in critical regions like the cerebellum, limbic system, and cerebral cortex [19]. Despite observations of decreased movement, increased heart-rate variability, and alterations in autonomic nervous system stability in the fetuses of zinc-deficient mothers, the evidence regarding the benefits of zinc supplementation for improving cognitive or motor development in children remains inconclusive [20].

## The Role of Vitamin D in Neurodevelopment and ADHD Risk

The relationship between prenatal vitamin D intake and the risk of hyperactivity/inattention has garnered attention, with studies by Li, Virk, D'Souza, and Julvez exploring this potential connection [8, 21, 22, 23]. However, the findings have been inconsistent. The Danish National Birth Cohort (DNBC) found an association between maternal multivitamin consumption and a reduced risk of hyperkinetic disorders and ADHD medication usage [21]. In contrast, the Growing Up study did not identify a correlation with hyperactivity-attention disorders [22]. The variation in vitamin combinations across these studies highlights the difficulty in standardizing research outcomes, pointing to the necessity of further investigation [8].

Globally, more than 50% of pregnant women are estimated to have vitamin D deficiency, a condition more common in pregnant women and newborns than in the general population [24]. Animal models underline vitamin D's importance for brain development, emphasizing its roles in neurotransmission modulation, neuroprotection [25], cell proliferation, differentiation, calcium signaling, and neurotrophic and neuroprotective actions within the brain. Given that the fetus depends on maternal vitamin D via the placenta, maternal deficiency could potentially impact fetal brain development.

Observational studies on maternal vitamin D deficiency during pregnancy and ADHD risk in offspring have yielded ambiguous results, often confounded by diet, lifestyle, and seasonal factors [24]. Research indicates that lower gestational vitamin D levels may intensify ADHD traits and symptoms in childhood [26-28], though not consistently across all studies [29,30].

A study on 1,650 mothers showed that increased vitamin D levels during pregnancy are associated with a lower risk of ADHD and ICD-10 hyperkinetic disorders in children [31]. The COPSYCH project, involving 700 mother-child pairs enrolled at week 24 of pregnancy, found that higher maternal preintervention 25(OH) vitamin D levels were linked to a lower risk of autism, reduced autistic symptoms, and a decreased risk of ADHD diagnosis [32]. However, high-dose vitamin D3 supplementation from week 24 of pregnancy to one week postpartum did not significantly reduce the overall risk of an ADHD diagnosis or symptom load in offspring at age 10, compared to a standard vitamin D3 dose [24, 32].

These insights underscore the complex interplay between maternal vitamin D levels during pregnancy and child neurodevelopmental outcomes, emphasizing the critical need for further research to elucidate vitamin D's protective effects against ADHD and other neurodevelopmental disorders.

### Folate

In a comprehensive study of the Danish National Birth Cohort (DNBC) involving 35,059 children in Denmark [21], it was found that the administration of folic acid supplements by mothers before or at the onset of pregnancy did not correlate with a clinical diagnosis of hyperkinetic disorders or the usage of ADHD medications [8, 21]. Meanwhile, in the Menorca cohort, multivitamins containing folic acid were linked to a decreased risk of hyperactivity/inattention [33]. However, it was linked to a decreased risk of hyperactivity and attention problems as measured by the Strengths and Difficulties Questionnaire (SDQ) in a subgroup of children monitored up to the age of seven years. Similar outcomes [8, 22, 23] were observed in New Zealand (in the Growing Up study with 6,247 participants) [22], and also in Spain (with 420 subjects) [23], indicating that folic acid supplementation before or at the start of pregnancy was not associated with the risk of developing hyperactivity-attention issues.

Furthermore, the KOMCHS study [34] conducted in Japan on 1,199 children revealed that a higher dietary intake of folates during pregnancy did not significantly reduce the risk of children's hyperactivity/attention problems, provided that folic acid supplementation was not considered. Additionally, a study in the UK involving 136 children [35] examined folate status and overall folic acid consumption in relation to ADHD risk. This research found that the concentration of folate in red blood cells at the start of pregnancy and the total intake of folate from food and supplements (excluding late pregnancy intake) were inversely related to the hyperactivity-attention score. However, this conclusion should be approached with caution due to the adjustment for a limited set of

covariates and the potential residual confounding from maternal lifestyle factors [8]. Consequently, there is insufficient strong evidence to demonstrate a link between dietary folic acid intake and/or supplementation and the risk of ADHD.

**The Impact of Mercury Exposure on ADHD Risk**

Mercury, a potent neurotoxin frequently encountered in the environment in both dietary and non-dietary forms, poses significant risks [36]. Prenatal exposure to mercury, especially through maternal consumption of contaminated fish, has been shown to adversely affect intelligence, language development, gross motor skills, visual-spatial abilities, memory, and attention in offspring [36,37].

A meta-analysis [37] examining the effects of exposure to thimerosal (which contains ethyl mercury) versus environmental mercury found positive significant associations between environmental mercury exposure and ADHD. In contrast, no significant associations were noted concerning thimerosal exposure. This discrepancy is attributed to ethyl mercury's faster breakdown rate compared to methylmercury, resulting in a lower risk of brain damage from ethyl mercury [38]. Additionally, exposure to methylmercury through maternal fish consumption has been significantly linked to an increased risk of ADHD in offspring, with both the duration and dose of mercury exposure influencing the disorder's incidence and prevalence [36].

These findings underscore the critical need for expecting mothers to be cautious about their dietary choices, particularly concerning fish known to have high mercury levels, to mitigate the risk of developmental disorders like ADHD in their children.

**Selenium (Se) Levels and Child Neurodevelopment**

The literature indicates that both selenium deficiency and excess can have harmful effects on health [2]. Notably, high levels of maternal selenium during pregnancy have been associated with negative impacts on neurological development in children. A prospective study involving 1,550 mother-child dyads from the Boston Birth Cohort identified a dose-dependent significant association between maternal erythrocyte selenium levels and the child's risk of developing ASD or ADHD [39]. This highlights the need for further research to elucidate how to optimize the health benefits of selenium while minimizing its potential adverse effects on pregnancy and long-term health outcomes.

These findings emphasize the importance of monitoring and managing dietary exposures to both mercury and selenium during pregnancy to protect against potential risks to child development and well-being.

**The relationship between PUFA administration and the risk of ADHD**

Limited evidence suggests that supplementation with omega-3 fatty acids during pregnancy may lead to favorable cognitive development in children. However, to date, no significant association has been identified between PUFA (Polyunsaturated Fatty Acids) administration in pregnant women and the risk of ADHD symptoms or diagnosis. Research by Miyake et al. [34] showed that neither total maternal intake of PUFAs nor specific intake of n-3 or n-6 PUFAs from food was associated with a child's risk of hyperactivity/inattention. A randomized clinical study in Mexico [40], which included 797 children, demonstrated that supplementation with 400 mg of DHA (Docosahexaenoic Acid) during the second half of pregnancy was not linked to a clinical risk of ADHD, though an improvement in attention among offspring of mothers who received DHA was noted.

In 2019, Lopez-Vincente et al. [41] highlighted the relationship between the n-6/n-3 ratio in cord blood plasma and ADHD symptoms. The study, involving 642 children, found an association between the n-6: n-3 ratio (AA/ [EPA + DHA]) in cord blood plasma and subclinical ADHD symptoms during childhood. Specifically, at the age of seven years, the number of ADHD symptoms increased by 13% for each unit increase in the omega-6: omega-3 ratio in cord blood plasma. This ratio was linked to the presence of ADHD symptoms but not to an ADHD diagnosis, and the association was not observed in children aged four years. The longitudinal nature of this study allowed the researchers to demonstrate that a higher prenatal n-6: n-3 LCPUFA (Long-Chain Polyunsaturated Fatty Acids) ratio could precede subclinical ADHD symptoms in childhood.

This overview underscores the complexity of understanding the impact of dietary fats on ADHD risk and highlights the need for further research to clarify the potential roles of specific fatty acids in neurodevelopment.

**The relationship between seafood intake during pregnancy and ADHD**

Currently, the evidence is insufficient to conclusively determine the relationship between seafood intake during pregnancy and the development of attention disorders or traits and behaviors similar to ADHD [42]. Research into the association between seafood consumption and the risk of ADHD in offspring has yielded inconsistent results and provides limited evidence for a direct link, with variations in exposure levels contributing to the ambiguity of findings [8].

However, the INMA cohort study observed a longitudinal association between high seafood intake (including total, lean, small, and large fatty fish) during early pregnancy and a reduction in ADHD symptoms (specifically attention-related) in children at the age of 8 years [43]. Conversely, the ALSPAC study, which included 8,946 children in the UK, found no significant association between seafood consumption during pregnancy and ADHD [44]. In contrast, a smaller study involving 217 children indicated that more frequent consumption of fish oil during pregnancy was linked to a decreased risk of hyperactivity/attention deficit [45].

Given these findings, it is advised that seafood intake during pregnancy be carefully monitored to mitigate the risk of mercury toxicity and its potential impact on fetal development [2]. The

conflicting evidence underscores the need for further research to clarify the relationship between maternal diet, specifically seafood consumption, and the neurodevelopmental health of children.

**The relationship between coffee consumption and ADHD**

Current safety guidelines recommend a regular consumption of caffeine up to 200 mg/day, which is considered safe for the fetus [46]. Generally, low to moderate caffeine consumption during pregnancy has not been linked to attention-hyperactivity problems in offspring [8,34,47-49]. The recommended upper limit for coffee consumption is between 300-384 mg/day, which is equivalent to three to four and a half cups of coffee per day [8,46,48].

However, in two extensive studies conducted in Denmark with over 70,000 participants [50,51], excessive caffeine intake (more than 8-10 cups of coffee per day) at the beginning of pregnancy was associated with an increased risk of ADHD. This correlation, observed in early pregnancy (up to 15 weeks) but not at 30 weeks, suggests a critical developmental window during which the fetal brain might be more vulnerable to the effects of caffeine [50].

These findings highlight the need for further research to understand the relationship between excessive caffeine consumption during pregnancy and the risk of ADHD. It underscores the importance of adhering to recommended caffeine intake limits to mitigate potential risks to fetal development.

**Prenatal exposure to alcohol**

Prenatal exposure to teratogenic substances, such as nicotine or alcohol, is associated with an increased risk of developing attention-deficit/hyperactivity disorder (ADHD) [52]. The direct effects of alcohol on prenatal brain development include interference with neurotrophic factors, cell adhesion molecules, altered glial maturation, and dysregulation of cell migration, potentially causing cell damage and loss through oxidative stress, neurotoxicity, or apoptosis mediated by glutamatergic antagonism [52,53]. Structural neuroimaging studies have identified brain changes in both ADHD and prenatal alcohol exposure that share remarkable similarities, suggesting that prenatal exposure to teratogenic substances might sometimes contribute to atypical brain development associated with ADHD. Observations of reduced volume in the whole brain, cerebellum, and caudate are consistent findings in children prenatally exposed to alcohol and those with ADHD [52,54]. A 2015 study involving approximately 20,000 parents discovered that children whose mothers consumed alcohol during pregnancy were 1.55 times more likely to develop ADHD [55]. However, the research presents mixed evidence regarding the risk of prenatal alcohol exposure and ADHD [55,56].

Consumption of alcohol during pregnancy can lead to Fetal Alcohol Spectrum Disorders (FASD) [56], characterized by facial abnormalities, growth retardation, and Central Nervous System (CNS) dysfunction. These conditions are associated with ADHD-like symptoms, including behavioral challenges, inattention, learning difficulties, poor memory, hyperactivity, and impulsivity [57]. An estimated 90.7% and 51.2% of children with FASD also have conduct disorder and ADHD, respectively [58]. There is some evidence that ADHD in FASD may be a specific clinical subtype, thus requiring a different treatment approach [59,60]. Research suggests that excessive alcohol consumption at any point during pregnancy or consistent consumption across all trimesters, even at low-moderate levels, significantly increases the likelihood of ADHD in offspring by age 12 [52,58]. Therefore, reducing binge drinking and regular alcohol use among pregnant women could significantly decrease the incidence of ADHD in their children. Evidence indicates that ADHD in FASD might represent a distinct clinical subtype, necessitating a tailored treatment strategy [52,60,61].

**Smoking**

Tobacco smoke, known for its thousands of toxic components including nicotine and carbon monoxide, poses significant risks to prenatal development [62]. Nicotine, alongside other tobacco and electronic cigarette compounds, impacts early life through changes in enzymes, hormones, gene expression, micro RNAs, and proteins, potentially leading to adverse outcomes in children exposed to maternal smoking [62,63]. Such exposure is linked to an increased risk of neurodevelopmental disorders like Attention-Deficit Hyperactivity Disorder (ADHD), anxiety, and depression, affecting brain circuits, neurotransmitter responses, and brain volume [64].

Prenatal smoking detrimentally influences cognitive and neurobehavioral development, resulting in behaviors such as hyperactivity, inattention, and deficits in auditory processing, reading, and language development [62,65,66]. Reviews have associated maternal smoking with higher rates of conduct disorder and ADHD in exposed children compared to non-exposed peers [67-70]. However, the link to ADHD symptoms might be indirect, influenced by socio-environmental and genetic factors, including parental psychopathology [62,71,72].

A meta-analysis by Han [72] involving 12 cohort study involving 17304 pregnant women suggested that smoking during pregnancy elevates the risk of ADHD in offspring, especially among children of heavy smokers. Additionally, Jansone, et al. [73] reported that prenatal tobacco exposure alters resting-state EEG patterns in school-aged children, indicating increased delta and theta brain activity related to the quantity of cigarettes smoked.

Given the clear risk of ADHD associated with maternal smoking, raising awareness about the dangers of smoking during pregnancy and promoting cessation are essential steps in reducing ADHD risks in children.

**Impact of Prenatal Exposure to Various Substances on Offspring Neurodevelopment and ADHD Risk**

**Pesticides and ADHD:** Prenatal exposure to organophosphorus pesticides (OPPs), commonly found in agricultural communities

and residential insecticides, has been associated with childhood attention-deficit/hyperactivity disorder (ADHD) [74]. This association underscores the potential neurodevelopmental hazards posed by these chemicals.

**Medications and ADHD**

**Antibiotics:** The association between prenatal exposure to antibiotics, including penicillins, betalactams, and macrolides, and ADHD in offspring has been documented [75,76]. The Codibine study revealed that maternal prescriptions of penicillin up to 2 years before birth increased ADHD risk, especially with multiple prescriptions. This was associated with lower neonatal levels of Epidermal Growth Factor (EGF) and soluble Tumor Necrosis Factor receptor I (sTNF RI), suggesting a complex interaction between maternal medication use and offspring neurodevelopment [77].

**Mental Disorder Medications:** The largest association between offspring ADHD and maternal medication was observed with maternal use of medication for mental disorders before pregnancy [78]. This aligns with the genetic component of ADHD and its association with other psychiatric disorders [79-82].

**ADHD Medication during Pregnancy:** Children born to mothers who continued ADHD medication during pregnancy did not have a higher likelihood of neurodevelopmental disorders than those whose mothers discontinued medication [83].

**Antiepileptics:** Studies found no risk related to lamotrigine exposure but observed an increased risk of ASD and ADHD with maternal use of valproic acid, suggesting some antiepileptics may be safer during pregnancy than others [84-86].

**Acetaminophen:** A meta-analysis involving over 70,000 children from six European cohorts indicated that prenatal exposure to acetaminophen was associated with a 19% and 21% increased likelihood of having ASC and ADHD symptoms, respectively [87]. This finding supports previous analyses reporting increased odds for ADHD related to prenatal acetaminophen exposure [88,89].

Further research is necessary to determine whether the increased risk of ADHD is directly linked to the metabolic products of substances like paracetamol or related to the inflammation for which these medications were prescribed.

**Maternal Prenatal Inflammation as a Predictor of ADHD and Other Neurodevelopmental Disorders (NDDs)**

Research underscores a crucial connection between maternal prenatal inflammation and an increased risk of ADHD symptoms and other NDDs in children. It reveals the intricate dynamics between prenatal environmental factors and child neurodevelopment. A study by Gustafsson HC in 2020 [90] points out that maternal cytokines during pregnancy not only foresee ADHD in early childhood but also serve as a conduit for various prenatal risks, such as maternal distress, affecting child psychopathology. This influence is mediated through several biological pathways:

**Impact of Maternal Cytokines:** These cytokines are capable of crossing the placental barrier, enhancing cytokine levels in the amniotic fluid and fetal brain, which may interrupt normal development. They could lead to epigenetic modifications within the placenta, increasing cytokine expression and modifying the fetal environment. Their role in activating immune cells within the decidua further increases cytokine release, affecting the maternal-fetal interface and thus fetal development. This may trigger a fetal inflammatory response, fostering a pro-inflammatory state in the fetal brain that could significantly impact brain development, leading to behavioral and cognitive changes detectable early in life [91].

**Maternal Immune Activation (MIA) Hypothesis:** Current studies back the MIA hypothesis, which suggests that disruptions in the maternal immune system during pregnancy can impair fetal neurodevelopment, possibly leading to NDDs such as ASD, ADHD, and TS. This hypothesis is partially grounded on research connecting elevated maternal cytokine levels during pregnancy to these disorders [90,92-96]. Factors like obesity, asthma, autoimmune diseases, infections, and psychosocial stress are identified as triggers for maternal immune activation, each associated with an increased risk of NDDs in offspring [93].

**Broader Implications and the Role of Prenatal Stress**

The consequences of prenatal stress, including inflammation, extend beyond ADHD, influencing various aspects of cognitive and emotional development in children. The necessity for comprehensive prenatal care strategies that include mental health and stress management to mitigate these risks is emphasized.

**Influence of the COVID-19 Pandemic**

The COVID-19 pandemic, a significant global stressor, has notably impacted mental health across different populations. Studies by Popa [97] and Hernandez-Lorca [98] highlight the mental health challenges during lockdowns, suggesting a compounded effect of pandemic-related stress on prenatal and postnatal development, calling for enhanced support and interventions for expectant mothers.

**COVID-19 and Maternal Inflammation**

Understanding the impact of viral infections like COVID-19, which can trigger a cytokine storm, on offspring is crucial. The Kuwait Cohort Study [99] showed that children of mothers infected with SARS-CoV-2 had a higher incidence of neurodevelopmental and behavioral delays, underscoring the need for further research into the role of microglia and cytokine production in the offspring of infected pregnancies [95].

Research into cord blood changes during maternal COVID-19 infection indicates a fetal immune response characterized by proinflammatory cytokine release, which can continue post-infection, risking developmental disorders. Elevated IL-6 levels in pregnant women with COVID-19 and their newborns have been linked to reduced cognitive abilities in infants [100-102].

A study by Suleri, et al. [103] found a correlation between continuous maternal inflammation and reduced cerebellar volume in children, hinting at a potential connection to various developmental and behavioral disorders. The timing of maternal inflammation might also differentially affect neurological development, with early inflammation linked to aggression and impulsivity, and later inflammation associated with withdrawal and anxiety [103-105].

Concerning maternal COVID-19 vaccination and its impact on offspring, studies by Atyeo and Boelig [106], and Alhousseini [107] found no significant changes in neonatal cord blood IL-6 levels among vaccinated, infected, or control groups. Research by Sabharwal [108] on 53 mother-infant pairs showed a decrease in IL-1β and an increase in IFN-λ1 in infants born to vaccinated mothers. Additionally, a prospective cohort study [109] indicated no increased risk of developmental delays in infants with maternal exposure to the COVID-19 vaccine, affirming its safety regarding early neurodevelopment. These findings highlight the need for further studies to validate these results and provide clinical guidance, though the overall impact of maternal vaccination on cytokine profiles and inflammatory responses in offspring remains to be fully understood.

**Breastfeeding and ADHD**

Breast milk delivers essential nutrients that support neurological development, including long-chain polyunsaturated fatty acids, which are essential for brain growth and function. The act of breastfeeding fosters the mother-infant bond, potentially influencing the child's behavioral and emotional regulation [110, 111].

Epidemiological studies suggest that breastfed children may be less likely to develop ADHD later in life. For instance, Mimouni-Bloch et al. [112] observed that children diagnosed with ADHD were less likely to have been breastfed at 3 months compared to their non-ADHD counterparts. This hypothesis, proposing breastfeeding's protective effects against ADHD, gains support from research emphasizing early nutrition's role in brain development and its potential influence on the prevalence of developmental disorders [113].

The benefits of breastfeeding for infant neurodevelopment are consistently noted among infants who are exclusively or additionally breastfed for long periods of time. Breastfeeding has been positively associated with several outcomes indicative of early brain development and cognitive functioning. Brain neuroimaging studies have demonstrated that children who are exclusively breastfed exhibit increased volumes of white matter and subcortical gray matter compared to those who are formula-fed. Nevertheless, distinguishing the specific effects of nutrition in breast milk from other confounding factors influencing brain development presents a challenge, particularly in human studies [114, 115].

However, infants breastfed for shorter durations (less than the average or median duration) might not fully experience these benefits [115]. Specific components of human milk, such as long-chain polyunsaturated fatty acids (LC-PUFA), phospholipids, and cholesterol, are known to promote the development and synthesis of the myelin sheath [116]. Gangliosides, crucial for cell membrane structure and healthy infant brain development, are consistently found in breast milk throughout lactation [117]. As children grow and their caloric intake needs increase, prolonged and enhanced breast milk consumption naturally boosts their intake of gangliosides, LC-PUFA, phospholipids, cholesterol, and other neurodevelopment-promoting components [115, 118].

Research in this domain must consider numerous confounding factors, such as genetic predisposition to ADHD, parenting behaviors, and socioeconomic status, which may influence both breastfeeding practices and the risk of ADHD in children [114].

While some studies indicate a protective effect, others find no significant link between breastfeeding and a reduced risk of ADHD, highlighting the necessity for further and more rigorous research to elucidate this relationship [119].

The World Health Organization and other health authorities recommend exclusive breastfeeding for the first six months of life due to its wide-ranging health benefits, underscoring the importance of this practice as research continues to explore its specific effects on ADHD [120].

## Future Perspectives and Conclusions

ADHD deeply affects academic results, well-being, and social interactions. As a result, this disorder is of great cost both to individuals and to society. Despite the availability of knowledge regarding the mechanisms involved in ADHD, there is still much to be learned and explored in terms of treatment and prevention, especially during pregnancy. Implementation of early interventions and targeted strategies is essential to create a healthier trajectory for future generations. This requires a comprehensive approach to antenatal and postnatal care that holistically addresses the environmental, nutritional and psychosocial domains, thereby mitigating the predisposition and impact of NDD and ADHD.

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