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REVIEW ARTICLE

Environmental Risk Factors in Autism Spectrum Disorder: A Narrative Review

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Abstract: Existing evidence indicates that environmental factors might contribute up to 50% of the variance in autism spectrum disorder (ASD) risk. This structured narrative review offers a comprehensive synthesis of current knowledge on environmental risk factors in ASD, including evaluation of conflicting evidence, exploration of underlying mechanisms, and suggestions for future research directions. Analysis of diverse epidemiological investigations indicates that certain environmental factors, including advanced parental age, preterm birth, delivery complications, and exposure to toxic metals, drugs, air pollutants, and endocrine-disrupting chemicals, are linked to an increased ASD risk through various mechanisms such as oxidative stress, inflammation, hypoxia, and its consequences, changes in neurotransmitters, disruption of signaling pathways and some others. On the other hand, pregnancy-related factors such as maternal diabetes, maternal obesity, and caesarian section show a weaker association with ASD risk. At the same time, other environmental factors, such as vaccination, maternal smoking, or alcohol consumption, are not linked to the risk of ASD. Regarding nutritional elements data are inconclusive. These findings highlight the significance of environmental factors in ASD etiology and emphasize that more focused research is needed to target the risk factors of ASD. Environmental interventions targeting modifiable risk factors might offer promising avenues for ASD prevention and treatment.

Keywords: Autism spectrum disorder, epidemiology, risk factors, environmental factors, toxic metals, pregnancy.

1. INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that can significantly impair social, behavioral, and communication domains. ASD is characterized by deficits in three main domains: (1) verbal and nonverbal communication, (2) social interaction, and (3) restricted and repetitive behaviors and interests [1]. In 1943, Austrian-American psychiatrist Leo Kanner (1894-1981) first described autism as an innate inability to establish natural emotional connections with others [1].

In 1983, the Diagnostic and Statistical Manual (DSM) did not include Asperger's syndrome or pervasive developmental disorder-not otherwise specified (PDD-NOS), and autistic disorder had a more restrictive criterion. The DSM-IV included Asperger's Syndrome, autistic disorder, PDD-NOS, and childhood disintegrative disorder, which resulted in inconsistent diagnoses. Recognizing that there is still much to learn, the new DSM-5 edition consolidated the four previous disorders into one diagnosis, ASD [2]. The DSM-5 introduced a change in which the criteria for social and communication deficits were merged into a single domain, and it also introduced a rating of severity. Furthermore, the DSM-5 introduced a new diagnosis, social communication disorder, separate from ASD [2].

Individuals with ASD commonly experience impairments in intellectual functioning, with approximately 30% of cases also exhibiting intellectual disability [3]. Attention deficits are also frequently observed, occurring in about 30-40% of cases, along with sensory sensitivities, gastrointestinal problems, anxiety, sleep disturbances, depression, immune deficits, and other is-

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sues [4, 5]. Furthermore, up to 15% of cases may be associated with genetic abnormalities such as fragile X syndrome, Timothy syndrome, and tuberous sclerosis [6].

Symptoms of ASD typically start to appear by age three, although they may not be fully present until school or later age. Some research has suggested that symptoms can be detected as early as six to 18 months of age [7]. However, milder cases are less likely to be identified and diagnosed younger than severe cases [8].

Early intervention is essential in promoting healthy development and optimizing the potential benefits for people with ASD throughout their lifespan. While extensive research has been conducted on the disorder, the etiological factors of ASD are not fully understood—however, significant progress in the identification of some of this condition's genetic and neurobiological foundations. ASD has been found to have heritability, with environmental factors also playing an important role [9, 10].

This review aims to provide an overview of the major environmental risk factors linked to ASD. Through synthesizing relevant research findings, the paper seeks to increase the understanding of potential causes and contributing factors to ASD development. By highlighting the key environmental risk factors, the review may help inform future research and interventions to prevent or manage ASD.

2. ASD PREVALENCE AND DEMOGRAPHICS

According to a paper that systematically reviewed studies published from 2012 to 2021, the global median ASD prevalence in children is 1% [11]. However, the reported figure may not accurately reflect the true prevalence of ASD in low- and middle-income countries, which suggests that the actual prevalence might be underestimated. A study performed in South Korea in 2011 reported a prevalence rate of 2.6 percent [12].

ASD is a condition that impacts individuals from all ethnic and socioeconomic backgrounds [13]. Males are affected by ASD about four times more often than females, although this sex ratio decreases as the severity of the disorder increases [14]. However, this statistic does not consider the presence of ASD in gender-diverse populations, which have a higher prevalence of ASD. Minority groups are often diagnosed later and less frequently [13, 15].

In 2016, data collected by the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network indicated that about one in 54 US children (one in 34 boys and one in 144 girls) had an ASD diagnosis. This represents a ten percent rise from the rate of one in 59 reported in 2014, a 105 percent rise from one in 110 in 2006, and a 176 percent rise from one in 150 in 2000 [16]. According to the last update by the CDC's ADDM Network one in 36 (2.8%) 8-year-old children has been diagnosed with ASD. These most recent statistics surpass the findings of 2018 which was 1 in 44 (2.3%) [17]. However, comparing rates of autism over the past few decades is challenging because of changes in the diagnostic ASD criteria outlined in the DSM. During the last decade, milder ASD cases have increased most in the estimates of CDC, while less change has been seen in the ASD prevalence along with intellectual disability [18].

3. ECONOMIC BURDEN OF ASD IN THE UNITED STATES

ASD imposes a substantial economic burden on the United States, with most costs attributed to adult services. Estimates from 2014 show that adult services for ASD range from USD 175 to USD 196 billion per year, three times higher than that for neurotypical children, from USD 61 to USD 66 billion per year [19]. These high costs can be attributed to the need for specialized services and therapies, increased healthcare utilization, and long-term care and support for individuals with ASD throughout their lifespan.

ASD is not just a childhood condition [20]; it has lifelong impairments and associated comorbidities such as injury [21] and increased mortality risk [22, 23]. Medical expenditures for children and adolescents with ASD are 4.1 to 6.2 times bigger than those without ASD [24]. Addressing the economic burden of ASD requires a comprehensive approach that involves early intervention, improved access to services, and increased research to identify effective treatments and interventions.

Mothers of children with ASD often take on the role of case manager and advocate for their child, which makes it less likely for them to work outside the home. Compared to mothers of children with no health limitations, these mothers work fewer hours per week and earn 56 percent less. Furthermore, they make 35 percent less than mothers of children with other disabilities or disorders [25].

In 2015, the estimated direct and indirect costs of providing care for individuals with ASD in the United States were USD 268.3 billion, exceeding the costs of stroke and hypertension. These costs include education, healthcare, and other lifelong services, ranging from USD 1.4 million to USD 2.4 million per year per

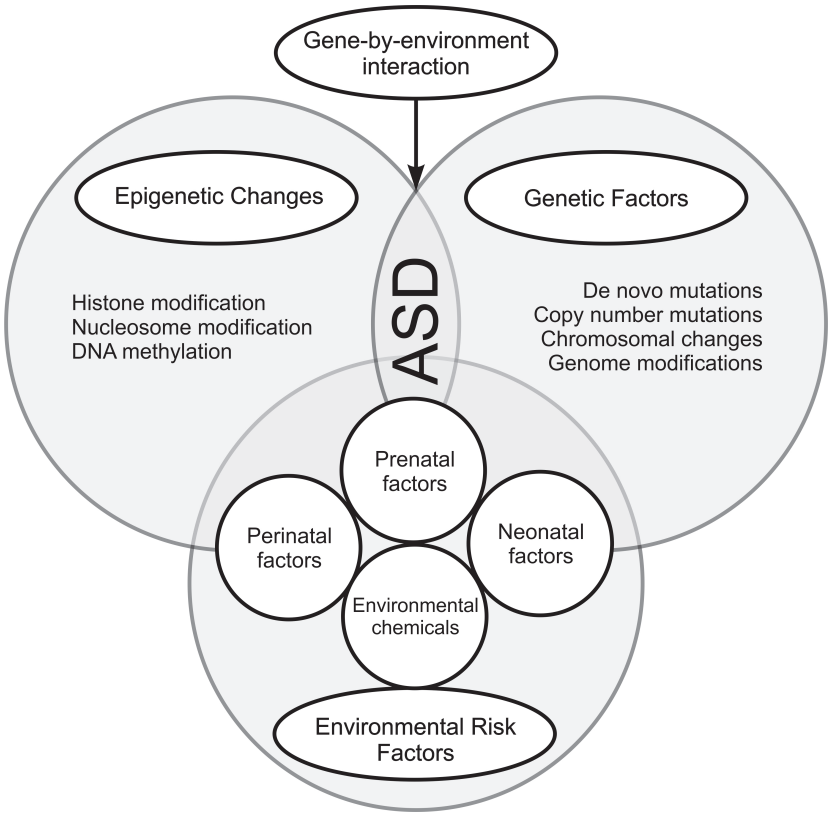

Fig. (1). Interplay of autism spectrum disorder's risk factors. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

individual with ASD [26]. Such high costs have significant economic impacts and necessitate bigger investments in effective interventions and support systems for individuals with ASD and their families.

4. ENVIRONMENTAL RISK FACTORS

Some studies suggest that genetic and non-genetic factors contribute to ASD approximately equally [27]. Although genetics contribute to ASD, the genetic heterogeneity and phenotypic of the disorder support a multifactorial etiology (Fig. **1**). Identifying environmental risk factors is particularly important because they are potentially preventable, unlike genetic ones.

5. PRENATAL, PERINATAL, AND NEONATAL FACTORS

There have been identified over 20 factors that occur before, during, and shortly after birth linked to ASD risk [28-31].

6. PRENATAL RISK FACTORS

Prenatal risk factors that have been consistently associated with ASD include parental age, interpregnancy interval, immune factors (such as autoimmune diseases and infections during pregnancy), medication use (especially antidepressants, anti-asthmatics, and anti-epileptics), maternal metabolic conditions (such as diabetes, gestational weight gain, and hypertension), and maternal dietary factors (such as folic acid and related nutrients use, maternal iron (Fe) intake, maternal vitamin D levels, and polyunsaturated fatty acid (PUFA) intake).

6.1. Parental Age

Advanced maternal and paternal age are consistent prenatal risk factors for ASD [28, 32, 33] (Table **1**). Meta-analyses by Wu *et al.* indicate that every 10-year increase in maternal and paternal age raises the risk of ASD in the offspring by 18% and 21%, respectively [34]. The risk of ASD varied depending on parental age combinations, with the highest risk when both parents were older [35, 36]. Studies in humans and animals support the hypothesis that de novo mutations contribute to the association between paternal age and ASD while advancing maternal age is associated with chromosomal changes and genomic modifications. Possible mechanisms underlying these associations include epigenetic modification, pregnancy risks associated with age, and social factors influencing reproductive age [35].

6.2. Interpregnancy Interval

Numerous studies have reported an increased ASD risk with both short (<12 months) and long (>60-84 months) interpregnancy intervals (IPIs), while an inverse, linear relationship between IPI and observed ASD risk [36-42] (Table **1**). Research has shown a two-fold or three-fold increase in ASD risk for second-born children when IPIs are less than 12 months compared to those with 36 months. Short and long IPIs are also associated with perinatal complications such as preterm birth and low birth weight, which are risk factors for ASD. The underlying mechanisms for the association between ASD and short and long IPIs may differ, with maternal nutrient depletion, stress, infertility, and inflammation being possible mechanisms for short IPIs. In contrast, infertility and related complications may be potential mechanisms for long IPIs [43].

6.3. Immunological Factors

Several studies have linked maternal hospitalization due to infection during pregnancy with an increased ASD risk, including a large study of over two million individuals who reported an elevated risk associated with both viral and bacterial infections during the prenatal period [44, 45] (Table **1**). Previous research has shown that viral infections during the prenatal period can initiate ASD in some children. Cases of ASD have been reported following exposure to measles, rubella, and mumps during gestation, as well as perinatal herpes simplex virus, congenital cytomegalovirus, and congenital rubella infections. The study results are consistent with animal models showing maternal immune system activation leading to phenotypes resembling autism in their offspring [46]. Furthermore, maternal antibodies from viruses or bacteria can pass through the placenta, leading to disturbances in fetal neurodevelopment *via* molecular mimicry [47]. Studies have also reported that ASD-associated copy number variations (CNVs) modify the prenatal exposure effect [48].

Increased risk of ASD linked to a familial history of autoimmune disease [49, 50]. Maternal autoimmune reactions and immune-mediated conditions [45, 51] can also impact the risk of ASD through antibody transfer and the impact of immune markers on the developing nervous system (Table **1**). Maternal anti-fetal brain antibodies were reported in some ASD cases in several small-sample studies, with no antibodies observed in controls [52].

Studies examining biomarkers have found an elevated ASD risk associated with changes in C-reactive protein (CRP), interferon-gamma (IFN-γ), interleukin-4 (IL-4), and interleukin-5 (IL-5) levels in maternal sera [53, 54]. In contrast, the estimated levels of immune markers in newborn blood are more inconsistent [55, 56]. However, the methodological limitations of these studies, including high correlation among variables, indicate the need for further research.

6.4. Medication Use

Historically, exposure to teratogenic medications has been associated with an increased risk of ASD [57]. However, other studies have indicated that exposure to antidepressants, anti-epileptics, and anti-asthmatics (*i.e.*, β-2 adrenergic receptor agonists) during prenatal development poses a risk (Table **1**). Although these drugs possess different pharmacological activities, they can cross the blood-brain barrier and the placenta and be transmitted to the child *via* breastfeeding. Animal models have provided evidence of neurological effects in prenatally exposed offspring [58, 59].

The investigations have mainly focused on selective serotonin reuptake inhibitors (SSRIs), which are commonly prescribed as antidepressants. Still, the evidence conflicts with some studies reporting an elevated risk of ASD, while others say there is no association. Conversely, several studies of anti-epileptics [60-62] and β-2 adrenergic receptor agonists [63] have consistently reported autistic traits or elevated ASD risk [60, 62].

7. PERINATAL AND NEONATAL FACTORS

Much evidence suggests that various perinatal factors are associated with an increased risk of ASD. These factors include lower gestational age or preterm birth [64-66], gestational small or large size [64, 66], maternal metabolic conditions such as diabetes, gestational weight gain, hypertension, and the use of labor and delivery drugs.

Gestational age, especially early gestational age, is associated with adverse health outcomes, including developmental delays and later intellectual impairments in childhood and adolescence. It has been associated with various cognitive and psychiatric difficulties in children, including speech and language problems, attention problems, social problems, hyperactivity, and learning disabilities. Low birth weight is a likely indicator of fetal growth problems.

Maternal metabolic conditions such as diabetes, gestational weight gain, and hypertension have been linked to mechanisms relevant to ASD, such as oxidative stress, fetal hypoxia, and chronic inflammation (Table **1**) [67-72]. These conditions can lead to prolonged or acute hypoxia in the fetus, which may be a significant risk factor for neurodevelopmental disturbances.

Table 1. Summary of prenatal, perinatal, and neonatal risk factors associated with ASD.

Prenatal Risk Factors	Perinatal and Neonatal Risk Factors
Parental age	Lower gestational age/preterm birth
Interpregnancy interval	Small or large size of gestation
Immune factors (bacterial and viral infection during pregnancy, autoimmune diseases)	Cesarean delivery
Medication use (antidepressants, anti-asthmatics, anti-epileptics)	Assisted labor
Maternal dietary factors (folic acid and related nutrients, prenatal maternal iron intake, prenatal maternal vitamin D levels, prenatal polyunsaturated fatty acid intake)	Labor and delivery drugs
Maternal metabolic conditions (diabetes, gestational weight gain, hypertension)	Assisted conception
Maternal lifestyle factors (alcohol, smoking)	-

Recent studies have also suggested a possible association between the use of labor and delivery drugs and the development of ASD [71, 73], particularly with the increased rates of epidurals and labor-inducing medications in the past 30 years [72]. However, some studies contradict such findings and suggest no association between using labor-inducing drugs and the risk of developing ASD [57, 71].

The risk of ASD with cesarean delivery is a topic of ongoing debate [74, 75]. While a meta-analysis of 21 studies showed a little increased risk of ASD with cesarean delivery [76], a recent animal study demonstrated experimentally that cesarean delivery induced ASD-like traits in offspring mice [77]. A multi-national cohort study of five million births found that emergency or planned cesarean delivery is consistently associated with a mildly elevated risk of ASD from gestational weeks 36 to 42 compared to vaginal delivery [78].

Assisted conception overall is not associated with a significantly increased risk of ASD [79, 80]. However, some specific treatments may increase the risk of ASD [81-83], and adequately powered studies are necessary to examine therapies and separate the influence of infertility conditions from the effect of medicine itself [84].

Taken together, perinatal factors play a significant role in the development of ASD. Identifying and managing these factors early on is essential to reduce the risk of neurodevelopmental disturbances. Further research is necessary to understand the complex interplay between perinatal factors and ASD.

8. MATERNAL DIETARY FACTORS

In recent years, there has been growing interest in examining the relationship between maternal dietary factors during pregnancy and the risk of ASD. Maternal prenatal diet significantly impacts fetal neurodevelopment, as established by several studies. For instance, there are well-established associations between folic acid deficiency, neural tube defects, and other adverse neurodevelopmental outcomes [85].

Studies have shown that certain minerals and trace elements, such as zinc [86], magnesium [87], and selenium (Se) [88], are essential for proper fetal brain development. Inadequate intake of these nutrients during pregnancy has been associated with an increased risk of neurodevelopmental disorders, including ASD. Conversely, excessive maternal intake of certain nutrients, such as Fe [89] and copper [86, 89], has also been linked to an increased risk of ASD in offspring. This highlights the importance of maintaining a balance of essential nutrients during pregnancy to ensure optimal fetal brain development.

8.1. Prenatal Vitamins and ASD

The role of prenatal vitamins in reducing the risk of ASD has been investigated in several studies. Two studies in the United States and Norway reported a nearly 40% decline in ASD risk associated with prenatal vitamin use [90, 91]. The US study also found a significant decrease in ASD risk with increasing mean daily folic acid intake [92]. However, a study conducted in Denmark did not find any association between pre--conceptional and prenatal folic acid or multivitamin use and ASD [93]. One study that measured folate blood concentrations during pregnancy (at 11-21 weeks gestation) found no association with ASD traits. It is important to note that differences in folate levels and fortification practices across countries [94], genetic mechanisms that affect the carbon pathway [91], and the timing of exposure assessments may account for discrepancies in findings.

One study suggested that attention deficits, rather than ASD, were associated with lower prenatal maternal vitamin D levels [95] (Table **1**). According to Zhong *et al.* (2020), adequate prenatal intake of folic acid and vitamin D were each associated with a lower possibility of having offspring with ASD [96]. Saad *et*

al. (2015) conducted a cross-sectional analysis on 122 Egyptian ASD children to assess their vitamin D status and the relationship between vitamin D deficiency and autism severity. 57% of the patients had vitamin D deficiency. Lower vitamin D levels were associated with severe autism and vitamin D supplementation improved outcomes in 80.72% of participants in an open-label trial [97]. El-Ansary *et al.* (2018) analyzed 28 Saudi males with ASD for the correlation between vitamin D levels, inflammation/oxidative stress biomarkers, and ASD presence/severity. The study discovered that Saudi ASD children had lower vitamin D and higher hs-CRP/8-OH-dG levels than neurotypical controls. CYP1B1 and 25(OH)D3 biomarkers correlated with ASD severity on the Childhood Autism Rating Scale (CARS), and all four biomarkers displayed good sensitivity and specificity for early ASD diagnosis. However, further research is required to validate these findings.

8.2. Polyunsaturated Fatty Acids

Due to their essential role in these processes, polyunsaturated fatty acids (PUFAs) are a key area of interest in studying brain development and function. Specifically, both omega-3 and omega-6 PUFAs have been extensively researched in this area. Maternal fish intake is a source of PUFAs and mercury (Hg), a known neurotoxicant. Lyall et. al (2013) found a significant decrease in the risk of ASD with higher prospectively reported prenatal PUFA intake [97] (Table **1**). Fish oil supplements have not been consistently associated with ASD, although statistical power was limited in some studies [90, 98]. Further investigation is necessary to examine all maternal dietary factors using rigorously designed prospective studies.

9. MATERNAL LIFESTYLE FACTORS

9.1. Alcohol and Smoking

Although smoking and alcohol consumption during pregnancy are well-known to have adverse neonatal consequences, several studies have reported no association between maternal prenatal use of these substances and ASD risk [99, 100]. Although fewer studies have been conducted regarding maternal prenatal alcohol consumption, the largest study found no association [101]. However, a recent meta-analysis from the US found that maternal smoking from six months before conception until delivery was persistently associated with an increase in autism-related symptoms [102].

Given the current lack of conclusive evidence, it is difficult to establish a clear association between maternal alcohol consumption or smoking and the development of ASD. Therefore, further research is needed to fully assess the potential impact of these factors on ASD risk.

10. ENVIRONMENTAL CHEMICALS

The impact of environmental chemicals on fetal neurodevelopment is an area of growing concern. Many of these chemicals can cross the placenta and the blood-brain barrier, accumulating in the developing brain and disrupting normal neurodevelopment. Additionally, certain chemicals can interfere with hormone or inflammatory pathways, further exacerbating the detrimental effects on neurodevelopment.

In recent years, there has been an increase in epidemiological research investigating the potential link between environmental chemicals and ASD risk. Specifically, research has focused on two main areas: air pollution and endocrine-disrupting chemicals (EDCs). By understanding the role that these environmental factors play in ASD development, it may be possible to develop strategies to minimize their impact and improve neurodevelopmental outcomes.

Neurodevelopmental disorders such as ASD may be linked to widespread neurotoxicant exposure, and these disorders have a male preponderance [103]. Research suggests that males may be more vulnerable to toxic exposures than females due to several factors, including a greater neuroinflammatory response and reduced vulnerability to oxidative stress in females. Additionally, females have greater glutathione availability, sulfate-based detoxification capacity, and neuroprotective effects from female hormones. The neurotoxicants that exhibit consistent gender-specific effects, with males being more affected, include lead (Pb), Thimerosal/ethyl Hg, some organochlorine pesticides, and air pollution [103].

10.1. Air Pollution

Numerous studies in the United States suggest that prenatal exposure to air pollution may be a risk factor for ASD [104-114]. These studies have mainly focused on air toxics, criteria air pollutants (including nitrogen dioxide (NO_2), ozone, and particulate matter (PM)), and traffic exposure (Table **2**). For example, one study conducted in Northern California found moderately increased risks of ASD with several metals and chlorinated solvents [105]. Other studies in several regions have reported risks from additional toxicants such as Pb, Hg, cadmium (Cd), solvents, methylene chloride, styrene, and diesel particulate matter [106, 107, 109, 112]. Two Californian studies have suggested associations with criteria air pollutants such as NO_2, PM2.5,

and PM10 [104, 110]. In contrast, studies conducted over larger regions in the United States have reported increased ASD risk with elevated PM10 and PM2.5 exposure [108, 114].

Table 2. Summary of environmental chemicals associated with ASD*

1.	Hazardous air pollutants (solvents, methylene chloride, styrene, diesel particulate matter, *etc.*)
2.	Criteria air pollutants (nitrogen dioxide, ozone, particulate matter less than 2.5 or 10 μm in diameter, *etc.*)
3.	Endocrine-disrupting chemicals (organophosphate pesticide, trans-nonochlor pesticide, organochlorine pesticide, polychlorinated biphenyls, *etc.*)
4.	Heavy metals (lead, cadmium, mercury, *etc.*)
5.	Vaccines

Note: * The association between each category and ASD in the studies cannot be definitively categorized due to data complexities and limitations.

Exposure assignment for these studies was based on linkages to the Air Now network, which monitors near-roadway air pollution, focusing on traffic density, dispersion models, and distance to roadways. Two of these studies particularly mentioned the third trimester of pregnancy as the most important exposure window [105, 114]. One study also found susceptibility to NO_2 exposure to be increasingly associated with a genetic variant near the MET gene locus [115]. However, studies conducted outside the United States have reported conflicting results. For example, an analysis of four European birth cohorts found no association between NO_2 exposure and ASD traits [116]. Null results were also registered by examination of the air pollution-autistic traits relationship in a Swedish twin sample [117]. In contrast, analysis of a large cohort from Taiwan indicated elevated ASD risk with higher exposures to four pollutants, ozone and NO_2 [118].

Several factors could contribute to the discrepancy in findings on ASD or related traits outside the United States. One possible explanation is that international studies often use different assessment methods and examine individuals of different ages than most US studies. Additionally, the correlation between social factors and air pollution with ASD status might be more confounding in US studies, especially those relying on community-acquired ASD diagnoses. Further, although these studies examined similar criteria pollutants, their mixture, and levels differ across regions and countries, making the exposures incomparable.

Further studies to better understand the associations between ASD risk and air pollution are needed [119]. For further investigation, epidemiologic research will be required to address outcome and exposure measurement issues and potential residual confounding. Researchers should also carefully consider the effects of mixtures of highly correlated air pollutants and examine windows of vulnerability. *In vivo* and *in vitro* studies have begun exploring potential mechanisms considering indirect (*i.e.*, oxidative stress or immune activation) and direct (*i.e.*, small particle deposition in the developing nervous system) effects. Finally, one study suggests that prenatal air pollution exposure is associated with early-life cognitive and behavioral impairment, further highlighting the importance of addressing this issue [120].

10.2. Endocrine-Disrupting Chemicals

The current evidence from epidemiologic studies investigating the association between early life exposure to endocrine-disrupting chemicals (EDCs), including environmentally persistent organic pollutants and certain non-persistent chemicals, and ASD risk is scarce and uncertain. However, EDCs warrant investigation due to their ability to interfere with hormone activity, which can impact neurodevelopment [121]. Additionally, EDCs have been linked to a wide range of neurodevelopmental outcomes [122], and exposure to EDCs is widespread in developed countries [123].

Several studies have explored the association between prenatal pesticide exposure and ASD traits. One study found an association between maternal concentrations of a marker of organophosphate (OP) pesticide exposure and pervasive developmental disorder traits [124]. Another study reported an association between exposure to trans-nonochlor, an organochlorine (OC) pesticide, and ASD symptoms [125]. However, a third study did not find significant associations between prenatal levels of two OC pesticides and ASD [126]. Two studies reported an association between residential proximity to OC pesticide applications during early gestation [127] or in mid to late pregnancy [128] and ASD, but the results were not consistent.

The association between prenatal exposure to polychlorinated biphenyls (PCBs) and ASD risk has been examined (Table **2**). One study reported a suggestive association between total PCBs and ASD [129]. At the same time, another found an inverse association with PCB-178 and no significant associations with other PCB congeners for autistic behaviors [125]. A third study found an increased risk of ASD with two PCB congeners and suggestions of higher risk with several other congeners [126].

For other EDCs, evidence is more limited. Studies investigating prenatal exposure to levels of phthalates, bisphenol A (BPA), polybrominated diphenyl Ethers (PBDEs), and perfluorinated compounds (or surrogates of exposure) associated with ASD [125, 130, 131].

Future studies should address the limitations of previous research by expanding the sample size, incorporating data on exposure during different potential etiologic windows, and considering exposure mixtures. This will help to clarify the association between early life exposure to EDCs and ASD risk and enable the development of effective prevention strategies.

10.3. Toxic Metals and ASD

Toxic metals, including Hg and Pb, are well-known neurotoxicants that can negatively impact cognitive and developmental outcomes. Metals like Pb, Hg, aluminum (Al), and arsenic (As) cause harm by inducing neuroinflammation, elevating cytokine levels, and activating nuclear factor kappa B (NF-κB) [132]. With pollution levels on the rise globally, it is imperative to investigate the impact of these pollutants on neurodevelopmental disorders, taking into account genetic susceptibility and polymorphism. Understanding how toxic metals affect neurodevelopment is crucial for developing effective therapeutic interventions and preventive strategies for ASD. Additionally, some metals may act as endocrine-disrupting chemicals (EDCs) [133, 134]. However, the evidence on low-level exposure to Pb in relation to ASD is limited.

Mostafa *et al.* (2016) measured blood Pb (BPb) levels and serum anti-ribosomal P protein antibodies in 60 ASD children and 60 neurotypical children. The children with ASD in the study had significantly higher BPb levels and a higher frequency of seropositivity of anti-ribosomal P antibodies. These findings suggest a potential relationship between BPb and autoimmunity in ASD children [135]. Neurokinin A is a pro-inflammatory neuropeptide that may play a role in autoimmune neuroinflammatory diseases like ASD. Mostafa *et al.* (2016) conducted a study involving 84 Saudi ASD children and 84 neurotypical children as controls. The study found that ASD children had significantly higher levels of serum neurokinin A than neurotypical children.

Additionally, the study revealed a positive correlation between CARS scores, serum neurokinin A, and blood Hg (BHg) levels. A positive correlation was observed between serum neurokinin A and BHg levels in children with moderate and severe ASD. Research indicates an association between Hg concentration and ASD [136]. One potential protective element is selenium (Se), which can form non-toxic complexes with Hg and act as an antioxidant [137, 138]. In a study by El-Ansary *et al.* (2017), the Pb, Hg, and Se levels were measured in the red blood cells (RBCs) of 35 Saudi children with ASD and 30 age- and gender-matched neurotypical children using atomic absorption spectrometry. Receiver operating characteristics (ROC) analysis was conducted to determine the predictive value of their absolute and relative concentrations. The results showed a significant increase in Hg and Pb levels and a decrease in Se levels in the RBCs of children with ASD compared to the healthy controls. The Se to Pb and Hg ratios were also significantly altered, indicating heavy metal neurotoxicity in the ASD group. The study also suggests that Se may be important for preventing and/or treating heavy metal neurotoxicity in individuals with ASD [139]. Sulaiman *et al.* (2020) conducted a systematic review and meta-analysis, which reported significant associations between Al, Cd, and Hg and ASD. Still, the associations were inconsistent [140]. More research is needed to identify the critical period when exposure may alter development, to examine the longitudinal effects of these toxic metals on the risk of ASD, and to investigate potential factors that may heighten or lessen the impact of metals.

10.4. Vaccines and ASD

To date, no significant epidemiologic evidence shows an elevated ASD risk with vaccines [141]. A 2004 Institute of Medicine (IOM) report investigated the evidence and found no support for a causal association between vaccines and ASD [142]. However, there were some limitations, including small sample sizes, lack of control groups, confounding and/or the utilization of specific clinical samples, and shortcomings of confounder-adjusted statistical analyses in a limited number of small studies that reported positive results, IOM reports and independent reviews of studies in the United States and other countries consistently stated that there is not enough evidence to support an association between vaccines, including the Measles, Mumps and Rubella (MMR) vaccine or the preservative thimerosal, and ASD [141, 143, 144].

11. FURTHER RESEARCH DIRECTIONS

While significant progress has been made in identifying environmental risk factors for ASD, several areas still require further investigation. Future research should aim to expand our understanding of the complex interplay between environmental factors and ASD development and explore additional risk factors that may contribute to the disorder's etiology.

Future studies should adopt a developmental psychopathology approach to investigate the dynamic and interactive processes that underlie the development of ASD. This approach recognizes the importance of considering developmental trajectories, individual differences, and the influence of environmental factors at various stages of development. Longitudinal studies that follow individuals from early childhood to adolescence and adulthood can provide valuable insights into how environmental risk factors interact with genetic and neurobiological factors over time.

To establish a causal relationship between environmental factors and ASD, prospective study designs are essential. Prospective cohort studies that collect detailed information on environmental exposures before and during pregnancy, as well as throughout early childhood, can help overcome the limitations of retrospective studies and provide stronger evidence for the impact of specific risk factors. These studies should also consider the potential cumulative effects of multiple exposures and interactions between different environmental factors.

Accurate measurement of environmental exposures is crucial for robust research in this field. Future studies should employ advanced methods for assessing exposure levels, including biomonitoring techniques, environmental monitoring, and validated questionnaires. This will ensure more precise and reliable exposure estimates, minimizing potential misclassification and measurement errors that can weaken associations between environmental factors and ASD.

Understanding the critical periods of vulnerability is essential for identifying the timing and duration of exposures that significantly impact ASD risk. Future research should investigate the sensitive windows of development during which environmental factors exert the most influence on neurodevelopment and ASD susceptibility. This knowledge can help inform public health interventions and targeted strategies for ASD prevention and early intervention.

Elucidating the molecular mechanisms underlying the relationship between environmental factors and ASD is a key research priority. Future studies should investigate the specific biological pathways through which environmental risk factors influence neurodevelopment and contribute to the pathogenesis of ASD. This may involve assessing biomarkers of exposure and exploring how environmental factors modulate gene expression, epigenetic modifications, immune function, oxidative stress, and neural connectivity.

Given the complex nature of ASD, research should investigate gene-environment interactions to understand better how genetic susceptibility interacts with environmental factors to influence ASD risk. Identifying genetic variants that modify the effects of environmental exposures can provide valuable insights into individual differences in vulnerability and resilience. Large-scale genome-wide association studies (GWAS) and gene-environment interaction studies are needed to unravel the complex interplay between genes and the environment in ASD etiology.

Identifying modifiable risk factors is crucial for developing effective preventive strategies and interventions for ASD. Future research should focus on exploring environmental factors amenable to intervention, such as dietary modifications, reduced exposure to toxic substances, and improved air quality. Intervention studies should assess the effectiveness of targeted environmental interventions in reducing the risk of ASD and improving outcomes in individuals already diagnosed with the disorder.

CONCLUSION

The evidence presented in this paper suggests that certain factors, such as vaccination, maternal smoking, and alcohol consumption, are not linked to ASD risk. However, parental age and preterm birth are consistently associated with an elevated risk of ASD. While other pregnancy-related factors, such as maternal diabetes, maternal obesity, and caesarian section, have shown a weaker association with ASD risk, delivery complications related to trauma or hypoxia have shown a stronger association. Conflicting results exist regarding the association between ASD risk and certain dietary components, such as folic acid, polyunsaturated fatty acids, vitamin D, and maternal Fe intake. Additionally, some studies suggest a potential link between ASD and toxic metals, such as Pb and Hg. Exposure to endocrine-disrupting chemicals, air pollution, infectious diseases, and other factors may also increase ASD risk.

Further research is needed to identify additional risk factors and fully understand the complex interplay of environmental factors in ASD development. Future studies should take a developmental psychopathology approach, use prospective designs, accurate exposure measurement, and reliable timing of exposure related to critical developmental periods.

AUTHORS' CONTRIBUTIONS

Study Concept: K.Y.; Design and Methodology: K.Y. and M.M.; Acquisition of Data: K.Y., M.M., and G.B.; Analysis and Interpretation of the Data: K.Y., M.M., and G.B.; Drafting of the Manuscript: K.Y.,

M.M., and G.B.; Critical Revision of the Manuscript for Important Intellectual Content: K.Y and G.B; Supervision: K.Y., Procurement of Funding: K.Y. All authors have read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

ASD = Autism Spectrum Disorder

CNVs = Copy Number Variation

SSRIs = Selective Serotonin Reuptake Inhibitor

CARS = Childhood Autism Rating Scale

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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