

Review

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Review

Autism Spectrum Disorder as a Multifactorial Disorder: The Interplay of Genetic Factors and Inflammation

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Abstract: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by difficulty with social communication, behavior, and sensory integration. With its prevalence rising worldwide in recent decades, understanding and mitigating the origins of ASD has become a priority. Though its etiology is multifactorial, current research highlights two major contributors: genetic susceptibilities and environmental inflammatory exposures leading to oxidative stress during critical developmental periods. We explore how genetic variations, particularly those affecting cerebral folate metabolism, and various inflammatory triggers intersect to influence the development of ASD, each giving rise to specific symptoms seen in autism.

Keywords: Autism; ASD; Leucovorin; folate; cerebral folate deficiency; inflammation; oxidative stress; maternal immune activation

1. Introduction

Autism diagnosis has seen a dramatic rise in the 21st century, increasing approximately five-fold, and becoming a public health priority [1]. There are striking parallels between ASD and other multifactorial diseases such as cancer. In both conditions, risk is influenced by an interplay of genetic predispositions and environmental factors, particularly triggers of inflammation, which lead to oxidative stress. Just as cancer risk can be increased by inherited mutations and external exposures like toxins or infections, ASD may also arise from a combination of genetic vulnerability and environmental stressors. In both diseases, these factors modulate susceptibility rather than determining certainty of onset, effectively raising the probability of development becoming neurodivergent.

Furthermore, recent findings in both fields suggest an important role for the gut microbiome in modulating immune and neurological outcomes. Nutritional and dietary choices appear to influence disease trajectories in both ASD and cancer. For example, diets that reduce inflammation or support detoxification pathways are known to reduce cancer risk and may contribute to better outcomes in ASD as well.

Another similarity with cancer is that ASD is presumed to have multiple variants, with differing etiologies. To date, over 70 genes have been correlated with ASD, with hundreds more believed to be related to ASD susceptibility [2–4]. The wide array of genes may help explain the diversity of expression of ASD, as well as point to a rationale for some of the comorbidities commonly diagnosed with ASD [5].

These insights invite a new perspective on ASD, not just as a static diagnosis, but as a dynamic condition potentially influenced by modifiable risk factors. This opens the door to discussing strategies for reducing risk, and even the possibility of partial or complete remission under certain therapeutic regimens. Understanding the contributing causes of ASD could lead to more personalized, preventive, and responsive treatments.

2. Genetic Factors in ASD

Many genes have been implicated as having a role in autism, with multiple categories involved [6–8]. There is evidence from brain organoids of a form of idiopathic autism that some of the genes involved lead to an imbalance in excitatory cortical neurons [9]. Given that there are presumed to be several autism variants, the associated genes are ones that are correlated with a greater risk of developing ASD. Some have specific pathways that are involved and others are correlated with ASD but in a non-defined manner. Sections 2.3 and 2.4 provide a brief look at some of the developmental genes that have traditionally been considered for their role in ASD.

Genes associated with folate transport (Section 2.1) are related to folate delivery to the brain and a biomarker for cerebral folate deficiency (CFD). Therapeutic intervention can overcome CFD, as described in this section. A potentially related genetic risk is for mitochondrial dysfunction (Section 2.2), which may play a role in the autism regression seen in some children as they grow.

2.1. Cerebral Folate Deficiency

2.1.1. Folate Metabolism and Brain Development

Folate is essential for DNA synthesis, repair, and methylation, all of which are essential processes during early brain development. The transport of folate into the central nervous system (CNS) is tightly regulated by specific transport mechanisms, primarily the folate receptor alpha (FR α) and the reduced folate carrier (RFC).

2.1.2. Genetic Variants Impairing Folate Transport

Mutations in the FOLR1 gene can impair FR α function, leading to CFD. Similarly, polymorphisms such as the SLC19A1 variant rs1051266 can reduce RFC efficiency. Both impair the brain's ability to maintain adequate folate levels, resulting in developmental impairments and ASD features, such as decreased social communication and decreased emotional recognition [10,11].

2.1.3. Folate Receptor Alpha Autoantibodies (FRAAs)

FRAAs, which block or bind to FR α , are much more prevalent in ASD children (about 70% of ASD children, compared with 5-10% in the general population). These autoantibodies suppress folate transport across the blood-brain barrier, contributing to CFD. FRAAs are believed to result from environmental exposure,[12] further linking genetic and inflammatory pathways.

2.1.4. Therapeutic Interventions

Folinic acid supplementation has shown promise in reversing CFD symptoms in children with ASD in multiple clinical trials (based in USA, France, or India) published between 2018-2025 [13–16]. Dietary modifications, such as avoiding cow's milk products (which may trigger FRAAs),[12] have also demonstrated potential benefits. These findings support the clinical importance of identifying and treating CFD in ASD patients.

2.2. Mitochondrial Dysfunction

There is growing evidence that mitochondrial dysfunction may contribute to neurodevelopmental regression in children [17–20]. This condition is seen when an ASD child shows strong learning, language and memory initially, only to regress later in childhood [21]. Of note, while non-regressed children showed inflammation and immune dysregulation occurs first, while in regressed children mitochondrial dysfunction is first observed, with an impact on immune activity possibly occurring later [19].

2.3. Synapse and Signaling Genes

Genes that have been recognized as ASD-related and act by impairing neural connectivity include those involved in synapse formation and function: SHANK3, NRXN1, NGLG3/4 [22–24]. Additionally, the gene SCN2A is tied to an alteration in neuronal activity due to its role in ion channels [25].

2.4. Regulation, Cell Growth and Plasticity Genes

The genes involved in cell growth, TSC1 and TSC2 can lead to abnormal brain structures by alteration of the mTOR pathway [26,27]. This is a common signaling cascade with central roles in translation, lipid and nucleotide synthesis and growth factor signaling [28].

Variations in genes involved in gene regulation, CHD8 and MECP2, can result in disrupted brain development, while variants of a gene from RNA translation, FMR1, is related to learning and memory issues [29–31].

3. Inflammation During Critical Developmental Periods and ASD Risk

3.1. The Developing Brain and Vulnerability to Inflammation

Neurodevelopment is highly sensitive to environmental insults during prenatal and early postnatal periods. Inflammation during these times can disrupt neuronal migration, synaptogenesis, synaptic pruning, and brain connectivity, all of which are critical to neurotypical brain function [32]. Many causes of inflammation have been documented, some of which are acute, such as viral infection and fever, and others are chronic, such as microplastics and malnutrition. When inflammation occurs during critical periods in brain development, then neurotypical development can be delayed or arrested, resulting in a child reaching milestones later, or aberrantly, or possibly not at all if the inflammation exceeds the duration of the critical period [32–35]. Summary schematics of the categories of inflammation and their presumed action are outlined in Figures 1 and 2.

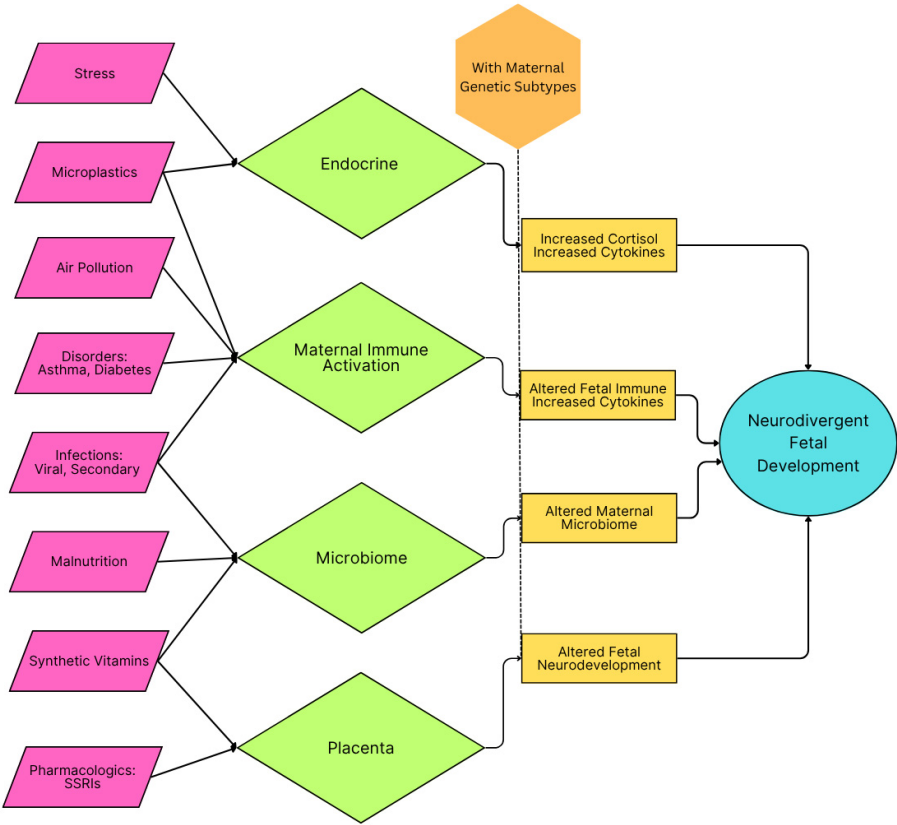


Figure 1. Schematic of maternal inflammatory categories and their impact on fetal development that can lead to conditions conducive for development of autism spectrum disorder. A genetic propensity and agents causing oxidative stress are presumed to be the preconditions for neurodivergent fetal development. A similar schematic is seen in Figure 2 for the child.

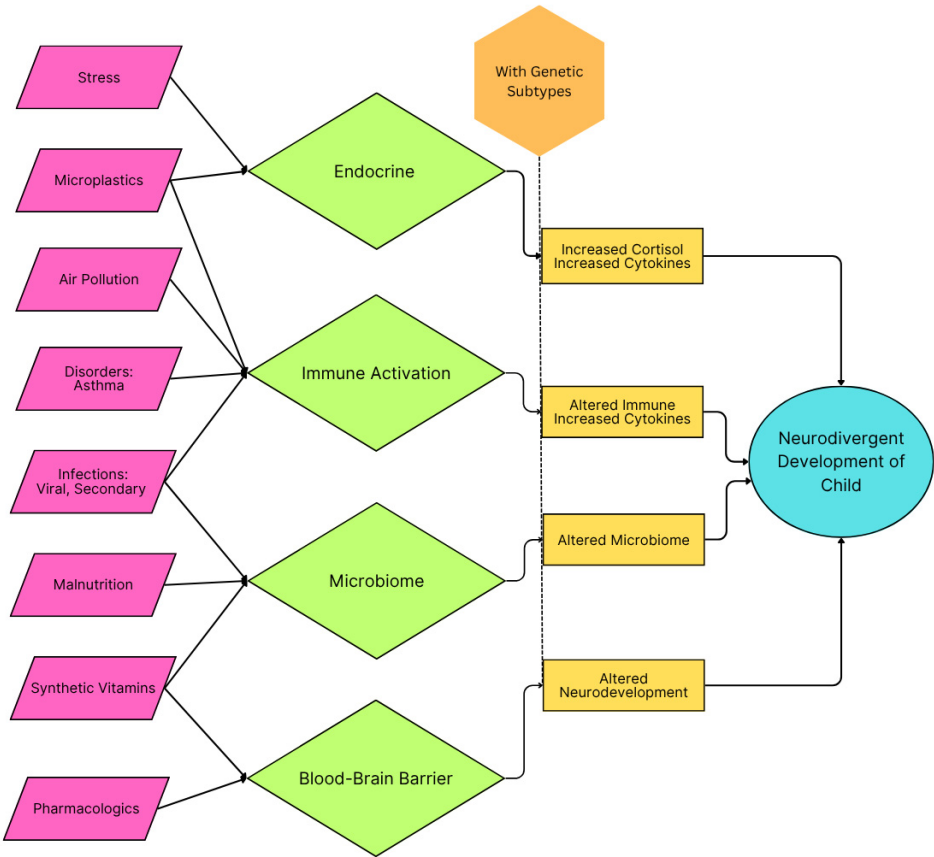


Figure 2. Schematic of inflammatory categories in childhood and their impact on early childhood development that can lead to autism spectrum disorder symptoms. A genetic propensity and agents causing oxidative stress are presumed to be the preconditions for neurodivergent development.

3.2. Categories of Inflammation

3.2.1. Viral Infections

Maternal infections such as influenza, rubella, or COVID-19 have been linked to increased ASD risk due to maternal immune activation (MIA). Postnatal viral infections can also contribute to neuroinflammatory states [33,35–38].

Evaluation of the studies in a meta-analysis shows there is an association between maternal infection and subsequent autism diagnosis in the child, with little variation based on when the infection occurred during pregnancy or what type of infection it was [39,40]. A genetic analysis showed the increased risk for ASD with maternal infections may be correlated with a genetically distinct subtype of autism, a subtype that come from the interaction between genetic susceptibility and exposure to infections in pregnancy [41]. Thus, since the maternal infections may not be causal in the development of ASD, it is unclear if prevention of infection may reduce autism incidence [42].

3.2.2. Air Pollution & Maternal Asthma

Environmental pollutants are associated with ASD incidence [43]. Exposure to particulate matter (e.g., PM_{2.5}) during pregnancy has been associated with neuroinflammation[44] and developmental disorders, with an increased risk of development of ASD [32,44–49]. Airborne toxins can activate microglia and oxidative stress pathways in the fetal brain [50].

Additional studies have examined air pollution from roadways as being particularly problematic, pointing to a potential link to plasticizers used in the manufacture of tires and tailpipe exhaust, as risk was related to distance from roadways [51,52]. Given that immune dysregulation is a common comorbid feature with ASD, the link to maternal exposure to air pollution may be indicating a mechanism of action in the development of autism. In this regard, multiple studies have found elevated risk of autism in infants born to asthmatic mothers, and that this risk is related to an increase in inflammatory biomarkers [53–55].

Of concern, in a study of air pollution pre-conception, women exposed to particulate matter and nitric oxide in the three months prior to conception had children with greater growth in body weight in their first two years of life [56]. The authors report that the critical period of exposure is the three months prior to conception.

3.2.3. Maternal Immune Activation

Maternal inflammation during pregnancy is associated with an increased risk of ASD, with this maternal immune activation (MIA) being evaluated in animal models, where it leads to behavioral changes resembling ASD [57]. The immune activation raises levels of cytokines, especially interleukin-6 (IL-6) and interleukin 17a (IL-17a), which are implicated in disrupting fetal brain development, in what may lead to some ASD behaviors. The effect of the MIA on the developing fetus may be impacted by the fetus' genetic makeup, with certain genetic profiles making the fetal brain more impacted by the maternal inflammation, implicating a gene-environment interaction in the etiology of ASD [57–60].

3.2.4. Microplastics

Emerging studies in animal models suggest that prenatal and early postnatal exposure to microplastics, especially bisphenol A and phthalates, may lead to inflammation-driven behavioral changes reminiscent of ASD [61–65]. The action may be through immune and epigenetic mechanisms, or as endocrine disruptors. In this regard, plastic food containers and films were tested and found to contain thousands of chemicals, with many being endocrine disruptors (including an estrogen receptor alpha activator, and an androgen receptor inhibitor) and metabolism disruptors [66]. Samples tested that were made with fewer chemicals also had fewer toxic chemicals that entered the food. Additionally, exposure to polystyrene nanoplastics causes depression and anxiety in a mouse model,[67] and it decreased oligodendrocyte activity and enhanced hyperactivity and aggression in zebrafish,[68] while exposure to polyethylene led to repetitive behaviors and diminished social interaction [69].

3.2.5. Malnutrition

Deficiencies in nutrients with anti-inflammatory properties, such as omega-3 fatty acids, zinc, and vitamins B12, B9, A, D, and K may increase susceptibility to inflammation and neurodevelopmental disorders [70–75]. The vitamin A deficiency may have its effect by impact on the gut microbiome [76,77]. Other micronutrients appear to play important roles in neurotypical development [78]. There is also evidence that autistic children, who frequently eat the same food each day, are lacking in certain nutrients,[79,80] or are receiving an abundance of one macronutrient to the exclusion of others, which may contribute to symptoms [81].

3.2.6. Emotional Stress

Maternal stress during pregnancy can result in elevated cortisol and pro-inflammatory cytokines, potentially disrupting fetal brain development. Chronic stress in the early life of the child may also affect immune and neurological outcomes [39,82–86]. One measure of such stress on the child can be quantified by evaluating adverse childhood experiences (ACEs), as ASD children who are at increased risk of bullying, parental divorce, income and food insecurity, have an increased risk of comorbid health disorders [87].

3.2.7. Pharmaceuticals

Certain medications, particularly selective serotonin reuptake inhibitors (SSRIs), have been implicated in altering fetal brain development when used during pregnancy [88]. SSRIs cross the placental barrier and can influence serotonin signaling pathways critical to neurodevelopment. Research suggests that prenatal SSRI exposure may disrupt synaptogenesis and increase neuroinflammation, particularly in genetically susceptible offspring [89]. These effects may contribute to ASD-like phenotypes in animal models and warrant careful consideration of risk-benefit ratios in clinical practice [88,90–92].

3.2.8. Maternal Disorders, Diabetes

A recent study in California found higher ASD incidence for children born to mothers with asthma or obesity, and a much higher incidence for mothers with both conditions [93]. The authors speculate that the incidence increase may be due to the increased inflammatory conditions during pregnancy, and that earlier screening of children born to mothers with asthma and obesity during pregnancy may be warranted.

Meta-analysis of over 200 studies, and including over 50 million pregnancies, has revealed that children born to mothers with diabetes have an increased risk of neurodevelopmental disorders. This was especially true for mothers with pre-gestational diabetes, and less so for gestational diabetes. There was a 25-30% increased risk for ASD, ADHD and intellectual disability, with a 15-20% increased risk for communication learning disorders [94].

3.2.9. Synthetic Vitamins

Excessive or poorly metabolized synthetic folic acid may provoke immune responses, especially in individuals with impaired folate pathways. This imbalance can exacerbate inflammation and contribute to FRAA development, which leads to CFD. Additionally, intake of folic acid in excess of a few hundred micrograms per day (the typical level of folic acid that can be converted to usable folate in the gut) has been shown to result in unmetabolized folic acid in the blood, which interferes with absorption of folate across the blood brain barrier or across the placenta [95–98].

3.2.10. Vaccines

While the scientific consensus supports vaccine safety, there is speculation that vaccines trigger inflammatory responses in genetically susceptible individuals, as detailed in a recent comprehensive report [99]. If such inflammation occurs during critical periods, it can elevate risk of altering brain development. This was a larger concern in previous decades, for example when the earlier pertussis vaccine (in the 1980s) triggered fever in some children, or when the thiomersal (thimerosal) preservative in the measles vaccine was used (until 2001) that could be inflammatory in some children. The fact that diagnosed autism cases has increased five-fold from 2000-2025[1,100] while inflammation from vaccines has diminished indicates this is likely not a significant factor in this neurodevelopmental disorder.

3.2.11. Microbiome and Metabolic Disorders

This topic may merit a separate category, as processing by the microbiome seems to be essential for absorption of key nutrients as well as inactivation of inflammatory agents, and digestive disorders are frequently comorbid with ASD [100–103]. In this regard, restoring microbiome function with probiotics may alleviate some ASD symptoms [104] and use of fecal transfer has shown some effectiveness in treating autism symptoms [105].

Several studies have shown a link between the gut microbiome and neurological disorders [106]. Propionic acid, a microbial byproduct, is known to cause neuroinflammation and over-proliferation of glia in mice offspring born to mothers exposed to propionic acid through pregnancy and weaning [107]. This provides direction as to a mechanism of action by which inflammation may be caused and neural correlates of its action.

Screening of the gut microbiome of autistic children and non-autistic siblings revealed categories of bacteria and fungi that were at different levels in the ASD individuals [108]. When these were fed to mice, there was a concomitant change in behavioral patterns, indicating the use of certain probiotics may provide some benefit in autism. A similar study found differences in ASD and non-ASD microbiomes, and observed that ASD regression children had higher levels of *Proteobacteria* [109]. This link to ASD regression may provide another avenue to explore.

Additional evaluation of mitochondrial metabolism finds changes in energy pathways in ASD children [110]. when metabolic analysis is made of cord blood, to look at such parameters at birth, and in maternal mid-gestational blood, a machine-learning analysis found that cord blood was more predictive of ASD and that this was true for girls and boys [111]. A later study showed that elevation of a specific cord blood component, acylcarnitine, was predictive of both ASD and ADHD outcomes [112].

3.3. Mechanistic Insights

Inflammation can alter neural circuitry by affecting synaptic pruning, neuronal connectivity, and neurotransmitter systems, and this may occur due to alterations in the neural immune system. Genetic predispositions, such as those affecting folate metabolism, may intensify the brain's vulnerability to these inflammatory insults. Microglial priming and sustained cytokine exposure during development may create a neuroimmune environment conducive to ASD [37,113–117].

3.4. Therapeutic Interventions

Therapeutic intervention to reduce neuroinflammation typically involves reducing exposure to the causative agents. Given the great diversity of such potential sources, and the rampant exposure in daily living to most of these agents, such action is likely to be futile. Some things clearly can be done, such as reducing exposure to those agents that are one has control over, and seeking medical attention reduce risk from illnesses during pregnancy.

Additionally, where mechanisms are posited for inflammatory action, and when the impact of such action can be ameliorated, then use of specific products may provide benefit. In this regard, with maternal infection there is a concomitant reduction in N-acetyl cysteine and taurine associated with neuroinflammation due to a decrease in microglial cells. Each of these compounds can be supplemented into diet to reduce impact on the brain's immune function to deter fetal injury.

There is a recent report in a mouse model of autism that an extract of basil, *Ocimum basilicum*, reduced damage in the pups that was induced by maternal separation, and reduced autism behaviors via antioxidant and anti-inflammatory properties of the extract [118]. This opens an avenue to considering other proven antioxidants in an ASD model. In this regard, the comparison with cancer may be apt, as there are decades of research identifying mechanisms of action of antioxidant nutritive extracts on cancer cell cultures [119,120]. Some of these may also prove to have an impact in deferring ASD development.

4. Integrative Perspective: Gene-Environment Interactions in ASD

4.1. Synergistic Effects

Genetic susceptibilities, such as impaired folate transport (described above), may amplify the effects of environmental insults. For example, exposure to synthetic folic acid or infections in a child with FOLR1 or RFC polymorphisms may result in a greater risk of ASD due to insufficient levels of natural folate reaching the brain or the uterus [74,98,117].

4.2. Epigenetic Modifications

Disruptions in folate metabolism may lead to altered DNA methylation and gene expression, affecting neurodevelopmental outcomes. These epigenetic changes may bridge the gap between genetic and environmental risk factors.

4.3. Implications for Prevention and Treatment

Screening for CFD in the fetus by testing for parental FRAAs, nutritional support (including prenatal vitamins with natural folate instead of folic acid), and inflammation-reducing strategies during pregnancy could reduce ASD risk [35].

The use of machine learning systems to successfully identify ASD in children could provide much earlier diagnosis [121,122]. Such machine learning provides hope that a similar system may be devised that can identify future ASD risk during pregnancy.

Personalized approaches considering both genetic background and environmental exposures hold promise for future interventions. Follow on care in early childhood may successfully identify developing ASD risk, and reduce severity autism severity by treating CFD and nutritional deficits at earlier ages, and by reducing inflammatory stimuli or reducing widespread neural inflammation.

We project that ASD treatment may parallel other multifactorial disorders, such as cancer, with a targeted approach to lessen risk and improve neurotypical outcomes, with a similar goal of extended remission to provide an outcome of raised quality of life. Given that such treatment has a lower societal and health maintenance cost, and has been demonstrated to have no deleterious effects, we propose engaging such a model of treatment now.

Figure 3 provides a review of some of the oxidative stress and genetic factors that may give rise to specific symptoms observed in ASD [35].

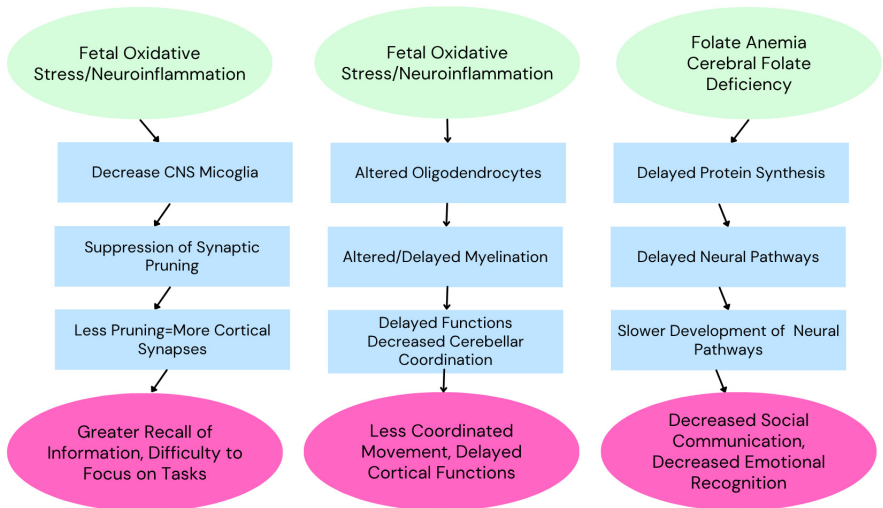


Figure 3. Development of autism spectrum disorder is multifactorial, with various factors presumably responsible for the various symptoms observed. Adapted from Ayoub (2024)[35].

5. Conclusions

ASD arises from a complex interplay between genetic and environmental factors. Genetic variants impairing folate metabolism and inflammatory exposures during critical periods each play significant roles in disrupting brain development. Understanding and addressing these risk factors through early detection, targeted interventions, and public health strategies may help reduce the incidence and severity of ASD in future generations.

Identifying the genetic causes and treating their ramifications, such as treating CFD with levo-leucovorin, has been shown repeatedly to make a substantial difference in resolving the communication difficulties of a young autistic child. It is time to have this become the standard of practice for all ASD children at the earliest ages.

Addressing inflammation causes can also be accomplished now, focusing on the most readily addressable ones first. In this way, reducing infection in pregnancy, eliminating malnutrition of mothers and children, and find ways to alleviate stress may have a lasting impact in reducing the severity of autism. And providing support during inflammation to help retain immune functioning, such as has been reported by using N-acetyl cysteine and taurine to replenish their levels when depleted by inflammation, may be an appropriate next step. It is most important to address the readily resolvable inflammation causes, specifically stress, malnutrition and health protection from disease now, and to extend efforts to work as a society to reduce the impact of inflammatory agents such as microplastics and pollution in order to provide the healthiest environment for neurotypical brain development in all children, and thus build a better and more productive future for all.

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Abbreviations

The following abbreviations are used in this manuscript:

ASD	Autism Spectrum Disorder
CNS	Central Nervous System
FRα	Folate Receptor alpha
RFC	Reduced Folate Carrier
FRAA	Folate Receptor Auto Antibody
CFD	Cerebral Folate Deficiency
MIA	Maternal Immune Activation
SSRI	Selective Serotonin Reuptake Inhibitor

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