

## REVIEW ARTICLE

## Prenatal maternal autoimmune disorders and the risk of developmental disorders

George Ayoub\*

Department of Psychology, Santa Barbara City College, Santa Barbara, California, United States of America

## Abstract

Mothers with certain autoimmune disorders give birth to children who develop autism at over twice the rate as mothers without these disorders. While many maternal autoimmune disorders increase the risk of several types of mental disorders in offspring, lupus and Hashimoto's disease are most pronounced, doubling the risk of autism. Thus, these two conditions may place a significant immune load on the developing fetus, presumably coinciding with critical periods in fetal nervous system development. This maternal immune activation may be further impacted by environmental stressors that, along with genetic mechanisms, further compromise fetal development. It is thus critically important for prenatal care to be multidisciplinary, particularly for women with autoimmune disorders. Managing the environmental oxidative stressors may help mitigate the increased risk due to autoimmune disorders and allow fetal development to proceed on schedule. Given that the environmental stressors such as malnutrition, infection, and pollution can adversely affect fetal development, implementing proactive strategies to address these factors during pregnancy, combined with improved early screening of children, would offer significant societal benefits. This review examines evidence for a link between maternal autoimmunity and considers mechanisms that may be in play to increase the propensity of autism development.

**\*Corresponding author:**George Ayoub  
(neuro@sbcc.edu)

**Citation:** Ayoub G. Prenatal maternal autoimmune disorders and the risk of developmental disorders. *Microbes & Immunity*. 2026;3(2):025290061. doi: 10.36922/MI025290061

**Received:** July 14, 2025**Revised:** August 14, 2025**Accepted:** September 1, 2025**Published online:** October 3, 2025

**Copyright:** © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

**Publisher's Note:** AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Keywords:** Autism; Maternal immune activation; Autoimmunity; Inflammation; Hashimoto's disease; Lupus

## 1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition with multifactorial etiology, involving both genetic and environmental risk factors. Epidemiological and mechanistic studies have highlighted an association between maternal autoimmune diseases, including systemic lupus erythematosus (SLE) and Hashimoto's thyroiditis, and increased incidence of ASD in offspring.<sup>1-4</sup> These findings underscore the importance of maternal immune status as a potential contributor to ASD risk.

A central hypothesis emerging from this body of research is that maternal immune activation (MIA), whether from chronic autoimmune disease, acute infection, or other inflammatory conditions, can disrupt fetal neurodevelopment.<sup>1,2</sup> Autoimmune diseases are characterized by the production of autoantibodies and pro-inflammatory cytokines,

both of which can cross the placenta and influence the developing brain. Elevated maternal cytokines, for instance, may alter neuronal proliferation, migration, and synapse formation, thereby increasing vulnerability to ASD.<sup>1</sup> Furthermore, external sources of inflammation, such as maternal obesity or infections during pregnancy, may synergize with underlying autoimmune conditions to further elevate ASD risk.<sup>1,2</sup>

Another emerging area of interest is the role of cerebral folate deficiency (CFD) in ASD pathogenesis. CFD, often caused by autoantibodies against the folate receptor alpha (FR $\alpha$ ), impairs the transport of folate into the brain and has been detected in a significant proportion of children with ASD.<sup>5-7</sup> The presence of FR $\alpha$  autoantibodies is notably higher in ASD populations, suggesting a mechanistic link between maternal or child autoimmunity, disrupted folate metabolism, and neurodevelopmental outcomes.<sup>6,7</sup> Treatment with folinic acid has shown promise in improving core ASD symptoms in children with CFD, highlighting the clinical relevance of this pathway.<sup>5-7</sup>

This review aims to systematically evaluate the incidence of ASD in children born to mothers with lupus, Hashimoto's disease, or other autoimmune disorders, and critically examine the roles of immune load, both intrinsic and extrinsic inflammation, and CFD in mediating this risk. By integrating epidemiological data with emerging mechanistic insights, the goal is to clarify the constellation of risk factors that contribute to ASD, thereby informing both preventive strategies and targeted interventions for at-risk populations.

## 2. Maternal autoimmunity and autism risk

It is known that women with an autoimmune disorder have nearly twice the rate of mental health disorders.<sup>8</sup> In addition, epidemiological studies support an association between maternal autoimmune diseases and an increased risk of ASD in offspring. Multiple large-scale, population-based studies and meta-analyses have provided quantitative estimates of this risk and explored disease-specific associations.

Meta-analyses indicate that children born to mothers with any autoimmune disease have approximately a 30% increased odds of developing ASD compared to those born to mothers without such conditions.<sup>9</sup> This association has been observed across diverse populations and study designs, suggesting a robust link between maternal immune dysregulation and neurodevelopmental outcomes in children.

A cohort study utilizing data from over 100,000 mother-child pairs in Taiwan region found that the cumulative

incidence of ASD was significantly higher among children whose mothers had been diagnosed with autoimmune diseases before pregnancy compared to matched controls (4.26% compared to 3.20%).<sup>3</sup> After adjusting for confounders such as maternal age, urbanization, family income, and pregnancy-related complications, the hazard ratio for ASD in offspring of mothers with autoimmune disease was 1.25.<sup>3</sup> Similar findings were reported in an Australian cohort, where maternal autoimmune disease was associated with an adjusted odds ratio of 1.25 for ASD in offspring.<sup>2</sup>

A Danish cohort of over two million children born over four decades found increased odds ratios from any maternal autoimmune disorder, including type 1 diabetes and rheumatoid arthritis. Their cohort revealed that the increased risk for mental disorders following exposure to any maternal autoimmune disorder was elevated by 50% for organic disorders, 35% for schizophrenia, 40% for obsessive compulsive disorder, 12% for mood disorders, 21% for autism, and 19% for attention-deficit hyperactivity disorder (ADHD).<sup>10</sup> An earlier report that included a Chinese database containing 10,000 cases found similar odds ratio of 1.34 for ASD in children whose mothers had autoimmune disease.<sup>11</sup> A recent literature analysis compiled data from 1.4 million parents with autoimmune disorders evaluating the contribution of each parent.<sup>12</sup> When the mother had the autoimmune condition, the odds ratios for ASD and ADHD were 1.27 and 1.31, respectively, while when the father had the autoimmune condition, the odds ratios were 1.18 for ASD and 1.14 for ADHD.<sup>12</sup>

While the overall risk is elevated for autoimmune diseases as a group, certain conditions appear to confer higher risks:

- (i) Lupus and Hashimoto's thyroiditis: Although not all studies provide disease-specific breakdowns, meta-analyses have highlighted SLE and Hashimoto's thyroiditis as autoimmune conditions with some of the highest reported associations with ASD, with risk estimates approaching twofold for lupus and threefold for Hashimoto's, compared to the general population.<sup>9</sup> In addition, a study of children of hypothyroid women revealed ASD rates were about 30% higher, but not as high as that seen in children of women with Hashimoto's.<sup>4</sup> A similar finding has recently been reported in a preprint archive.<sup>13</sup> These would seem to indicate that low thyroid hormone may be a risk factor, but that autoimmunity is a more substantial risk factor
- (ii) Sjögren's syndrome and rheumatoid arthritis: The Taiwanese cohort study found that both Sjögren's syndrome and rheumatoid arthritis in mothers were

significantly associated with increased ASD risk in their children.<sup>3</sup> These findings were consistent after controlling for a range of potential confounders, and the rheumatoid arthritis correlation was similar to that found in another Taiwanese study.<sup>14</sup>

The association between parental autoimmune disease and ASD risk is not limited to mothers. Several studies have also found that paternal autoimmune conditions are associated with increased ASD risk in offspring, though typically with lower effect sizes than maternal exposures.<sup>9,12</sup> This suggests a possible shared genetic or familial susceptibility component, in addition to direct maternal immune effects during pregnancy.

Some research has explored potential interactions between maternal autoimmune disease and other exposures, such as early childhood infections. One large Australian study found that both maternal autoimmune disease and childhood infections before age two independently increased ASD risk, but there was no evidence of a synergistic interaction between these exposures.<sup>2</sup> This indicates that maternal autoimmune disease is an independent risk factor for ASD, rather than simply reflecting broader immune dysregulation or increased infection risk.

Supporting this finding is a meta-analysis that evaluated published reports of maternal risk factors and ASD, finding that autoimmune conditions such as maternal diabetes elevated ASD risk in a child, but so did maternal obesity, preeclampsia, or SSRI use before pregnancy, with each of these raising the ASD risk by about 30%, while maternal SSRI use during pregnancy increased the ASD risk by 85%.<sup>15</sup>

Analyses consistently adjust for a range of confounding variables, including maternal age, socioeconomic status, urbanization, pregnancy complications (*e.g.*, gestational diabetes, preterm birth), and neonatal factors.<sup>3</sup> Even after these adjustments, the association between maternal autoimmune disease and ASD risk remains significant, supporting a likely causal relationship.

As an indication of the connection between developmental disorder and autoimmunity, one analysis of a birth cohort of 30,000 identified 1000 ASD individuals in the population. The ASD fraction was at higher risk of comorbidity of an autoimmune disorder diagnosed before age 20, with a reported odds ratio of 1.74.<sup>16</sup> While this may indicate that ASD is associated with yet another comorbidity to consider, it also raises the possibility of a link between autoimmunity risk and developmental disorders. This is consistent with the recent finding that individuals with autoimmune disorders have nearly double the rate of affective disorders.<sup>8</sup>

Epidemiological evidence from multiple large, well-controlled studies demonstrates that maternal autoimmune diseases are associated with a modest but statistically significant increase in ASD risk in offspring. This risk appears to be particularly elevated for certain autoimmune conditions such as lupus, Hashimoto's thyroiditis, Sjögren's syndrome, and rheumatoid arthritis. The association persists after adjustment for numerous confounders and is observed in diverse populations, underscoring the importance of maternal immune status in early neurodevelopment.<sup>2,3,9</sup>

### 3. Mechanistic hypotheses: Immune load and inflammation

A growing body of research implicates MIA as a key mechanistic pathway linking maternal autoimmune disorders and increased risk of ASD and other neurodevelopmental disorders in offspring.<sup>17</sup> MIA refers to the activation of the maternal immune system during pregnancy, often triggered by autoimmune disease, infection, or other inflammatory conditions, resulting in increased levels of inflammatory mediators such as cytokines and chemokines. MIA has been linked to neurodevelopmental disorders, including ASD, in both epidemiological and animal studies. Epidemiological studies demonstrate that maternal infections or autoimmune states during the first or second trimester are associated with a significantly elevated risk of neurodevelopmental disorders, including ASD, in children.<sup>18,19</sup> Experimental models have demonstrated that maternal exposure to immune challenges, such as polyinosinic: polycytidylic acid (poly I:C) or lipopolysaccharide, induces behavioral and neuroanatomical abnormalities in offspring that mirror key features of ASD.<sup>20</sup>

Epidemiological studies suggest that maternal immune conditions are more strongly associated with ASD in male offspring.<sup>21</sup> The reasons for this sex-specific vulnerability are not fully understood but may relate to differences in fetal brain development, hormonal milieu, or immune response patterns between males and females.

The immune load in mothers with autoimmune diseases is characterized by chronic activation of immune pathways and sustained production of pro-inflammatory cytokines. This heightened immune status increases the likelihood that inflammatory mediators such as interleukin (IL)-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) will cross the placenta and impact fetal brain development.<sup>22,23</sup> Rodent models of MIA have shown that maternal exposure to immune challenges leads to microglial activation, oxidative stress, and mitochondrial dysfunction in the developing brain, creating a self-perpetuating cycle of neuroinflammation and altered neurodevelopmental trajectories.<sup>23</sup>

Pro-inflammatory cytokines released during MIA can cross both the placenta and the fetal blood-brain barrier, activating resident immune cells in the fetal brain and initiating cascades that disrupt neuronal proliferation, migration, and synapse formation.<sup>22,23</sup> The timing of immune activation is critical; disturbances during critical periods of neurodevelopment can result in persistent changes in brain structure and function, leading to behavioral phenotypes characteristic of ASD and related disorders.<sup>18</sup>

Cytokines, including interleukin-6 (IL-6), interleukin-1 beta (IL-1 $\beta$ ), and TNF- $\alpha$ , play essential roles in brain development, such as regulating neurogenesis, synaptic pruning, and neuronal migration.<sup>24</sup> However, excessive or dysregulated cytokine signaling during critical periods of fetal brain development can have deleterious effects. Elevated maternal IL-6, for example, has been shown to cross the placenta and alter fetal brain gene expression, leading to abnormal cortical development and behavioral deficits in animal models.<sup>25</sup>

Inflammatory markers such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$  have been consistently linked to both systemic and central nervous system inflammation, with direct consequences for brain maturation. IL-6, in particular, is not only a marker of systemic inflammation but also a modulator of neurogenesis, especially in regions such as the hippocampus and prefrontal cortex.<sup>22,26</sup> Elevated maternal IL-6 levels have been associated with reduced gray matter volume and impaired cognitive function in offspring.<sup>26</sup> Similarly, TNF- $\alpha$  and IL-1 $\beta$  can impair synaptic plasticity, long-term potentiation, and neurogenesis, further contributing to neurodevelopmental deficits.<sup>22,26</sup>

Neurodevelopment is altered by cytokine changes during pregnancy. Increased pro-inflammatory cytokines such as interferon gamma, IL-4, and IL-5 have been linked to increased incidence of ASD.<sup>22</sup> ASD children frequently exhibit abnormal cytokine and chemokine profiles, both in blood and cerebrospinal fluid. Studies have reported elevated levels of pro-inflammatory cytokines such as IL-6, IL-8, and TNF- $\alpha$ , as well as chemokines such as CCL2 and CXCL8.<sup>27</sup> These inflammatory mediators are associated with the severity of behavioral symptoms and cognitive impairment in ASD.<sup>28</sup>

Recent Mendelian randomization studies have identified causal relationships between specific immune cell populations (*e.g.*, CD8<sup>+</sup> T cells, B cells, dendritic cells) and ASD risk as well as between circulating inflammatory factors (*e.g.*, TNF- $\alpha$ , IL-6) and neurodevelopmental outcomes.<sup>29</sup> These findings suggest that both the quantity and quality of immune activation, reflected in the profile of circulating cytokines and immune cells, are critical determinants of neurodevelopmental risk.

Experimental evidence also indicates that inflammation impairs the maturation and function of neurons in the developing brain, leading to reduced electrical activity and long-term deficits in cognitive, social, and motor domains.<sup>30</sup> Such impairments are detectable through clinical neurophysiological measures, highlighting the translational relevance of these mechanistic insights.<sup>30</sup>

In autoimmune conditions like lupus and Hashimoto's disease, maternal autoantibodies can cross the placenta and target fetal brain proteins. These autoantibodies may disrupt neuronal proliferation, migration, and synapse formation, processes vital for normal neurodevelopment.<sup>31</sup> Studies have identified specific maternal autoantibodies associated with increased ASD risk in offspring, supporting a direct mechanistic link.<sup>31</sup> Table 1 has a list of maternal autoimmune disorders that may increase risk of ASD in a child and the mechanisms that are involved.

Beyond lupus and Hashimoto's disease, other maternal immune-mediated conditions—including asthma, celiac disease, type 1 diabetes, and rheumatoid arthritis—have been linked to increased ASD risk in offspring.<sup>32</sup> This broad association underscores the potential role of maternal immune dysregulation and inflammation, rather than disease-specific mechanisms, in ASD pathogenesis.

Meta-analysis of autoantibodies produced by autistic children shows a number of specific autoantibodies, with six found to be at higher levels in ASD children as compared to neurotypical controls.<sup>33</sup> These six autoantibodies are directed against FR $\alpha$ , anti-myelin-associated glycoprotein, anti-myelin basic protein, anti-ribosome P protein, anti-endothelial cell, and antinuclear antibody.<sup>33</sup>

Chronic maternal inflammation can lead to persistent activation of microglia and astrocytes in the developing brain. Activated microglia release pro-inflammatory

**Table 1. Disease-specific evidence**

Autoimmune disease	ASD risk increase	Key mechanisms/findings
Lupus (SLE)	~2×	Maternal antibodies, cytokines <sup>2,38,39</sup>
Hashimoto's thyroiditis	~3×	Thyroid hormone, immune dysregulation <sup>2,4,13</sup>
Rheumatoid arthritis	Elevated	Anti-brain antibodies, inflammation <sup>3,32,38</sup>
Sjögren's syndrome	Elevated	Immune activation, inflammation <sup>3</sup>
Celiac disease	Elevated	Familial autoimmunity <sup>32</sup>
Type 1 diabetes	Elevated	Immune-mediated mechanisms <sup>32</sup>

Abbreviations: ASD: Autism spectrum disorder; SLE: Systemic lupus erythematosus.



cytokines and reactive oxygen species, which can impair neurogenesis and synaptic refinement.<sup>34</sup> Similarly, reactive astrocytes amplify neuroinflammation and contribute to neuronal dysfunction.<sup>35</sup>

Microglia and astrocytes—the primary immune cells of the central nervous system—are frequently activated in ASD brains.<sup>36</sup> Chronic activation of these glial cells can lead to sustained neuroinflammation, synaptic dysfunction, and impaired neuronal connectivity, all of which are implicated in ASD.<sup>37</sup>

#### 4. MIA and neurodevelopmental disruption

MIA disrupts neural development through a cascade of inflammatory pathways that impact the fetal brain at molecular, cellular, and systems levels. Evidence points to five key mechanisms.

- (i) *Cytokine transfer and placental signaling.* During MIA, maternal infections, autoimmune conditions, or other inflammatory states elevate circulating pro-inflammatory cytokines such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$ . These cytokines can cross the placenta or stimulate placental cytokine production, exposing the fetus to inflammatory signals.<sup>18,40,41</sup> This exposure is linked to altered neurodevelopmental trajectories and increased risk for disorders such as autism and schizophrenia.<sup>18,40,42</sup>
- (ii) *Altered gene expression and epigenetic changes.* MIA induces rapid changes in gene expression within the conceptus, including upregulation of genes related to antiviral and inflammatory responses, and downregulation of genes critical for nervous system development.<sup>41,43</sup> For example, increased expression of IL-6 and IL-1 $\beta$  is observed in fetal tissues following maternal immune challenge, while genes involved in neuronal growth and differentiation are suppressed.<sup>41</sup> Epigenetic modifications, such as delayed DNA methylation patterns, further disrupt the maturation of cortical neurons, contributing to long-term neurodevelopmental abnormalities.<sup>40,43</sup>
- (iii) *Disruption of neural circuit formation.* Elevated maternal cytokines, particularly IL-6 and C-reactive protein (CRP), are associated with altered functional connectivity in newborn brain networks, including the anterior cingulate, insula, and medial prefrontal cortex.<sup>44</sup> Structural disruptions have been observed in key white matter tracts, such as the uncinate fasciculus, and in regions like the hippocampus, prefrontal cortex, and amygdala.<sup>42,44</sup> These changes are linked to impaired neuronal excitability, reduced neuron and glial cell proliferation, and abnormal synaptic protein expression, ultimately remodeling embryonic brain architecture.<sup>41,42,44</sup>

- (iv) *Microglial priming and neuroinflammation.* MIA can “prime” fetal microglia—the brain’s resident immune cells—toward a pro-inflammatory state, increasing their sensitivity to subsequent immune challenges.<sup>40,44</sup> This priming may contribute to persistent neuroinflammation and abnormal synaptic pruning, processes implicated in ASD and other neurodevelopmental disorders.<sup>40,44</sup>
- (v) *Behavioral and cognitive outcomes.* Animal studies demonstrate that prenatal exposure to MIA leads to offspring with deficits in memory, emotion, and cognition, mirroring symptoms seen in human neurodevelopmental disorders.<sup>41,42</sup> These behavioral abnormalities are thought to arise from the cumulative effects of disrupted neuronal development, altered connectivity, and persistent neuroinflammation.

In summary, MIA disrupts fetal neural development by transmitting inflammatory signals across the placenta, altering gene expression and epigenetic regulation, impairing neural circuit formation, and priming microglia for heightened neuroinflammatory responses. These mechanisms are supported by both human epidemiological data and experimental animal models, providing a robust framework for understanding how maternal inflammation increases the risk of neurodevelopmental disorders in offspring. Table 2 presents the factors involved and potential autism symptoms that may result, with the connecting mechanism underlying the developmental changes that give rise to each symptom.

#### 5. Is CFD a factor?

CFD is characterized by low levels of 5-methyltetrahydrofolate in the cerebrospinal fluid despite normal peripheral folate levels.<sup>45,46</sup> CFD has been implicated in various neurodevelopmental disorders, including ASD, particularly in cases where autoantibodies to the FR $\alpha$  are present.<sup>46</sup> CFD can be treated with supplemental leucovorin, easing communication symptoms in approximately 50% of ASD children treated.<sup>47–49</sup>

Maternal autoimmune conditions can result in the production of FR $\alpha$  autoantibodies, which may cross the placenta and inhibit folate transport to the developing fetal brain.<sup>50</sup> This disruption can lead to reduced folate availability during critical periods of neurodevelopment, potentially contributing to ASD pathogenesis.

While CFD is a plausible contributory factor, current evidence does not support it as a necessary mediator in the association between maternal lupus or Hashimoto’s disease and ASD. Not all children with ASD or those born to mothers with autoimmune diseases exhibit CFD or FR $\alpha$  autoantibodies.<sup>6</sup> Furthermore, the increased ASD risk

**Table 2. Autism symptoms that are influenced by immune and environmental factors**

Factor	Mechanism/Pathway	Neurodevelopmental changes	Potential autism symptoms
Maternal autoimmune disease (SLE, Hashimoto's)	<ul style="list-style-type: none"> <li>• Autoantibodies cross the placenta</li> <li>• Pro-inflammatory cytokines elevated</li> </ul>	<ul style="list-style-type: none"> <li>• Altered neuronal migration</li> <li>• Disrupted synapse formation</li> <li>• Changes in cortical layering</li> </ul>	<ul style="list-style-type: none"> <li>• Social communication deficits</li> <li>• Repetitive behaviors</li> <li>• Sensory sensitivities</li> </ul>
MIA/High immune load	<ul style="list-style-type: none"> <li>• Chronic inflammation</li> <li>• Activation of fetal microglia</li> <li>• Placental inflammation</li> </ul>	<ul style="list-style-type: none"> <li>• Impaired synaptic pruning</li> <li>• Imbalanced excitatory/inhibitory signaling</li> <li>• Neuroinflammation</li> </ul>	<ul style="list-style-type: none"> <li>• Social withdrawal</li> <li>• Cognitive rigidity</li> <li>• Heightened anxiety</li> </ul>
Cerebral folate deficiency (via folate receptor alpha autoantibodies)	<ul style="list-style-type: none"> <li>• Impaired folate transport to the fetal brain</li> <li>• Homocysteine accumulation</li> <li>• Disrupted methylation pathways</li> </ul>	<ul style="list-style-type: none"> <li>• Myelination defects</li> <li>• Impaired neurotransmitter synthesis</li> <li>• Oxidative stress</li> </ul>	<ul style="list-style-type: none"> <li>• Language delay</li> <li>• Poor attention</li> <li>• Seizures in some cases</li> </ul>
Environmental co-exposures (pollutants, infections)	<ul style="list-style-type: none"> <li>• Synergistic increase in inflammation</li> <li>• Disruption of the placental barrier</li> <li>• Added oxidative stress</li> </ul>	<ul style="list-style-type: none"> <li>• Exacerbation of cytokine responses</li> <li>• Increased vulnerability to neurotoxicants</li> </ul>	<ul style="list-style-type: none"> <li>• Increased symptom severity</li> <li>• Earlier symptom onset</li> <li>• Comorbid allergies/asthma</li> </ul>
Combined effects	<ul style="list-style-type: none"> <li>• Social conditions and health interactions amplify risk</li> </ul>	<ul style="list-style-type: none"> <li>• Global disruption of neural circuits for social, language, and motor skills</li> </ul>	<ul style="list-style-type: none"> <li>• Broad ASD phenotype across multiple domains</li> </ul>

Abbreviations: ASD: Autism spectrum disorder; MIA: Maternal immune activation; SLE: Systemic lupus erythematosus.

in offspring of mothers with various immune-mediated conditions suggests that multiple inflammatory and immune pathways may be involved, with CFD representing one of several possible mechanisms.

Recognition of CFD in ASD has led to trials of folinic acid supplementation, which has been shown to benefit subgroups of children with FR $\alpha$  autoantibodies.<sup>47–49</sup> However, the overall contribution of CFD to ASD risk in the context of maternal autoimmunity remains to be fully elucidated.

## 6. Public health implications

The association between maternal autoimmune diseases and increased risk of ASD in offspring has significant clinical and public health ramifications. Recognizing these implications is essential for optimizing maternal and child health through targeted screening, risk assessment, and early intervention strategies.

Emerging evidence supports the use of maternal autoantibody profiles as biomarkers for ASD risk. Studies have demonstrated that specific patterns of maternal autoantibodies, particularly those targeting fetal brain proteins, are highly predictive of ASD, with odds ratios approaching eightfold increases in risk when certain autoantibody combinations are present.<sup>51,52</sup> These findings suggest that screening for maternal autoantibodies during pregnancy could identify a subset of children at elevated risk of ASD, enabling closer developmental monitoring and earlier intervention.

Moreover, integrating antibody testing with established ASD screening tools (such as the Modified Checklist for Autism in Toddlers or Social Communication Questionnaire) has been shown to increase diagnostic confidence and post-test probability of ASD, especially in high-risk groups such as siblings of children with ASD or preterm infants.<sup>10,52</sup> This approach could refine risk stratification and optimize resource allocation for early developmental support.

For women with known autoimmune diseases, preconception and prenatal counseling should include discussion of the modestly increased risk of ASD in offspring.<sup>3</sup> While the absolute risk remains moderate, awareness allows for informed decision-making and proactive management. Clinicians should emphasize the importance of optimal disease control before and during pregnancy, as MIA and inflammation are hypothesized contributors to neurodevelopmental risk.<sup>9</sup>

In addition, interdisciplinary care involving obstetricians, immunologists, and pediatricians may be warranted for women with high-risk autoimmune conditions (e.g., lupus, Hashimoto's thyroiditis, Sjögren's syndrome, rheumatoid arthritis).<sup>3</sup> This team-based approach can facilitate tailored monitoring and timely referral to developmental services if early signs of ASD emerge.

The identification of maternal immune-mediated risk factors for ASD underscores the importance of early developmental screening in children born to mothers with autoimmune diseases. Given that early intervention

improves outcomes in ASD, prioritizing these children for routine developmental assessments and, if available, biomarker testing, could enable earlier diagnosis and access to support services.<sup>51-53</sup>

The recent development of remote fetal monitoring systems capable of tracking maternal and fetus parameters, including electrocardiography, electromyography, and fetal mobility, may offer a novel tool for identifying the risk of fetal development of ASD during pregnancy.<sup>54</sup> This could be combined with maternal health evaluations (of illness and exposures) in determining useful biomarkers and early signs of neurodivergent development.

From a public health perspective, increased awareness of the link between maternal autoimmune diseases and ASD risk should inform surveillance strategies and educational campaigns targeting both healthcare providers and the public. Enhanced surveillance can improve epidemiological understanding and guide resource allocation for maternal and child health programs.

The growing body of evidence highlights the need for further research into the mechanisms linking maternal autoimmunity and ASD, as well as the development and validation of biomarker-based screening tools.<sup>51,52</sup> Consideration should be given to supporting longitudinal studies and integrating maternal immune status into perinatal health guidelines.

The clinical and public health implications of maternal autoimmune disease as a risk factor for ASD are multifaceted: they include the potential for biomarker-driven risk assessment, the need for enhanced clinical counseling and interdisciplinary care, the prioritization of early developmental screening, and the importance of continued research and public health education.<sup>3,51,52</sup>

## 7. Conclusion

Maternal autoimmune diseases, notably lupus and Hashimoto's thyroiditis, are associated with a significantly increased risk of ASD in offspring. Both immune-mediated and genetic mechanisms likely contribute to this association. This raises the importance of multidisciplinary care for women with autoimmune diseases before and during pregnancy, and enhanced monitoring of children born to these women to allow early intervention if ASD symptoms develop.

## Acknowledgments

None.

## Funding

None.

## Conflict of interest

The author declares no conflict of interest.

## Author contributions

This is a single-authored article.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data

Not applicable.

## References

1. Vinet É, Pineau CA, Clarke AE, *et al.* Increased risk of autism spectrum disorders in children born to women with systemic lupus erythematosus: Results from a large population-based cohort. *Arthritis Rheumatol.* 2015;67(12):3201-3208.  
doi: 10.1002/art.39320
2. Nielsen TC, Nassar N, Shand AW, *et al.* Association of maternal autoimmune disease and early childhood infections with offspring autism spectrum disorder: A population-based cohort study. *Autism Res.* 2022;15(12):2371-2380.  
doi: 10.1002/aur.2824
3. Chen CC, Lin CH, Lin MC. Maternal autoimmune disease and risk of offspring autism spectrum disorder - a nationwide population-based cohort study. *Front Psychiatry.* 2023;14:1254453.  
doi: 10.3389/fpsyt.2023.1254453
4. Getahun D, Jacobsen SJ, Fassett MJ, *et al.* Association between maternal hypothyroidism and autism spectrum disorders in children. *Pediatr Res.* 2018;83(3):580-588.  
doi: 10.1038/pr.2017.308
5. Frye RE, Rossignol DA, Scahill L, McDougall CJ, Huberman H, Quadros EV. Treatment of folate metabolism abnormalities in autism spectrum disorder. *Semin Pediatr Neurol.* 2020;35:100835.  
doi: 10.1016/j.spen.2020.100835
6. Frye RE, Sequeira JM, Quadros EV, James SJ, Rossignol DA. Cerebral folate receptor autoantibodies in autism spectrum disorder. *Mol Psychiatry.* 2013;18(3):369-381.  
doi: 10.1038/mp.2011.175
7. Rossignol DA, Frye RE. Cerebral folate deficiency, folate receptor alpha autoantibodies and leucovorin (folinic acid) treatment in autism spectrum disorders: A systematic review and meta-analysis. *J Pers Med.* 2021;11(11):1141.

- doi: 10.3390/jpm11111141
8. Rakshasa-Loots AM, Swiffen D, Steyn C, Marwick KFM, Smith DJ. Affective disorders and chronic inflammatory conditions: Analysis of 1.5 million participants in Our Future Health. *BMJ Ment Health*. 2025;28(1):e301706.  
doi: 10.1136/bmjment-2025-301706
  9. Gardner RM, Brynne M, Sjöqvist H, Dalman C, Karlsson H. Maternal immune activation and autism in offspring: What is the evidence for causation? *Biol Psychiatry*. 2025;97(12):1127-1138.  
doi: 10.1016/j.biopsych.2024.11.009
  10. He H, Yu Y, Liew Z, *et al.* Association of maternal autoimmune diseases with risk of mental disorders in offspring in Denmark. *JAMA Netw Open*. 2022;5(4):e227503.  
doi: 10.1001/jamanetworkopen.2022.7503
  11. Chen SW, Zhong XS, Jiang LN, *et al.* Maternal autoimmune diseases and the risk of autism spectrum disorders in offspring: A systematic review and meta-analysis. *Behav Brain Res*. 2016;296:61-69.  
doi: 10.1016/j.bbr.2015.08.035
  12. Ellul P, Acquaviva E, Peyre H, *et al.* Parental autoimmune and autoinflammatory disorders as multiple risk factors for common neurodevelopmental disorders in offspring: A systematic review and meta-analysis. *Transl Psychiatry*. 2022;12(1):112.  
doi: 10.1038/s41398-022-01843-y
  13. Elbedour L, Weinberg M, Meiri G, Michaelovski A, Menashe I. Maternal thyroid hormone imbalance and risk of autism spectrum disorder. 2025.  
doi: 10.1101/2025.01.07.25320099
  14. Sun CK, Cheng YS, Chen IW, *et al.* Impact of parental rheumatoid arthritis on risk of autism spectrum disorders in offspring: A systematic review and meta-analysis. *Front Med*. 2022;9:1052806.  
doi: 10.3389/fmed.2022.1052806
  15. Kim JY, Son MJ, Son CY, *et al.* Environmental risk factors and biomarkers for autism spectrum disorder: An umbrella review of the evidence. *Lancet Psychiatry*. 2019;6(7):590-600.  
doi: 10.1016/S2215-0366(19)30181-6
  16. Villarreal VR, Katusic MZ, Myers SM, Weaver AL, Nocton JJ, Voigt RG. Risk of autoimmune disease in research-identified cases of autism spectrum disorder: A longitudinal, population-based birth cohort study. *J Dev Behav Pediatr*. 2024;45(1):e46-e53.  
doi: 10.1097/DBP.0000000000001232
  17. Kwon HK, Choi GB, Huh JR. Maternal inflammation and its ramifications on fetal neurodevelopment. *Trends Immunol*. 2022;43(3):230-244.  
doi: 10.1016/j.it.2022.01.007
  18. Hall MB, Willis DE, Rodriguez EL, Schwarz JM. Maternal immune activation as an epidemiological risk factor for neurodevelopmental disorders: Considerations of timing, severity, individual differences, and sex in human and rodent studies. *Front Neurosci*. 2023;17:1135559.  
doi: 10.3389/fnins.2023.1135559
  19. Estes ML, McAllister AK. Maternal immune activation: Implications for neuropsychiatric disorders. *Science*. 2016;353(6301):772-777.  
doi: 10.1126/science.aag3194
  20. Hsiao EY, McBride SW, Chow J, Mazmanian SK, Patterson PH. Modeling an autism risk factor in mice leads to permanent immune dysregulation. *Proc Natl Acad Sci*. 2012;109(31):12776-12781.  
doi: 10.1073/pnas.1202556109
  21. Patel S, Dale RC, Rose D, *et al.* Maternal immune conditions are increased in males with autism spectrum disorders and are associated with behavioural and emotional but not cognitive co-morbidity. *Transl Psychiatry*. 2020;10(1):286.  
doi: 10.1038/s41398-020-00976-2
  22. Osman HC, Moreno R, Rose D, Rowland ME, Ciernia AV, Ashwood P. Impact of maternal immune activation and sex on placental and fetal brain cytokine and gene expression profiles in a preclinical model of neurodevelopmental disorders. *J Neuroinflammation*. 2024;21(1):118.  
doi: 10.1186/s12974-024-03106-7
  23. Zawadzka A, Cieřlik M, Adamczyk A. The role of maternal immune activation in the pathogenesis of autism: A review of the evidence, proposed mechanisms and implications for treatment. *Int J Mol Sci*. 2021;22(21):11516.  
doi: 10.3390/ijms222111516
  24. Deverman BE, Patterson PH. Cytokines and CNS development. *Neuron*. 2009;64(1):61-78.  
doi: 10.1016/j.neuron.2009.09.002
  25. Smith SEP, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. *J Neurosci*. 2007;27(40):10695-10702.  
doi: 10.1523/JNEUROSCI.2178-07.2007
  26. Rosano C, Marsland AL, Gianaros PJ. Maintaining brain health by monitoring inflammatory processes: A mechanism to promote successful aging. *Aging Dis*. 2011;3(1):16-33.
  27. Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah I, Van de Water J. Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. *Brain Behav Immun*. 2011;25(1):40-45.  
doi: 10.1016/j.bbi.2010.08.003



28. Goines PE, Ashwood P. Cytokine dysregulation in autism spectrum disorders (ASD): Possible role of the environment. *Neurotoxicol Teratol.* 2013;36:67-81.  
doi: 10.1016/j.ntt.2012.07.006
29. Liu Z, Wang L, Yu L, *et al.* Identification of immune cells and circulating inflammatory factors associated with neurodevelopmental disorders by bidirectional Mendelian randomization and mediation analysis. *Sci Rep.* 2025;15(1):12840.  
doi: 10.1038/s41598-025-98020-0
30. Kelly SB, Dean JM, Zahra VA, *et al.* Progressive inflammation reduces high-frequency EEG activity and cortical dendritic arborisation in late gestation fetal sheep. *J Neuroinflammation.* 2023;20(1):124.  
doi: 10.1186/s12974-023-02805-x
31. Braunschweig D, Krakowiak P, Duncanson P, *et al.* Autism-specific maternal autoantibodies recognize critical proteins in developing brain. *Transl Psychiatry.* 2013;3(7):e277.  
doi: 10.1038/tp.2013.50
32. Atladóttir HÓ, Pedersen MG, Thorsen P, *et al.* Association of family history of autoimmune diseases and autism spectrum disorders. *Pediatrics.* 2009;124(2):687-694.  
doi: 10.1542/peds.2008-2445
33. Zou T, Liu J, Zhang X, Tang H, Song Y, Kong X. Autoantibody and autism spectrum disorder: A systematic review. *Res Autism Spectr Disord.* 2020;75:101568.  
doi: 10.1016/j.rasd.2020.101568
34. Bilbo SD, Schwarz JM. The immune system and developmental programming of brain and behavior. *Front Neuroendocrinol.* 2012;33(3):267-286.  
doi: 10.1016/j.yfrne.2012.08.006
35. Sofroniew MV. Astrocyte barriers to neurotoxic inflammation. *Nat Rev Neurosci.* 2015;16(5):249-263.  
doi: 10.1038/nrn3898
36. Morgan JT, Chana G, Pardo CA, *et al.* Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. *Biol Psychiatry.* 2010;68(4):368-376.  
doi: 10.1016/j.biopsych.2010.05.024
37. Tetreault NA, Hakeem AY, Jiang S, *et al.* Microglia in the cerebral cortex in autism. *J Autism Dev Disord.* 2012;42(12):2569-2584.  
doi: 10.1007/s10803-012-1513-0
38. Brimberg L, Sadiq A, Gregersen PK, Diamond B. Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder. *Mol Psychiatry.* 2013;18(11):1171-1177.  
doi: 10.1038/mp.2013.101
39. *Children Whose Mothers have Lupus Might be at Increased Risk of Autism Spectrum Disorders.* ScienceDaily. Available from: <https://www.sciencedaily.com/releases/2013/10/131027123140.htm> [Last accessed on 2025 Jul 05].
40. Han VX, Patel S, Jones HF, Dale RC. Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. *Nat Rev Neurol.* 2021;17(9):564-579.  
doi: 10.1038/s41582-021-00530-8
41. Baines KJ, Hillier DM, Haddad FL, Rajakumar N, Schmid S, Renaud SJ. Maternal immune activation alters fetal brain development and enhances proliferation of neural precursor cells in rats. *Front Immunol.* 2020;11:1145.  
doi: 10.3389/fimmu.2020.01145
42. Moravcikova L, Moravcik R, Csatosova K, Lacinova L, Jezova D, Dremencov E. Maternal immune activation impairs hippocampal pyramidal neuron excitability in newborn rat offspring: Implications for neurodevelopmental disorders. *Brain Med.* 2025;1(2):46-52.  
doi: 10.61373/bm025a.0029
43. Lai CY, Arzavala J, Pinto-Duarte A, *et al.* Maternal immune activation disrupts epigenomic and functional maturation of cortical excitatory neurons. 2025.  
doi: 10.1101/2025.04.28.651094
44. Spann MN, Bansal R, Aydin E, *et al.* Maternal prenatal immune activation associated with brain tissue microstructure and metabolite concentrations in newborn infants. *Brain Behav Immun.* 2024;122:279-286.  
doi: 10.1016/j.bbi.2024.08.025
45. Ramaekers VT, Rothenberg SP, Sequeira JM, *et al.* Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. *N Engl J Med.* 2005;352(19):1985-1991.  
doi: 10.1056/NEJMoa043160
46. Ramaekers V, Blau N, Sequeira J, Nassogne MC, Quadros E. Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits. *Neuropediatrics.* 2007;38(6):276-281.  
doi: 10.1055/s-2008-1065354
47. Frye RE, Slattery J, Delhey L, *et al.* Folinic acid improves verbal communication in children with autism and language impairment: A randomized double-blind placebo-controlled trial. *Mol Psychiatry.* 2018;23(2):247-256.  
doi: 10.1038/mp.2016.168
48. Renard E, Leheup B, Guéant-Rodriguez RM, Oussalah A, Quadros EV, Guéant JL. Folinic acid improves the score of Autism in the EFFET placebo-controlled randomized trial. *Biochimie.* 2020;173:57-61.  
doi: 10.1016/j.biochi.2020.04.019

49. Panda PK, Sharawat IK, Saha S, Gupta D, Palayullakandi A, Meena K. Efficacy of oral folinic acid supplementation in children with autism spectrum disorder: A randomized double-blind, placebo-controlled trial. *Eur J Pediatr.* 2024;183(11):4827-4835.  
doi: 10.1007/s00431-024-05762-6
50. Ramaekers VT, Sequeira JM, Blau N, Quadros EV. A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome. *Dev Med Child Neurol.* 2008;50(5):346-352.  
doi: 10.1111/j.1469-8749.2008.02053.x
51. Ramirez-Celis A, Croen LA, Yoshida CK, *et al.* Maternal autoantibody profiles as biomarkers for ASD and ASD with co-occurring intellectual disability. *Mol Psychiatry.* 2022;27(9):3760-3767.  
doi: 10.1038/s41380-022-01633-4
52. Mazón-Cabrera R, Liesenborgs J, Brône B, Vandormael P, Somers V. Novel maternal autoantibodies in autism spectrum disorder: Implications for screening and diagnosis. *Front Neurosci.* 2023;17:1067833.  
doi: 10.3389/fnins.2023.1067833
53. Lyall K, Ashwood P, Van de Water J, Hertz-Picciotto I. Maternal immune-mediated conditions, autism spectrum disorders, and developmental delay. *J Autism Dev Disord.* 2014;44(7):1546-1555.  
doi: 10.1007/s10803-013-2017-2
54. Li S, Yang Q, Niu S, Liu Y. Effectiveness of remote fetal monitoring on maternal-fetal outcomes: Systematic review and meta-analysis. *JMIR MHealth UHealth.* 2023;11:e41508.  
doi: 10.2196/41508