

Review

# Potential Mechanism Connecting Preeclampsia to Autism Spectrum Disorder in Offspring: The Role of Microglial Abnormalities

Ying Zhu<sup>1</sup>, Si-Yi Wei<sup>1</sup>, Xiao-Tong Fu<sup>1</sup>, Xi Cheng<sup>2</sup>, Xian-Hua Lin<sup>1,3,\*</sup><sup>1</sup>Obstetrics and Gynecology Hospital, Institute of Reproduction and Development, Fudan University, 200011 Shanghai, China<sup>2</sup>Department of Obstetrics and Gynecology, Chinese Academy of Medical Sciences and Peking Union Medical College, 100730 Beijing, China<sup>3</sup>Shenzhen Maternity and Child Healthcare Hospital, Southern Medical University, 518028 Shenzhen, Guangdong, China\*Correspondence: [xl\\_1290@126.com](mailto:xl_1290@126.com) (Xian-Hua Lin)

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## Abstract

Preeclampsia (PE) is a serious complication of pregnancy characterized by chronic inflammation and immune dysregulation, which significantly increases the risk of neurodevelopmental disorders in offspring, including the autism spectrum disorder (ASD). This review investigated the potential mechanisms linking PE to ASD, with a particular focus on the role of microglial abnormalities. Epidemiological studies have revealed that prenatal exposure to PE raised the risk of ASD, with affected offspring showing increased odds ratios. Microglia, the prime resident immune cells of the central nervous system (CNS), are critical for normal neurodevelopment, influencing processes such as neural stem cell (NSC) proliferation, synaptic pruning, and normal function of the neural circuit. Early-onset preeclampsia (EOPE) and late-onset preeclampsia (LOPE) may have an impact on the microglia abnormality and ASD through not exactly same pathway. Postmortem studies of ASD have further revealed increased microglial density, altered microglial morphology, and upregulated inflammatory markers in key brain regions, including the hippocampus and prefrontal cortex. Understanding the complex processes and potential mechanisms between EOPE, LOPE, microglial abnormalities, and ASD pathogenesis may highlight the importance of early screening and intervention for children born to mothers with PE. Targeting microglia-mediated pathways may offer novel therapeutic strategies to reduce the risk of ASD in these vulnerable populations.

**Keywords:** pre-eclampsia; autism spectrum disorder; microglia; prenatal exposure delayed effects; neurodevelopmental disorders

## 1. Introduction

Intrauterine development marks the earliest stage of life, where normal progression is essential for individual growth and long-term health. The relationship between fetal development and long-term health, known as the Developmental Origins of Health and Disease (DoHAD), has become a critical topic in non-communicable disease research. Investigating the impact of adverse exposures during early development, particularly intrauterine environmental influences on offspring's near and long-term health outcomes, is a central focus in modern medicine.

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by social deficits and repetitive behaviors, and whose incidence is steadily increasing [1]. In the United States, approximately 2.3% of children aged 8 years and 2.2% of adults are affected, and these numbers are rising [2]. ASD is more than four times as prevalent in boys as in girls and individuals with ASD are more likely to experience depression, anxiety, sleep disturbances, epilepsy, and severe intellectual disabilities, as well as language impairments and psychiatric conditions. These challenges impose significant burdens on families, healthcare systems, and society [3]. Despite extensive research, the etiology of ASD remains unresolved, complicating efforts in treatment and prevention. While genetic mutations

are considered primary contributors to ASD, growing evidence indicates that non-genetic factors account for approximately 17–50% of cases [4]. Among these, adverse intrauterine environments during pregnancy play a critical role in the pathogenesis of ASD [5].

Maternal conditions such as obesity, chronic inflammation, and preeclampsia (PE) may alter fetal neurodevelopment through acute and chronic immune stress, increasing the risk of ASD [6,7]. Hypertensive disorders of pregnancy (HDP), particularly PE, are among the most common pregnancy complications, affecting maternal and fetal outcomes globally [8]. PE, the most severe form of HDP, typically arises after 20 weeks of gestation and is a major cause of maternal and perinatal mortality. Its pathology involves impaired trophoblast invasion, endothelial activation, and maternal immune overactivation [9].

Epidemiological studies have increasingly demonstrated that PE exerts long-lasting effects on offspring neurodevelopment, significantly elevating the risk of ASD and other neurodevelopmental disorders (NDDs) independent of preterm birth or other obstetric complications [10–12]. Microglia, the resident immune cells of the central nervous system (CNS), account for 5–12% of CNS cells and mediate neuroinflammation. Substantial evidence indicates that microglia dysregulation contributed to ASD pathology by im-



pairing neurogenesis, synaptic pruning, and synaptic plasticity, leading to neuronal deficits, structural brain changes, and behavioral abnormalities [13].

This review aims to elucidate the evidence linking PE-induced microglia dysregulation to abnormal neurogenesis and synaptic plasticity, which may underlie the development of ASD in offspring.

## 2. Definition and Pathogenesis Preeclampsia

PE, the most severe form of HDP, has highly variable clinical manifestations and is a major cause of maternal and perinatal mortality [9]. According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), PE is defined as new onset hypertension (systolic >140 mmHg and diastolic >90 mmHg) accompanied by one or more target organ dysfunction including proteinuria, liver and kidney abnormality [14]. In the classification of PE, the terms “severe” and “mild” pre-eclampsia are thought to be used less frequently. Early-onset preeclampsia (EOPE) is diagnosed when the condition necessitates delivery before 34 weeks of gestation, whereas late-onset preeclampsia (LOPE) is defined by the requirement for delivery at or beyond 34 weeks of gestation. The classification is based on the gestational week at the time of diagnosis for PE, reflecting differences of pathophysiology and biochemical markers, and fetal outcomes [15,16].

EOPE is related to more severe neonatal mortality and is less commonly compared with LOPE [17], which is considered to be typically associated with placental dysfunction, preterm birth and restriction of fetal growth [15]. LOPE comprises about 80% to 90% of PE cases, and is associated with maternal cardiometabolic syndrome or diseases and is mainly the result of cardiovascular susceptibility and maternal endothelial dysfunction [18,19]. These two phenotypes have different etiologies and time lines, but both can trigger maternal inflammatory and immune responses of varying degrees that leads to adverse maternal and fetal outcomes [18,20]. In EOPE, this is triggered by insufficient perfusion of the placenta which results in a pro-inflammatory placental state. LOPE is more associated with systemic maternal inflammation due abnormal vessel response due to endothelial cell activation from the stress of pregnancy such as gestational diabetes mellitus and obesity, and inflammatory conditions found in pregnant females [20–22]. Although EOPE is more associated with poor placental function, LOPE can also lead to uteroplacental malperfusion as a result of compression of placental terminal villi when the placenta outgrows uterine capacity [18,23].

## 3. Neurodevelopmental Disorders and Autism

NDDs are a group of diverse conditions characterized by disruptions in brain development. They present with a wide range of clinical symptoms and severity and are

linked to varying levels of cognitive, adaptive functioning, and disability [24]. The etiology of NDDs is multifactorial, and both genetic and environmental factors play important roles in guiding and shaping the dynamically developing process and increasingly functional complexity of brain, as well as the development of NDDs [25]. ASD is recognized as one of canonical NDDs that are especially sensitive to early disturbance to the CNS [25]. According to family and population studies, ASD heritability is about 50% that of mental illness [26], while the genetic cause of the presence of ASD is clear in approximately only 20% of cases [27]. There were several proteins, including Phosphatase and tensin homolog (PTEN), Fragile X mental retardation protein (FMRP), Neurexins (NRXNs), the chromodomain helicase DNA-binding protein 8 (CHD8), SH3 and multiple ankyrin repeat domains protein 3 (SHANK3), have been reported related to ASD. PTEN is a tumor suppressor gene that regulate neuron positioning, dendritic development and synapse formation, and PTEN deficiency was associated with communication disorders, repetitive behaviors [28]. *CHD8* gene has been identified as a high-risk gene for ASD, which regulated the transcription of ASD risk factors in human neural progenitor cells, as well as neuronal differentiation, synaptic development, cell adhesion [29]. In addition, a lot of epidemiological researches revealed that early environmental factors, including toxicants, infections, medications, and maternal complications have been familiar to contribute to autism susceptibility [3]. Valproic acid (VAP) is a short-chain fatty acid. Clinical studies, along with other animal researches have reported an increased risk of neural tube defects, developmental delays, cognitive impairment and autism when VPA is taken during pregnancy [30,31]. Other maternal complications such as PE are risks factors of ASD as well [6].

## 4. Maternal Preeclampsia Increased the Risk of Autism Spectrum Disorder of Offspring

Several epidemiological studies had found that maternal PE increases the risk of offspring neurodevelopmental and psychiatric disorders [4,11,32–34], as shown in Table 1 (Ref. [4,11,33–38]). Systematic review and meta-analysis revealed a 1.5-fold increased risk of ASD exposure to maternal PE [4]. A population-based case-control study of 517 children with ASD and 350 controls with typical development (TD) from 20 California counties, found that children with ASD were twice as likely to have been exposed to PE in utero compared to controls (adjusted OR, 2.36; 95% CI, 1.18–4.68) [34]. Another study has also conducted cohort analyses to assess the risk of developing ASD in relation to PE exposure, and found approximately 1- to 3-fold increased risk [35]. However, the specific mechanisms as to how preeclampsia results in an increased risk of autism are unclear. Animal models mechanistically bridge PE and ASD phenotypes. Liu *et al.* [39] established a preeclampsia mouse model by N<sup>ω</sup>-nitro-L-arginine methyl ester (L-NA

**Table 1. Epidemiological evidence about increased ASD risk of children born from mother with preeclampsia.**

Reference	Type of study	Participants number	Exposure/case	Risk of ASD
Wang <i>et al.</i> 2021 [38]	Population-based cohort study	52,171 live-born singletons	Preeclampsia	Adjusted HR, 1.36 (95% CI, 1.30–1.42)
Sun <i>et al.</i> 2020 [11]	Prospective population-based cohort study	980,560 children born at term	Preeclampsia (Subtype unexplored)	Adjusted OR, 1.29 (95% CI, 1.08–1.54)
Chien <i>et al.</i> 2019 [37]	Observational study	323 probands with ASD, and 1504 of TDs	Preeclampsia	Significant factor to predict socio-communication deficits, stereotyped behaviors, and total scores of SRS; No risk reported.
Maher <i>et al.</i> 2018 [4]	Meta-analysis	11 studies (including 777,518 participants) 6 studies (including 378, 991 participants)	Hypertensive disorders of pregnancy preeclampsia	Pooled adjusted OR of 1.35 (95% CI, 1.11–1.64) Pooled adjusted OR of 1.50 (95% CI, 1.26–1.78), test for subgroup differences, $p = 0.33$
Dachew <i>et al.</i> 2018 [33]	Meta-analysis	10 studies	Preeclampsia	Pooled RR of 1.32 (95% CI, 1.20–1.45)
Walker <i>et al.</i> 2015 [34]	Population-based case-control	Children with ASD (517) vs Controls with TD (350)	Children with ASD	Adjusted OR of 2.36 (95% CI, 1.18–4.68)
Mann <i>et al.</i> 2010 [35]	Retrospective cohort study	87,677 births from 1996 through 2002	Preeclampsia or eclampsia	Adjusted OR, 1.69, $p = 0.0005$
Wallace <i>et al.</i> 2008 [36]	Retrospective study	228 families	Preeclampsia	Significantly associated with the ADI-R communication domain ( $t = 2.33$ , $p = 0.021$ ); No risk reported.

ASD, autism spectrum disorder; TD, typical development; HR, hazard ratio; CI, confidence interval; SRS, social responsiveness scale; ADI-R, autism diagnostic interview-revised; OR, odds ratio; RR, relative risk.

ME), and found there were increased anxiety repetitive behavior and defects of social behavior of adult offspring, as well as neuro morphologic abnormalities and changed expression genes related to ASD. High level of serum TNF- $\alpha$  was found to establish such an association between PE and ASD of offspring, indicating the effect of inflammation and immunity.

In addition, associations between preeclampsia and specific symptoms are also established both in epidemiological studies and animal models. Wallace *et al.* [36] observed a significant association between PE and higher communication scores using the Autism Diagnostic Interview-Revised (ADI-R) tool, which indicated a severe communication deficit in these children. However, another study found that probands with at least one prenatal factor among six, which include the PE, were associated with the severity of autistic symptoms across the assessments by the ADI-R, Social Communication Questionnaire (SCQ), and Social Responsiveness Scale (SRS), and that PE was one of the most significant factors to predict socio-communication deficits, stereotyped behaviors, and total scores of SRS [37]. The reasons for these inconsistent outcomes maybe related to the different symptoms assessing by ASD and the disparity in sample sizes. As for the animal model exploring the PE exposure and specific symptom of ASD, PE model by chronically infused with arginine vasopressin (AVP) found that PE-exposed adult males exhibited increased anxiety-like behavior and social approach while adult females exhibited impaired procedural learning and decreased excitatory synapse density in hippocampal dentate gyrus (DG), CA1, and CA3, which may indicating the microglia, which are responsible for synaptic pruning, are involved in the pathogenesis [40].

In addition to behavioral, psychiatric, and neurological risks observed in children born to mothers with preeclampsia, neuroimaging has also revealed structural changes in the brain. Offspring of PE exposure showed a significant association with cerebral palsy (adjusted OR, 1.30; 95% CI, 0.94–1.80) [11]. In a study of 7–10-year-old children from both preeclamptic and non-preeclamptic pregnancies, several brain regions, including the cerebellum, temporal lobe, brainstem, and bilateral amygdalae, were found to be enlarged relative to total intracranial volume in children exposed to preeclampsia. This was observed despite no significant differences in total intracranial volume or head circumference between the two groups [41].

These studies indicated that PE increased the risk of ASD in offspring, underscoring the importance of early ASD screening for children born to mothers with PE. Further exploration of the molecular mechanisms linking environmental factors, such as PE, to ASD is critical for future research.

## 5. Microglia and Autism Spectrum Disorder

### 5.1 Microglia in the Stage of Neurodevelopment

#### 5.1.1 The Origin of Microglia

Microglia, the resident immune cells of the CNS, play a dual role in coordinating neuroprotection, immune responses, and neuronal repair [42], comprising 5–12% of CNS cells [43]. Microglia are a special type of cells in the brain derived from a primitive yolk sac progenitors, which differ from other types of neural cells originating from the ectoderm [44]. Microglia arise early in the CNS and play a critical role in the development of the CNS. In the embryonic day 9.5 (E9.5), microglia appear in the neuroepithelium [45], and then rapidly proliferate to colonize the CNS, maturing into ramified microglia between E10.5 and birth [46]. Studies have found that microglia in the period of neurodevelopment, including the perinatal and early postnatal stage, have distinctly different morphologies and gene expression compared to the adult brain [47–49]. Schwarz *et al.* [47] found that there were more amoeboid microglia and microglia with stout processes than ramified microglia, which had longer or thinner processes in embryonic day 17, while ramified microglia were detected more in postnatal day 30. Microglia have unique gene expression profiles during different phases of development. Some genes of microglia such as *Fcrls*, *P2ry12*, are expressed very early in microglia development, whereas others including *Mafb*, *Tmem119*, are only expressed in adult microglia [48,49]. A study also found there was not substantial gene expression overlap between lipopolysaccharide (LPS)-stimulated microglia from the adult brain and microglia from a control neonatal brain [48].

#### 5.1.2 The Function of Microglia in Neurodevelopment

Microglia are critical for normal neural development but also maintain their role as primary CNS immune cells. Early neurodevelopment represents a particularly sensitive window during which diverse immune-activating challenges can induce long-term changes in brain function [47]. In neurodevelopment, microglia play essential roles in regulating neuronal activity, synaptic transmission, and the formation, remodeling, or elimination of synapses [50,51]. Microglia frequently interact with neurons, mediating neuronal functions including myelination, neurogenesis, and synaptic formation and maturation [52–55] through signaling molecules such as brain-derived neurotrophic factor (BDNF) [56], transforming growth factor-beta (TGF- $\beta$ ) [57], and complement proteins [58]. Microglia also phagocytize many products in the brain, including synaptic elements, myelin sheaths, living or dead cells, and axons [59,60], and further regulate neuronal processes and functions. Additionally, microglia actively phagocytose neural progenitor cells (NPCs) during developmental and adult neurogenesis, and thus contributes to controlling the size of the progenitor pool [52,61]. These microglia-neuron reg-

ulation processes are critical not only for brain development and maturation but also for various functions including learning, memory, cognition and social communication in the adult brain [62,63].

### 5.1.3 Factors Inducing Microglia Abnormalities in the Neurodevelopment

When macro-environmental challenges occur, microglial gene expression changes in a complex manner during development [59]. Under physiological conditions, microglia self-renew through proliferation and continuously monitor the CNS microenvironment [44]. However, when exposed to threats and adverse environment, microglia can adopt an abnormal state in response to injury, ischemia, or inflammatory stimulation in the brain [42]. This homeostasis is associated with proliferation, migration to injury sites, phagocytosis of cellular debris, and secretion of neurotoxic or neurotrophic factors [64]. Signals from bacterial products such as LPS, pathological proteins, ATP, and serum factors have been identified as triggers for microglia activation [46,65].

Brain development is particularly sensitive during early stages of life, especially in prenatal and early postnatal periods. Disruptions during these sensitive windows, whether due to genetic, environmental, or immune-related factors, can have profound effects on neurodevelopment [25]. Infections or other adverse states during pregnancy including preeclampsia can activate the maternal immune system, leading to the release of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  [66]. These cytokines can cross the placenta into the fetal circulation and breach the blood-brain barrier (BBB), where they activate fetal microglia and trigger neuroinflammatory cascades [67,68].

## 5.2 Microglia in the Autism Spectrum Disorder

### 5.2.1 Pathogenesis of ASD in Early Neurodevelopment

ASD is thought to result from complex interactions between genetic predispositions and environmental exposures [69]. Gestational factors that could affect neurodevelopment such as complications during pregnancy have been suggested to increase the risk of autism [70]. PE is one of the most severe complications of pregnancy and increases the risk of ASD.

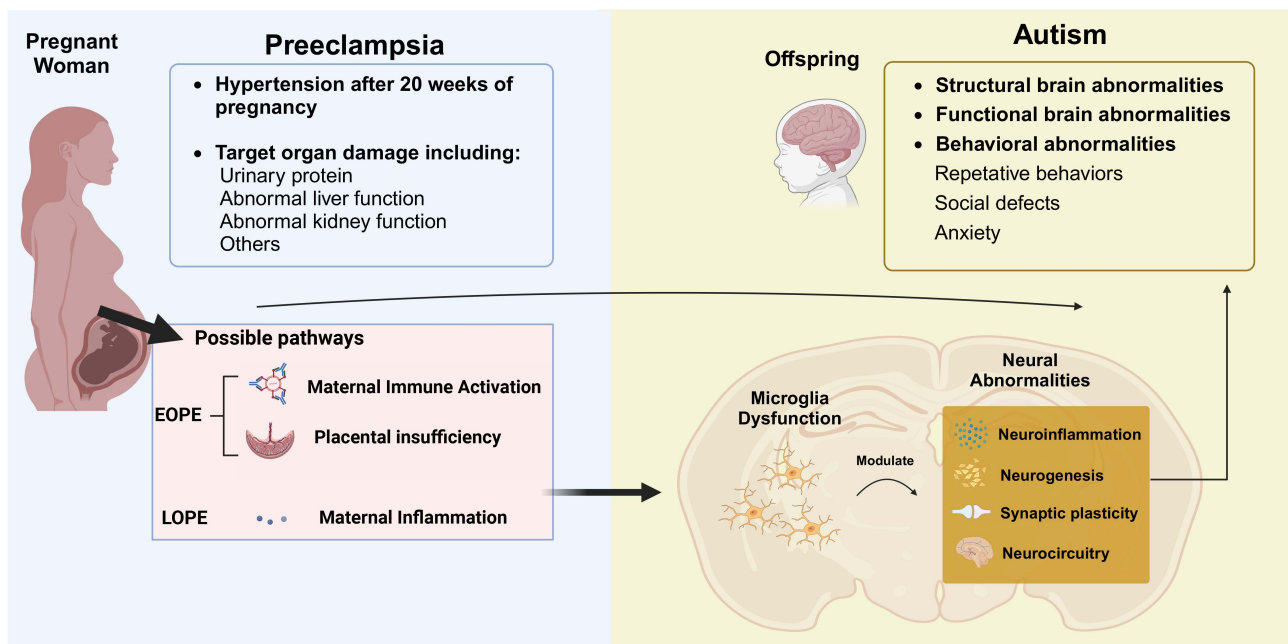
Early neurodevelopmental deficits are considered a fundamental basis for the onset and progression of ASD [71]. These deficits disrupt normal brain development during critical periods, leading to long-lasting structural and functional changes in the brain that underlie the core symptoms of ASD [72–74]. During early brain development, neurogenesis and synaptogenesis are crucial for establishing functional neural circuits [75,76]. Early deficits in neural circuit formation can lead to the impaired integration of sensory, motor, and cognitive information, which is characteristic of ASD [13,76]. Early developmental vulnerabilities can be exacerbated by maternal factors including PE,

which may interfere with the normal course of neurodevelopment, and therefore have a long-lasting impact on the nervous system, increasing the risk of ASD [77]. Postmortem studies of ASD brains have shown early structural brain abnormalities, such as altered connectivity in areas responsible for social cognition, sensory processing, and communication [76,78,79]. Neuroimaging studies in living individuals with ASD have revealed altered brain networks, including atypical connectivity patterns that reflect early developmental disruptions [25].

### 5.2.2 Microglia Involvement in the Development of ASD

The pathogenesis of ASD is complex, with dysregulated neuroinflammation identified as a critical factor in its development [80]. Human cognition and social function rely on a finely tuned and balanced immune response within the CNS [81]. Emerging research using single-cell sequencing of postmortem prefrontal cortex tissues from ASD patients has revealed a significant increase in the proportions of microglia [82,83]. Velmeshev *et al.* [82] used single-nucleus RNA sequencing (snRNA-seq) of cortical tissue from patients with ASD and found that the molecular state of microglia was preferentially affected in autism and microglia from ASD samples that were enriched for genes associated with microglial activation and transcriptional factors regulating developmental processes. Another study also found significant increases in reactive forms of microglia in ASD patients and an increase in microglia within gray matter laminae in ASD analyzed integrating the spatial transcriptomics data compared with control, along with an increase in reactive-state markers by highlighting the up-regulation of known pro-phagocytotic genes [83]. These findings underscore the role of neuro-inflammation in the pathogenesis of ASD [84].

Behavioral manifestations of ASD have been associated with multiple brain regions, including the amygdala, prefrontal cortex, and hippocampus [85]. Studies on structural changes of the hippocampus in the ASD have been inconsistent [86–89]. Several studies observed enlarged hippocampal volume in children [86] and adolescents [87,88] with ASD, while other studies found that the hippocampal volumes of ASD patients were smaller than those of healthy individuals [89]. In addition, studies also established a relationship between the dysfunction of the hippocampus and impairments in spatial reasoning and episodic memory, as well as social memory deficits in ASD [90–92]. The core symptoms of ASD are associated with abnormalities in neurogenesis, disrupted synaptic pruning, and dysfunction during CNS maturation [93]. Dysregulated microglia activity during critical periods of neurodevelopment can impair these processes, contributing to ASD [94,95]. Given their integral role in coordinating neurogenesis, immune regulation, synaptogenesis, and synaptic pruning, microglia dysregulation is considered a pivotal factor in the development of ASD.



**Fig. 1. The linking mechanic connector of microglia of offspring in the maternal preeclampsia and ASD of offspring.** Maternal preeclampsia is characterized by hypertension after 20 weeks of pregnancy and target organ damage, including urinary protein, abnormal liver function, and kidney dysfunction. The main manifestations of ASD include behavioral abnormalities such as repetitive behaviors, social deficits, and anxiety. The possible pathophysiological mechanisms of early-onset preeclampsia involve maternal immune activation, placental insufficiency, while late-onset preeclampsia involve maternal inflammation. These changes of PE may potentially impact the offspring's brain, leading to microglia dysfunction. The microglia modulate neural abnormalities, including neuroinflammation, impaired neurogenesis, disrupted synaptic plasticity, and altered neurocircuitry. These disruptions contribute to structural and functional brain abnormalities in offspring, as seen in autism. ASD, autism spectrum disorder; PE, preeclampsia; EOPE, early-onset preeclampsia; LOPE, late-onset preeclampsia. Created with [Biorender.com](https://www.biorender.com).

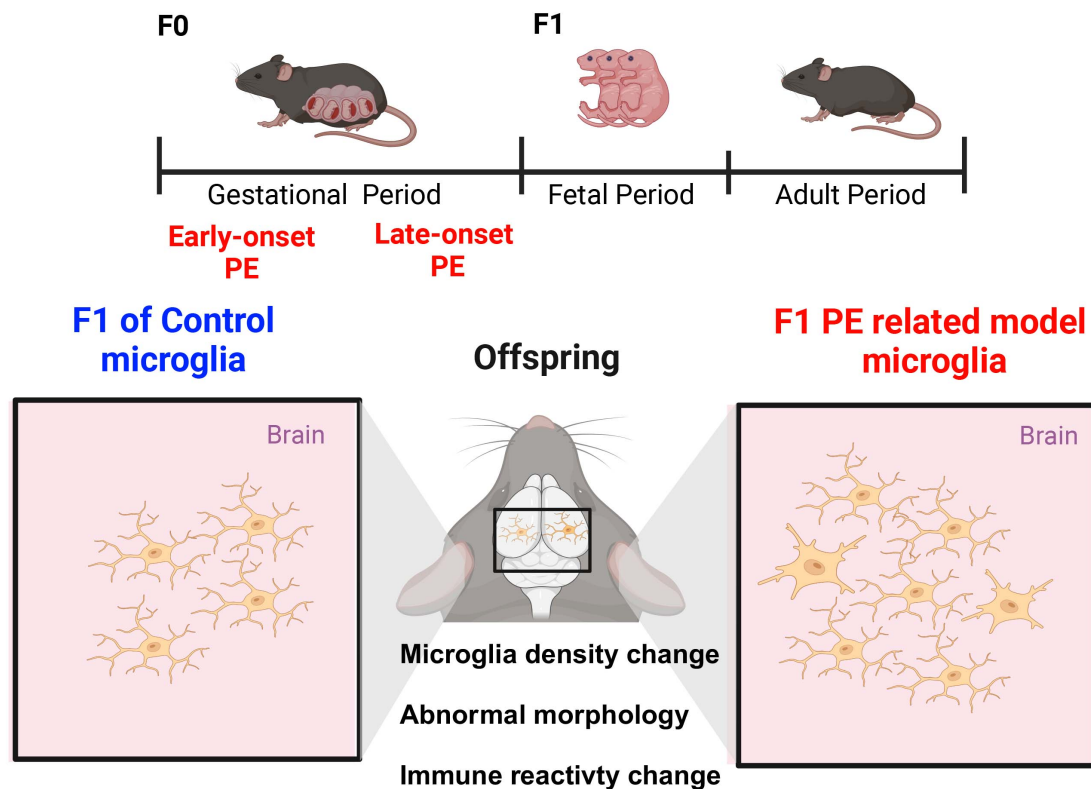
In conclusion, maternal factors, including PE, represent adverse intrauterine exposures that can impact the function of offspring microglia through various pathways, as will be explained in detail below. These effects ultimately result in early neurodevelopmental deficits, which disrupt key processes such as neurogenesis, synaptogenesis, and neural circuit formation, leading to the cognitive, social, and behavioral challenges characteristic of ASD (Fig. 1).

## 6. The Impacts of EOPE and LOPE on Microglial Abnormalities and ASD

Based on the differences in the pathogenesis of EOPE and LOPE, as well as their differential impacts on neonatal perinatal outcomes, it is valuable and meaningful to further classify preeclampsia into EOPE and LOPE for a deeper exploration of their respective effects on abnormal microglia in offspring and the potential association with ASD in the offspring.

Although various epidemiological studies have found that PE increased the risk of ASD in offspring, few studies discussed the risk of ASD by classifying the PE as EOPE and LOPE. Wang *et al.* [38] conducted a population-

based cohort study consisting of 52,171 live-born pregnancies in Denmark and Sweden and found that both EOPE and LOPE increased the risk of ASD with an adjusted HR of 1.74 (95% CI, 1.55–1.95) and 1.30 (95% CI, 1.24–1.37), respectively. EOPE was associated with an almost 2-fold risk of ASD in offspring, and the risk was smaller in those with LOPE. EOPE may confer a higher risk of offspring ASD compared to LOPE, partly due to its strong association with fetal growth restriction (FGR)—a well-established risk factor for neurodevelopmental impairments [96]. Unlike LOPE, which rarely involves FGR [18,20], EOPE-related placental insufficiency induces chronic hypoxia and systemic inflammation, disrupting fetal brain development. Animal studies suggest that FGR triggers microglial hyperactivation and excessive synaptic pruning via inflammatory pathways, such as the microbiota-IPA-brain axis, which promotes ASD-like behaviors [90]. Additionally, EOPE showed longer exposure time on fetal neuronal development compared to LOPE. However, the underlying mechanism is unclear and animal models are necessary for exploring the relationship among the two subtypes of PE, microglial abnormalities and ASD in offspring. Studies have used several kinds of animal models related to the pathologic mechanisms of PE, and explored the manifesta-



**Fig. 2. The abnormalities of microglia in the offspring of animal modeled by related pathologies of preeclampsia.** The abnormalities in microglia observed in the offspring (F1) of animal models exposed to early-onset preeclampsia (EOPE) and late-onset preeclampsia (LOPE) during the gestational period (F0). F1 of Control microglia exhibit normal microglia characteristics in the brain, including typical density, morphology, and immune reactivity. In contrast, F1 PE-related model microglia show significant alterations, including microglia density change, abnormal morphology and immune reactivity. The central diagram highlights these differences, emphasizing the impact of maternal PE-related pathologies on microglia development and function in the offspring's brain. Schematic diagrams were created using [BioRender.com](https://www.biorender.com).

tions of microglia as well as associated neural function in the brain of offspring (Table 2, Ref. [97–104]). However, these studies did not clearly define whether the PE models established were early-onset or late-onset and currently, there is a lack of timing to distinguish EOPE and LOPE in animal models. Mice have a relatively short length of gestation (19~20 days) compared with humans at 9 months, and several studies have established the mouse model of LOPE from embryonic day 16 or 17 [105–107]. As shown in the Fig. 2, animal models revealed cell density and morphological changes, as well as the abnormal immune reactivity of the microglia both in the EOPE and LOPE.

### 6.1 The Potential Impacts of EOPE on Microglia Abnormalities and ASD

The microglial abnormalities in the offspring of EOPE primarily manifest as alterations in microglial number, morphological changes indicative of activation, and dysregulated inflammatory states in the brain. The specific characteristics of these abnormalities may vary depending on the modeling approach. Notably, EOPE induced by maternal immune activation is associated with an increased num-

ber of microglia, whereas EOPE resulting from placental ischemia primarily affects microglial density [97–100,104].

Most studies establishing the animal model related to the pathologic mechanisms of PE were prior to gestational day 15, which is more closely aligned with the time points defined in previous research on EOPE. Systemic activation of the immune cells using during pregnancy has been studied as a model of preeclampsia [98,99,101,103,104,107]. Studies from animal models have shown that maternal exposure to polyinosine acid (poly I:C) from gestational day 9.5 induced increased density of microglia in diverse regions in the brain of offspring, especially in the hippocampus, and impaired short-term memory, deficits in social interaction were observed in these researches [103,104]. In addition, poly I:C and LPS exposure separately from gestational day 12 showed changes of morphology of activation-like microglia in different regions [99,101]. The former was observed in hippocampus and associated with impaired GABAergic transmission in the dentate gyrus, while the latter was observed in amygdala and associated with heightened anxiety and depression. These studies together indic-

**Table 2. Animal model related to the pathology of preeclampsia and the abnormality of microglia and neural or behavioral changes.**

Reference	Modeling methods	Pathology of PE	Dysfunction of microglia	Related change of neural function or behaviors
Katoh <i>et al.</i> 2022 [97]	Continuous injection of Ang II in pregnant C57BL/6 mice from gestational day 10.5.	Impaired vasoconstriction, vascular dysfunction, placental ischemia and hypoxia.	Higher solidity and circularity of microglia in the fetal brain <sup>↑</sup> , indicating a transformed amoeboid morphology and activated state.	Unexplored.
Hayes <i>et al.</i> 2022 [98]	Poly I:C (10–20 mg/kg at a volume five times the animal weight (5 mL/kg), i.p.), to pregnant C57BL/6 mice at gestational day 9.5.	MIA	Bulk RNA-seq and Single-cell RNA-seq analysis of microglia revealed that decrease of the contribution to inflammatory microglia states <sup>↓</sup> , while no distinct subpopulation change.	Dysfunctional connectivity of the ventral striatal circuit with a decrease in the glutamatergic presynaptic release probability specifically onto D2R MSNs.
Xia <i>et al.</i> 2020 [99]	Poly I:C (5 mg/kg, i.p.), to pregnant C57BL/6 mice at gestational day 12.	MIA	Total number of microglia <sup>↑</sup> , activated morphology of microglia <sup>↑</sup> in adult hippocampus.	Fewer parvalbumin positive cells and impaired GABAergic transmission in the dentate gyrus, accompanied by schizophrenia-like behavior in the adult offspring.
Giambrone <i>et al.</i> 2019 [100]	Sprague Dawley rats by surgical reduction of utero-placental perfusion (RUPP) at gestational day 14.	Placental ischemia	Microglial density in the sub-ventricular zone <sup>↓</sup> .	Unexplored.
O'Loughlin <i>et al.</i> 2017 [101]	LPS (50 μg/kg, i.p.), to pregnant C57BL/6 mice at gestational day 12.	MIA	Larger microglia bodies and thicker shortened processes in postnatal amygdala.	Cytoarchitecture changes of the postnatal amygdala, and may predispose offspring to amygdala-related disorders such as heightened anxiety and depression.
Schaafsma <i>et al.</i> 2017 [102]	LPS (0.05 mg/kg, i.p.) to pregnant C57BL/6 mice during gestation day 15–17	Maternal inflammation	Inflammation of fetal microglia, reduced LPS responsiveness in total brain microglia and increased LPS responsiveness in hippocampal microglia.	Reduced basal home cage activity, impaired learning.
Li <i>et al.</i> 2014 [103]	Poly I:C (20 mg/kg, i.p.), to pregnant C57BL/6 mice at gestational day 9.5.	MIA	Microglia number in the adult hippocampus <sup>↑</sup> .	Impaired short-term memory and altered dendritic architecture.
Zhu <i>et al.</i> 2014 [104]	Poly I:C (20 mg/kg, i.p.), to pregnant C57BL/6 mice at gestational day 9.5.	MIA	Microglia number in the adult hippocampus, thalamus, and cerebral cortex <sup>↑</sup> .	Hyperlocomotion, deficits in social interaction and prepulse inhibition.

Abbreviations: Poly I:C, polyinosinic-polycytidylic acid; LPS, lipopolysaccharide; MIA, maternal immune activation; Ang II, angiotensin II. Arrows indicate the direction of change: <sup>↑</sup> represents an increase, and <sup>↓</sup> represents a decrease.

ated the activation of microglia and impaired neural function. In addition, a recent study found that poly I:C injection from gestational day 9.5 blunted the reactivity of microglia both in the development and the adult offspring, and contributed to the injury seen in striatal circuit development [98]. Disturbed neuroregulatory and immunological functions of microglia resulted from maternal immune activation harm the key processes of brain development, affecting neurogenesis, neuronal migration, myelination, neural circuit formation, and synaptic refinement, potentially resulting in long-term impairments in brain function and behavior.

The pathology of placental insufficiency of the PE may consistently influence the microglia of offspring, which alters aggravating inflammatory functions. Reduction of utero-placental perfusion (RUPP) is a classical placental insufficiency animal model, which have a surgical operation at gestational day 14. A study in an animal model of RUPP in Sprague Dawley rats found increased pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and IL-18 in the fetal brain, and reduced microglia density in proliferative brain areas [100]. Another mouse model of PE induced by angiotensin II (Ang II) also showed increased expression of cytokines, IL-6, IL-17a, TNF- $\alpha$ , interferon- $\gamma$  (IFN- $\gamma$ ), IL-12, IL-4, and IL-10. Higher solidity and circularity of the microglia was observed on E17.5 of the fetal brain of the Ang II-administered group compared to those of the control group, which suggests that the microglia had transformed to an amoeboid morphology and were activated [97]. In short, the evidence from the animal model of EOPE we have so far indicate the abnormality of microglia is diverse and controversial, including variation of microglia density, changes of morphology of activation-like microglia in brain and blunted immune reactivity, which may differ resulted from the mechanism of animal model of PE. However, all of the abnormalities of microglia showed impaired neural function and behaviors on a different level, which may relate to the ASD.

### 6.2 The Potential Impacts of LOPE on Microglial Abnormalities and ASD

Very few animal studies explored the impact of LOPE on microglia dysfunction and neurobehavioral abnormalities of ASD. LOPE modeled by LPS injection exhibits an abnormal microglial inflammatory state, with inconsistent changes observed between the whole brain and the hippocampus. Schaafsma *et al.* [102] explored the neurodevelopment outcomes by LPS administration to pregnant C57BL/6 mice during gestation day 15–17, during the period of LOPE. They found a fetal microglia pro-inflammatory response in which adult whole brain microglia displayed a persistent reduction in pro-inflammatory activation in response to a re-challenge with LPS and hippocampal microglia of these mice displayed an increased inflammatory response to an LPS re-challenge.

These findings were different from the microglia changes observed in the mice using LPS earlier in the maternal period. However, more research is needed to study LOPE to help to confirm and explain these differences. Adult offspring exposed to maternal LPS administration during gestation day 15–17 showed reduced home cage activity, reduced anxiety and reduced learning performance in a T-maze. A reduced expression of brain-derived neurotrophic factor (BDNF) from microglia may play a role in these processes. Given the limited animal modeling studies on LOPE, future research should focus on exploring the underlying mechanisms and refining animal models for this condition. This could provide valuable insights into the mechanisms by which LOPE may lead to NDDs, such as autism, and microglial abnormalities in offspring.

### 6.3 Potential Mechanisms Underlying the Differential Impacts on Microglial Abnormalities and ASD Risk

Preeclampsia is highly heterogeneous in its clinical manifestations and pathogenesis, which may explain why early-onset (EOPE) and late-onset preeclampsia (LOPE) exert distinct effects on microglia and ASD risk. Firstly, EOPE and LOPE occur at different gestational stages, coinciding with critical phases of microglial development, neurogenesis, and brain maturation. Microglia undergo migration, differentiation, and functional maturation during pregnancy, playing pivotal roles in synaptic pruning and immune regulation [108]. Thus, the timing and duration of preeclampsia exposure may differentially impact microglial function and neurodevelopment, influencing ASD risk. Secondly, EOPE and LOPE exhibit distinct placental pathologies. EOPE, often termed “placental preeclampsia”, is linked to impaired trophoblast invasion and early placental dysfunction, leading to severe placental hypoxia. In contrast, LOPE is associated with maternal metabolic dysfunction and systemic inflammation [18,19], which alter fetal environment, breach the fetal blood-brain barrier [67], leading to abnormal brain development. Thus, inconsistent uterine environment and placental function may contribute to different microglia response and further impact the neurodevelopment. Additionally, EOPE is strongly associated with fetal growth restriction (FGR), a known risk factor for neurodevelopmental delays [96], while LOPE is not [18,20]. Animal studies suggest that FGR and inflammatory pathways, such as the microbiota-IPA-brain axis, may drive microglial hyperactivation and synaptic over-pruning, increasing ASD susceptibility [90]. Thus, the divergent mechanisms underlying EOPE and LOPE likely contribute to their differential impacts on microglia and ASD risk.

## 7. The Potential Pathway that Preeclampsia Results in the Dysfunction of Microglia and ASD

The pathophysiology of PE is highly heterogeneous. Current animal models are designed to replicate its diverse

pathological processes by employing various approaches, including maternal immune activation, reduced uteroplacental perfusion, and vascular endothelial dysfunction, often with inconsistent modeling time points. These distinct modeling strategies, which specifically mimic either EOPE or LOPE, may differentially affect microglial development and susceptibility to ASD.

Although mechanistic studies directly linking PE-specific pathways to microglial abnormalities and ASD risk remain limited, a synthesis of existing fragmented evidence highlights potential mechanisms underlying EOPE, LOPE, microglial dysfunction, and ASD pathology.

### 7.1 The Potential Pathway that EOPE Results in the Dysfunction of Microglia and ASD

#### 7.1.1 Maternal Immune Activation

Maternal immune activation (MIA) is initially defined as those immune change triggered by infection in the pregnancy period. There is emerging evidence that EOPE can result in maternal immune activation [18,109]. Meanwhile, the immune hypothesis is regarded as a key factor in the pathogenesis of autism, and provides an explanation for the variability in clinical phenotypes and comorbidities that affect the progression and severity of this condition [110]. It has recently been suggested as a component potentially involved in the development of ASD [111]. Pregnancy represents a critical period of immune vulnerability, where maternal immune activation may adversely affect fetal immune and nervous system development, especially in the very early period of neural development influenced by EOPE. These effects can persist into adulthood, increasing the risk of NDDs in offspring [112]. Another study has also demonstrated a more pronounced imbalance in immune cell populations in the circulatory system of patients with EOPE compared with LOPE [21].

Various MIA animal models established in a similar gestational period to EOPE, and found the changes of cell density and morphology, as well as the immune reactivity of microglia, along with neural functional and behavioral abnormality such as the social communication deficits, which is related to ASD [103,104]. As primary immunoregulators of neural function, microglia are central to the sustained immune and/or neurodevelopmental changes associated with MIA. Microglia abnormality, driven by MIA, is thought to be a critical mechanism underlying these persistent changes in offspring [20].

#### 7.1.2 Insufficient and Dysfunctional Placenta

EOPE is characterized with placental ischemia and hypoxia, vascular dysfunction and increased antiangiogenic factors including soluble fms-like tyrosine kinase 1 (sflt1) and soluble endoglin (sENG) [8]. The placenta is an essential organ for proper fetal development. Placental insufficiency leads to an intrauterine environment in which the fetus is at risk of inadequate oxygen and nutrient exchange

[113], contributing to abnormal neuron development [4]. Villamor *et al.* [10] conducted population-based cohort and sibling-controlled studies and found that placental abruption was associated with increased HR of ASD in a general cohort analysis, and that syndromes linked to defective placentation are associated with an increased incidence of ASD in the offspring.

Although there is still a lack of specific and in-depth basic studies on the maternal placental dysfunction, the microglia abnormality and development of ASD, data from human studies have found that placental insufficiency of severe PE appears to be responsible for the increase in neurodevelopmental disorders and the risk of developmental delay (DD) [34]. The abnormality of microglia may serve as a bridge to the development of PE and ASD because of the similar changes of microglia both on the offspring exposed to PE and individuals with ASD, including evidence from animal models of placental insufficiency showing abnormal microglia and neuronal function related to ASD [97,100].

### 7.2 The Potential Pathway that LOPE Results in the Dysfunction of Microglia and ASD

#### Maternal Inflammation

LOPE is often associated with maternal conditions such as obesity, diabetes mellitus, and other metabolic diseases, which are considered to be characterized by chronic, low-grade systemic inflammation [21]. Systemic chronic inflammation is characterized by persistent, sterile, non-resolving inflammation that increases with age, and is implicated in many common disease states including PE [112]. Valencia-Ortega *et al.* [22] conducted an age-matched study and reported that maternal serum concentrations of IL-6 were significantly higher in late-onset pre-eclampsia, compared to early-onset preeclampsia or uncomplicated pregnancy. Moreover, IL-6 was only significantly associated with term pre-eclampsia, while the first and second trimester levels of IL-6 were not associated with pre-term preeclampsia, suggesting that elevations in IL-6 may be a late-stage feature of pre-eclampsia [114,115].

Substantial evidence indicates that chronic maternal inflammation, triggered by pregnancy complications such as PE, is a major environmental risk factor for ASD in offspring [5]. Population-based studies have linked elevated maternal interleukin (IL)-6 and C-reactive protein (CRP) levels during pregnancy to alterations in neonatal brain structure and functional connectivity [116]. Furthermore, children exposed to high intrauterine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels exhibit poorer performance on cognitive tests at seven years of age [117].

According to the animal study, injection of 0.05 mg/kg LPS on gestational days 15, 16, and 17 significantly elevated TNF- $\alpha$  serum levels in the pregnant mice and strongly upregulated pro-inflammatory genes, including IL-1 $\beta$ , TNF- $\alpha$ , and IL-6, in embryonic microglia, indicating inflammation in both the pregnant mice and fetal mi-

croglia. This maternal inflammation exposure during late gestation results in long-term changes in microglial responsiveness during adulthood [102].

## 8. Intervention Strategies for PE and ASD

Early intervention is important for improving behavior expression of children with ASD. There were inconsistent findings supporting that very early interventions on infants and toddlers with ASD have limited impact on neurodevelopmental outcomes by age 3 years [118]. As the neurodevelopmental and environment mechanisms underlying autism are better understood, a broader array of targets within the developmental cascade to autism is expected to emerge, including those linked to parental risk factors [93].

Given that PE is recognized as a risk factor for ASD of offspring, early prevention or management of PE starting from the perinatal period may represent a potential strategy for reducing the risk of ASD development. Currently, the management of preeclampsia involves preconception counseling, perinatal blood pressure monitoring and control, pharmacological therapy for high-risk women and close postpartum blood pressure monitoring [8]. Due to differences in the timing of diagnosis and underlying mechanisms between EOPE and LOPE, the approaches for intervention and treatment may also vary. In patients with EOPE and severe features, close monitoring of maternal and fetal well-being is crucial, and delivery should be considered at any point if there is deterioration in either maternal or fetal condition, as EOPE is strongly associated with neonatal mortality [8].

As the pathological processes of maternal PE and neural development often begin earlier than the clinical manifestations, identifying high-risk cases and applying preventive measures becomes even more critical. Moreover, the subtypes of PE must be considered in order to select and combine appropriate preventive and therapeutic strategies. For example, low-dose aspirin is now recommended for the prevention of PE in high-risk women [119]. Sildenafil, which is believed to reduce placental ischemia associated with the pathology of EOPE, has shown promise [120]. Metformin, an insulin sensitizer, has been associated with a reduced incidence of hypertensive disorders in pregnancy and can also be used as a preventive measure for PE, especially in women with diabetes mellitus, obesity, or metabolic abnormalities, who are at higher risk for developing LOPE [121].

In summary, the prevention of both EOPE and LOPE requires identifying high-risk factors for PE. However, the different subtypes of PE may indicate distinct pathologies, helping clinicians choose drugs targeting the associated mechanisms. Furthermore, addressing metabolic and vascular abnormalities may reduce the occurrence of LOPE. Since the role of microglia as a molecular link between maternal preeclampsia and offspring autism remains unclear, future research should focus on exploring the underlying

mechanisms to identify molecular targets in microglia. This could provide a foundation for developing early preventive strategies targeting microglia.

Several therapeutic strategies have been explored to mitigate the impact of PE on fetal microglial function and neurodevelopmental outcomes. Anti-inflammatory agents, such as low-molecular-weight heparin (LMWH) and aspirin, have been shown to attenuate placental inflammation by suppressing the TNF- $\alpha$ /IL-6 pathways [122], potentially reducing fetal microglial priming. Clinical trials, including the APRIL study, suggest that LMWH combined with low-dose aspirin effectively improves pregnancy outcomes in women at high risk for PE and its complications [123]. Additionally, preclinical models indicate that aspirin normalizes placental IL-1 $\beta$  levels, which is associated with improved microglial function [124,125]. Nutritional interventions also play a role in modulating placental and fetal inflammatory responses. Animal studies have demonstrated that omega-3 fatty acids downregulate maternal NF- $\kappa$ B signaling, enhance placental antioxidant capacity, reduce oxidative stress, and promote fetal and placental growth [126]. Among these, docosahexaenoic acid (DHA), a key omega-3 fatty acid, may block microglial NLRP3 inflammasome activation, a mechanism implicated in ASD-like behaviors in offspring [127]. Furthermore, microglia-specific modulators have shown promise in preclinical studies. Minocycline, a tetracycline antibiotic, directly inhibits microglial ROS production and suppresses M1 polarization [128]. In rodent models of PE, postnatal minocycline treatment has been found to alleviate social deficits by reducing hippocampal microgliosis, highlighting its potential as a neuroprotective strategy [129].

## 9. Conclusions

PE creates a pro-inflammatory intrauterine environment that can profoundly affect fetal brain development. Chronic maternal immune activation and inflammation associated with PE leads to dysregulated microglia dysfunction, which is strongly implicated in the pathogenesis of ASD. Microglia dysfunction impacts NSC proliferation, synaptic pruning, and neuroimmune modulation, contributing to structural and functional brain abnormalities. Post-mortem and animal studies consistently reveal microglia abnormality and neuroinflammation in ASD, highlighting their potential role as therapeutic targets. Given that different pathologies of EOPE and LOPE, it is possible that the effects of EOPE and LOPE on offspring neurodevelopmental outcomes may vary depending on the severity and clinical course of the disease.

Future research should focus on elucidating the molecular pathways connecting two subtypes of PE and microglia activation, as well as identifying biomarkers for early detection of ASD in high-risk populations. Early interventions targeting neuroinflammation and microglia dysregulation

have promise for reducing the burden of ASD in children born to PE-affected pregnancies.

## Author Contributions

Contribution to the conception and design of the manuscript—YZ, SYW, XTF, XC, XHL; writing—original draft preparation—YZ; writing—review and editing—YZ, SYW, XTF, XC; supervision—XHL; project administration—XHL. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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## Conflict of Interest

The authors declare no conflict of interest.

## Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGpt in order to improve language, which was mainly used in the “Abstract”, “Introduction” Sections, and check spelling and grammar in the main body of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

## References

- [1] Famitafreshi H, Karimian M. Overview of the Recent Advances in Pathophysiology and Treatment for Autism. *CNS & Neurological Disorders Drug Targets*. 2018; 17: 590–594. <https://doi.org/10.2174/1871527317666180706141654>.
- [2] Hirota T, King BH. Autism Spectrum Disorder: A Review. *JAMA*. 2023; 329: 157–168. <https://doi.org/10.1001/jama.2022.23661>.
- [3] Wang L, Wang B, Wu C, Wang J, Sun M. Autism Spectrum Disorder: Neurodevelopmental Risk Factors, Biological Mechanism, and Precision Therapy. *International Journal of Molecular Sciences*. 2023; 24: 1819. <https://doi.org/10.3390/ijms24031819>.
- [4] Maher GM, O’Keeffe GW, Kearney PM, Kenny LC, Dinan TG, Mattsson M, *et al.* Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2018; 75: 809–819. <https://doi.org/10.1001/jamapsychiatry.2018.0854>.
- [5] Yenkovyan K, Mkhitarian M, Björklund G. Environmental Risk Factors in Autism Spectrum Disorder: A Narrative Review. *Current Medicinal Chemistry*. 2024; 31: 2345–2360. <https://doi.org/10.2174/0109298673252471231121045529>.
- [6] Han VX, Patel S, Jones HF, Nielsen TC, Mohammad SS, Hofer MJ, *et al.* Maternal acute and chronic inflammation in pregnancy is associated with common neurodevelopmental disorders: a systematic review. *Translational Psychiatry*. 2021; 11: 71. <https://doi.org/10.1038/s41398-021-01198-w>.
- [7] Ahmad SR, Zeyauallah M, AlShahrani AM, Dawria A, Ali H, Mohieldin A, *et al.* Deciphering the Enigma of Neuron-Glial Interactions in Neurological Disorders. *Frontiers in Bioscience (Landmark edition)*. 2024; 29: 142. <https://doi.org/10.31083/j.fbl2904142>.
- [8] Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: Pathophysiology, Challenges, and Perspectives. *Circulation Research*. 2019; 124: 1094–1112. <https://doi.org/10.1161/CIRCRESAHA.118.313276>.
- [9] Deer E, Herrock O, Campbell N, Cornelius D, Fitzgerald S, Amaral LM, *et al.* The role of immune cells and mediators in preeclampsia. *Nature Reviews. Nephrology*. 2023; 19: 257–270. <https://doi.org/10.1038/s41581-022-00670-0>.
- [10] Villamor E, Susser ES, Cnattingius S. Defective placentation syndromes and autism spectrum disorder in the offspring: population-based cohort and sibling-controlled studies. *European Journal of Epidemiology*. 2022; 37: 827–836. <https://doi.org/10.1007/s10654-022-00884-3>.
- [11] Sun BZ, Moster D, Harmon QE, Wilcox AJ. Association of Preeclampsia in Term Births With Neurodevelopmental Disorders in Offspring. *JAMA Psychiatry*. 2020; 77: 823–829. <https://doi.org/10.1001/jamapsychiatry.2020.0306>.
- [12] Maher GM, O’Keeffe GW, Dalman C, Kearney PM, McCarthy FP, Kenny LC, *et al.* Association between preeclampsia and autism spectrum disorder: a population-based study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. 2020; 61: 131–139. <https://doi.org/10.1111/jcpp.13127>.
- [13] Luo Y, Wang Z. The Impact of Microglia on Neurodevelopment and Brain Function in Autism. *Biomedicines*. 2024; 12: 210. <https://doi.org/10.3390/biomedicines12010210>.
- [14] Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, *et al.* Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension*. 2018; 72: 24–43. <https://doi.org/10.1161/HYPERTENSIONAHA.117.10803>.
- [15] Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. *BMJ (Clinical Research Ed.)*. 2019; 366: 12381. <https://doi.org/10.1136/bmj.12381>.
- [16] Roberts JM, Rich-Edwards JW, McElrath TF, Garmire L, Myatt L, Global Pregnancy Collaboration. Subtypes of Preeclampsia: Recognition and Determining Clinical Usefulness. *Hypertension*. 2021; 77: 1430–1441. <https://doi.org/10.1161/HYPERTENSIONAHA.120.14781>.
- [17] Gupta AK, Gebhardt S, Hillermann R, Holzgreve W, Hahn S. Analysis of plasma elastase levels in early and late onset preeclampsia. *Archives of Gynecology and Obstetrics*. 2006; 273: 239–242. <https://doi.org/10.1007/s00404-005-0093-z>.
- [18] Staff AC. The two-stage placental model of preeclampsia: An update. *Journal of Reproductive Immunology*. 2019; 134–135: 1–10. <https://doi.org/10.1016/j.jri.2019.07.004>.
- [19] Robillard PY, Dekker G, Scioscia M, Saito S. Progress in the understanding of the pathophysiology of immunologic maladaptation related to early-onset preeclampsia and metabolic syndrome related to late-onset preeclampsia. *American Journal of Obstetrics and Gynecology*. 2022; 226: S867–S875. <https://doi.org/10.1016/j.ajog.2021.11.019>.

- [20] James JL, Whitley GS, Cartwright JE. Pre-eclampsia: fitting together the placental, immune and cardiovascular pieces. *The Journal of Pathology*. 2010; 221: 363–378. <https://doi.org/10.1002/path.2719>.
- [21] Aneman I, Pienaar D, Suvakov S, Simic TP, Garovic VD, McClements L. Mechanisms of Key Innate Immune Cells in Early- and Late-Onset Preeclampsia. *Frontiers in Immunology*. 2020; 11: 1864. <https://doi.org/10.3389/fimmu.2020.01864>.
- [22] Valencia-Ortega J, Zárate A, Saucedo R, Hernández-Valencia M, Cruz JG, Puello E. Placental Proinflammatory State and Maternal Endothelial Dysfunction in Preeclampsia. *Gynecologic and Obstetric Investigation*. 2019; 84: 12–19. <https://doi.org/10.1159/000491087>.
- [23] Redman CW, Sargent IL, Staff AC. IFPA Senior Award Lecture: making sense of pre-eclampsia - two placental causes of preeclampsia? *Placenta*. 2014; 35: S20–S25. <https://doi.org/10.1016/j.placenta.2013.12.008>.
- [24] Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders. *The Lancet. Psychiatry*. 2017; 4: 339–346. [https://doi.org/10.1016/S2215-0366\(16\)30376-5](https://doi.org/10.1016/S2215-0366(16)30376-5).
- [25] Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, *et al.* Maternal immune activation and abnormal brain development across CNS disorders. *Nature Reviews. Neurology*. 2014; 10: 643–660. <https://doi.org/10.1038/nrneuro.2014.187>.
- [26] Li Z, Zhu YX, Gu LJ, Cheng Y. Understanding autism spectrum disorders with animal models: applications, insights, and perspectives. *Zoological Research*. 2021; 42: 800–824. <https://doi.org/10.24272/j.issn.2095-8137.2021.251>.
- [27] De Rubéis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, *et al.* Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*. 2014; 515: 209–215. <https://doi.org/10.1038/nature13772>.
- [28] Lim HK, Yoon JH, Song M. Autism Spectrum Disorder Genes: Disease-Related Networks and Compensatory Strategies. *Frontiers in Molecular Neuroscience*. 2022; 15: 922840. <https://doi.org/10.3389/fnmol.2022.922840>.
- [29] Wilkinson B, Grepo N, Thompson BL, Kim J, Wang K, Evgrafov OV, *et al.* The autism-associated gene chromodomain helicase DNA-binding protein 8 (CHD8) regulates noncoding RNAs and autism-related genes. *Translational Psychiatry*. 2015; 5: e568. <https://doi.org/10.1038/tp.2015.62>.
- [30] Danzer SC. Valproic Acid Leads New Neurons Down the Wrong Path. *Epilepsy Currents*. 2019; 19: 132–133. <https://doi.org/10.1177/1535759719835366>.
- [31] Jiang S, He M, Xiao L, Sun Y, Ding J, Li W, *et al.* Prenatal GABAB Receptor Agonist Administration Corrects the Inheritance of Autism-Like Core Behaviors in Offspring of Mice Prenatally Exposed to Valproic Acid. *Frontiers in Psychiatry*. 2022; 13: 835993. <https://doi.org/10.3389/fpsy.2022.835993>.
- [32] Kong L, Chen X, Liang Y, Forsell Y, Gissler M, Lavebratt C. Association of Preeclampsia and Perinatal Complications With Offspring Neurodevelopmental and Psychiatric Disorders. *JAMA Network Open*. 2022; 5: e2145719. <https://doi.org/10.1001/jamanetworkopen.2021.45719>.
- [33] Dachew BA, Mamun A, Maravilla JC, Alati R. Pre-eclampsia and the risk of autism-spectrum disorder in offspring: meta-analysis. *The British Journal of Psychiatry: the Journal of Mental Science*. 2018; 212: 142–147. <https://doi.org/10.1192/bjp.2017.27>.
- [34] Walker CK, Krakowiak P, Baker A, Hansen RL, Ozonoff S, Hertz-Picciotto I. Preeclampsia, placental insufficiency, and autism spectrum disorder or developmental delay. *JAMA Pediatrics*. 2015; 169: 154–162. <https://doi.org/10.1001/jamapediatrics.2014.2645>.
- [35] Mann JR, McDermott S, Bao H, Hardin J, Gregg A. Pre-eclampsia, birth weight, and autism spectrum disorders. *Journal of Autism and Developmental Disorders*. 2010; 40: 548–554. <https://doi.org/10.1007/s10803-009-0903-4>.
- [36] Wallace AE, Anderson GM, Dubrow R. Obstetric and parental psychiatric variables as potential predictors of autism severity. *Journal of Autism and Developmental Disorders*. 2008; 38: 1542–1554. <https://doi.org/10.1007/s10803-007-0536-4>.
- [37] Chien YL, Chou MC, Chou WJ, Wu YY, Tsai WC, Chiu YN, *et al.* Prenatal and perinatal risk factors and the clinical implications on autism spectrum disorder. *Autism: the International Journal of Research and Practice*. 2019; 23: 783–791. <https://doi.org/10.1177/1362361318772813>.
- [38] Wang H, László KD, Gissler M, Li F, Zhang J, Yu Y, *et al.* Maternal hypertensive disorders and neurodevelopmental disorders in offspring: a population-based cohort in two Nordic countries. *European Journal of Epidemiology*. 2021; 36: 519–530. <https://doi.org/10.1007/s10654-021-00756-2>.
- [39] Liu X, Liu H, Gu N, Pei J, Lin X, Zhao W. Preeclampsia promotes autism in offspring via maternal inflammation and fetal NFκB signaling. *Life Science Alliance*. 2023; 6: e202301957. <https://doi.org/10.26508/lsa.202301957>.
- [40] Gumusoglu SB, Chilukuri ASS, Hing BWQ, Scroggins SM, Kundu S, Sandgren JA, *et al.* Altered offspring neurodevelopment in an arginine vasopressin preeclampsia model. *Translational Psychiatry*. 2021; 11: 79. <https://doi.org/10.1038/s41398-021-01205-0>.
- [41] Rätsep MT, Paolozza A, Hickman AF, Maser B, Kay VR, Mohammad S, *et al.* Brain Structural and Vascular Anatomy Is Altered in Offspring of Pre-Eclamptic Pregnancies: A Pilot Study. *AJNR. American Journal of Neuroradiology*. 2016; 37: 939–945. <https://doi.org/10.3174/ajnr.A4640>.
- [42] Nayak D, Roth TL, McGavern DB. Microglia development and function. *Annual Review of Immunology*. 2014; 32: 367–402. <https://doi.org/10.1146/annurev-immunol-032713-120240>.
- [43] Vidal-Itriago A, Radford RAW, Aramideh JA, Maurel C, Scherer NM, Don EK, *et al.* Microglia morphophysiological diversity and its implications for the CNS. *Frontiers in Immunology*. 2022; 13: 997786. <https://doi.org/10.3389/fimmu.2022.997786>.
- [44] Colonna M, Butovsky O. Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annual Review of Immunology*. 2017; 35: 441–468. <https://doi.org/10.1146/annurev-immunol-051116-052358>.
- [45] Ginhoux F, Prinz M. Origin of microglia: current concepts and past controversies. *Cold Spring Harbor Perspectives in Biology*. 2015; 7: a020537. <https://doi.org/10.1101/cshperspect.a020537>.
- [46] Kierdorf K, Erny D, Goldmann T, Sander V, Schulz C, Perdiguero EG, *et al.* Microglia emerge from erythromyeloid precursors via Pu.1- and Irf8-dependent pathways. *Nature Neuroscience*. 2013; 16: 273–280. <https://doi.org/10.1038/nn.3318>.
- [47] Schwarz JM, Sholar PW, Bilbo SD. Sex differences in microglial colonization of the developing rat brain. *Journal of Neurochemistry*. 2012; 120: 948–963. <https://doi.org/10.1111/j.1471-4159.2011.07630.x>.
- [48] Bennett ML, Bennett FC, Liddelow SA, Ajami B, Zamanian JL, Fernhoff NB, *et al.* New tools for studying microglia in the mouse and human CNS. *Proceedings of the National Academy of Sciences of the United States of America*. 2016; 113: E1738–E1746. <https://doi.org/10.1073/pnas.1525528113>.
- [49] Matcovitch-Natan O, Winter DR, Giladi A, Vargas Aguilar S, Spinrad A, Sarrazin S, *et al.* Microglia development follows a stepwise program to regulate brain homeostasis. *Science*. 2016; 353: aad8670. <https://doi.org/10.1126/science.aad8670>.
- [50] Umpierre AD, Wu LJ. How microglia sense and regulate neuronal activity. *Glia*. 2021; 69: 1637–1653. <https://doi.org/10.1002/glia.20111>.

1002/glia.23961.

- [51] Allen NJ, Lyons DA. Glia as architects of central nervous system formation and function. *Science*. 2018; 362: 181–185. <https://doi.org/10.1126/science.aat0473>.
- [52] Cunningham CL, Martínez-Cerdeño V, Noctor SC. Microglia regulate the number of neural precursor cells in the developing cerebral cortex. *The Journal of Neuroscience*. 2013; 33: 4216–4233. <https://doi.org/10.1523/JNEUROSCI.3441-12.2013>.
- [53] Hagemeyer N, Hanft KM, Akriditou MA, Unger N, Park ES, Stanley ER, *et al.* Microglia contribute to normal myelinogenesis and to oligodendrocyte progenitor maintenance during adulthood. *Acta Neuropathologica*. 2017; 134: 441–458. <https://doi.org/10.1007/s00401-017-1747-1>.
- [54] Miyamoto A, Wake H, Ishikawa AW, Eto K, Shibata K, Murakoshi H, *et al.* Microglia contact induces synapse formation in developing somatosensory cortex. *Nature Communications*. 2016; 7: 12540. <https://doi.org/10.1038/ncomms12540>.
- [55] Shigemoto-Mogami Y, Hoshikawa K, Goldman JE, Sekino Y, Sato K. Microglia enhance neurogenesis and oligodendrogenesis in the early postnatal subventricular zone. *The Journal of Neuroscience*. 2014; 34: 2231–2243. <https://doi.org/10.1523/JNEUROSCI.1619-13.2014>.
- [56] Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR, 3rd, Lafaille JJ, *et al.* Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell*. 2013; 155: 1596–1609. <https://doi.org/10.1016/j.cell.2013.11.030>.
- [57] Butovsky O, Jedrychowski MP, Moore CS, Cialic R, Lanser AJ, Gabriely G, *et al.* Identification of a unique TGF- $\beta$ -dependent molecular and functional signature in microglia. *Nature Neuroscience*. 2014; 17: 131–143. <https://doi.org/10.1038/nn.3599>.
- [58] Scott-Hewitt N, Mahoney M, Huang Y, Korte N, Yvanka de Soysa T, Wilton DK, *et al.* Microglial-derived C1q integrates into neuronal ribonucleoprotein complexes and impacts protein homeostasis in the aging brain. *Cell*. 2024; 187: 4193–4212.e24. <https://doi.org/10.1016/j.cell.2024.05.058>.
- [59] Lenz KM, Nelson LH. Microglia and Beyond: Innate Immune Cells As Regulators of Brain Development and Behavioral Function. *Frontiers in Immunology*. 2018; 9: 698. <https://doi.org/10.3389/fimmu.2018.00698>.
- [60] Hughes AN, Appel B. Microglia phagocytose myelin sheaths to modify developmental myelination. *Nature Neuroscience*. 2020; 23: 1055–1066. <https://doi.org/10.1038/s41593-020-0654-2>.
- [61] Nemes-Baran AD, White DR, DeSilva TM. Fractalkine-Dependent Microglial Pruning of Viable Oligodendrocyte Progenitor Cells Regulates Myelination. *Cell Reports*. 2020; 32: 108047. <https://doi.org/10.1016/j.celrep.2020.108047>.
- [62] Cornell J, Salinas S, Huang HY, Zhou M. Microglia regulation of synaptic plasticity and learning and memory. *Neural Regeneration Research*. 2022; 17: 705–716. <https://doi.org/10.4103/1673-5374.322423>.
- [63] Komori T, Okamura K, Ikehara M, Yamamuro K, Endo N, Okumura K, *et al.* Brain-derived neurotrophic factor from microglia regulates neuronal development in the medial prefrontal cortex and its associated social behavior. *Molecular Psychiatry*. 2024; 29: 1338–1349. <https://doi.org/10.1038/s41380-024-02413-y>.
- [64] Garden GA, Möller T. Microglia biology in health and disease. *Journal of Neuroimmune Pharmacology*. 2006; 1: 127–137. <https://doi.org/10.1007/s11481-006-9015-5>.
- [65] Kalkman HO, Feuerbach D. Antidepressant therapies inhibit inflammation and microglial M1-polarization. *Pharmacology & Therapeutics*. 2016; 163: 82–93. <https://doi.org/10.1016/j.pharmthera.2016.04.001>.
- [66] Smolders S, Notter T, Smolders SMT, Rigo JM, Brône B. Controversies and prospects about microglia in maternal immune activation models for neurodevelopmental disorders. *Brain, Behavior, and Immunity*. 2018; 73: 51–65. <https://doi.org/10.1016/j.bbi.2018.06.001>.
- [67] 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. *International Journal of Molecular Sciences*. 2021; 22: 11516. <https://doi.org/10.3390/ijms222111516>.
- [68] Esshili A, Manitz MP, Freund N, Juckel G. Induction of inducible nitric oxide synthase expression in activated microglia and astrocytes following pre- and postnatal immune challenge in an animal model of schizophrenia. *European Neuropsychopharmacology*. 2020; 35: 100–110. <https://doi.org/10.1016/j.eururo.2020.04.002>.
- [69] Tick B, Bolton P, Happé F, Rutter M, Rijdsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. 2016; 57: 585–595. <https://doi.org/10.1111/jcpp.12499>.
- [70] Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. *The British Journal of Psychiatry*. 2009; 195: 7–14. <https://doi.org/10.1192/bjp.bp.108.051672>.
- [71] Johnson MH, Gliga T, Jones E, Charman T. Annual research review: Infant development, autism, and ADHD—early pathways to emerging disorders. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. 2015; 56: 228–247. <https://doi.org/10.1111/jcpp.12328>.
- [72] Sungur AÖ, Schwarting RKW, Wöhr M. Early communication deficits in the Shank1 knockout mouse model for autism spectrum disorder: Developmental aspects and effects of social context. *Autism Research*. 2016; 9: 696–709. <https://doi.org/10.1002/aur.1564>.
- [73] Kim H, Kim D, Cho Y, Kim K, Roh JD, Kim Y, *et al.* Early postnatal serotonin modulation prevents adult-stage deficits in Arid1b-deficient mice through synaptic transcriptional reprogramming. *Nature Communications*. 2022; 13: 5051. <https://doi.org/10.1038/s41467-022-32748-5>.
- [74] Xiao Z, Qiu T, Ke X, Xiao X, Xiao T, Liang F, *et al.* Autism spectrum disorder as early neurodevelopmental disorder: evidence from the brain imaging abnormalities in 2–3 years old toddlers. *Journal of Autism and Developmental Disorders*. 2014; 44: 1633–1640. <https://doi.org/10.1007/s10803-014-2033-x>.
- [75] Li YD, Luo YJ, Chen ZK, Quintanilla L, Cherasse Y, Zhang L, *et al.* Hypothalamic modulation of adult hippocampal neurogenesis in mice confers activity-dependent regulation of memory and anxiety-like behavior. *Nature Neuroscience*. 2022; 25: 630–645. <https://doi.org/10.1038/s41593-022-01065-x>.
- [76] Wilson ES, Litwa K. Synaptic Hyaluronan Synthesis and CD44-Mediated Signaling Coordinate Neural Circuit Development. *Cells*. 2021; 10: 2574. <https://doi.org/10.3390/cells10102574>.
- [77] Fernández de Cossío L, Lacabanne C, Bordeleau M, Castino G, Kyriakakis P, Tremblay MÈ. Lipopolysaccharide-induced maternal immune activation modulates microglial CX3CR1 protein expression and morphological phenotype in the hippocampus and dentate gyrus, resulting in cognitive inflexibility during late adolescence. *Brain, Behavior, and Immunity*. 2021; 97: 440–454. <https://doi.org/10.1016/j.bbi.2021.07.025>.
- [78] Atladóttir HO, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, *et al.* Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *Journal of Autism and Developmental Disorders*. 2010; 40: 1423–1430. <https://doi.org/10.1007/s10803-010-1006-y>.
- [79] Nabgha-E-Amen, Eqani SAMAS, Khuram F, Alamdar A, Tahir A, Shah STA, *et al.* Environmental exposure pathway analysis of trace elements and autism risk in Pakistani children population. *The Science of the Total Environment*. 2020; 712: 136471. <https://doi.org/10.1016/j.scitotenv.2019.136471>.
- [80] Chandra S, Sisodia SS, Vassar RJ. The gut microbiome in

- Alzheimer's disease: what we know and what remains to be explored. *Molecular Neurodegeneration*. 2023; 18: 9. <https://doi.org/10.1186/s13024-023-00595-7>.
- [81] Bower JE, Kuhlman KR. Psychoneuroimmunology: An Introduction to Immune-to-Brain Communication and Its Implications for Clinical Psychology. *Annual Review of Clinical Psychology*. 2023; 19: 331-359. <https://doi.org/10.1146/annurev-clinpsy-080621-045153>.
- [82] Velmeshev D, Schirmer L, Jung D, Haeussler M, Perez Y, Mayer S, *et al*. Single-cell genomics identifies cell type-specific molecular changes in autism. *Science*. 2019; 364: 685-689. <https://doi.org/10.1126/science.aav8130>.
- [83] Wamsley B, Bicks L, Cheng Y, Kawaguchi R, Quintero D, Margolis M, *et al*. Molecular cascades and cell type-specific signatures in ASD revealed by single-cell genomics. *Science*. 2024; 384: eadh2602. <https://doi.org/10.1126/science.adh2602>.
- [84] Gupta S, Ellis SE, Ashar FN, Moes A, Bader JS, Zhan J, *et al*. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. *Nature Communications*. 2014; 5: 5748. <https://doi.org/10.1038/ncomms6748>.
- [85] Varghese M, Keshav N, Jacot-Descombes S, Warda T, Wicinski B, Dickstein DL, *et al*. Autism spectrum disorder: neuropathology and animal models. *Acta Neuropathologica*. 2017; 134: 537-566. <https://doi.org/10.1007/s00401-017-1736-4>.
- [86] Barnea-Goraly N, Frazier TW, Piacenza L, Minshew NJ, Keshavan MS, Reiss AL, *et al*. A preliminary longitudinal volumetric MRI study of amygdala and hippocampal volumes in autism. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2014; 48: 124-128. <https://doi.org/10.1016/j.pnpbp.2013.09.010>.
- [87] Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, Buonocore MH, *et al*. The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. *The Journal of Neuroscience*. 2004; 24: 6392-6401. <https://doi.org/10.1523/JNEUROSCI.1297-04.2004>.
- [88] Groen W, Teluij M, Buitelaar J, Tendolkar I. Amygdala and hippocampus enlargement during adolescence in autism. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49: 552-560. <https://doi.org/10.1016/j.jaac.2009.12.023>.
- [89] Aylward EH, Minshew NJ, Goldstein G, Honeycutt NA, Augustine AM, Yates KO, *et al*. MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. *Neurology*. 1999; 53: 2145-2150. <https://doi.org/10.1212/wnl.53.9.2145>.
- [90] Wang T, Chen B, Luo M, Xie L, Lu M, Lu X, *et al*. Microbiota-indole 3-propionic acid-brain axis mediates abnormal synaptic pruning of hippocampal microglia and susceptibility to ASD in IUGR offspring. *Microbiome*. 2023; 11: 245. <https://doi.org/10.1186/s40168-023-01656-1>.
- [91] Immordino-Yang MH, Singh V. Hippocampal contributions to the processing of social emotions. *Human Brain Mapping*. 2013; 34: 945-955. <https://doi.org/10.1002/hbm.21485>.
- [92] Schafer M, Schiller D. The Hippocampus and Social Impairment in Psychiatric Disorders. *Cold Spring Harbor Symposia on Quantitative Biology*. 2018; 83: 105-118. <https://doi.org/10.1101/sqb.2018.83.037614>.
- [93] Lai MC, Lombardo MV, Baron-Cohen S. Autism. *Lancet*. 2014; 383: 896-910. [https://doi.org/10.1016/S0140-6736\(13\)61539-1](https://doi.org/10.1016/S0140-6736(13)61539-1).
- [94] Bar E, Barak B. Microglia roles in synaptic plasticity and myelination in homeostatic conditions and neurodevelopmental disorders. *Glia*. 2019; 67: 2125-2141. <https://doi.org/10.1002/glia.23637>.
- [95] Pape K, Tamouza R, Leboyer M, Zipp F. Immunoneuropsi- chiatry - novel perspectives on brain disorders. *Nature Re- views. Neurology*. 2019; 15: 317-328. <https://doi.org/10.1038/s41582-019-0174-4>.
- [96] Check J, Shuster C, Hofheimer J, Camerota M, Dansereau LM, Smith LM, *et al*. Preeclampsia, Fetal Growth Restriction, and 24-Month Neurodevelopment in Very Preterm Infants. *JAMA Network Open*. 2024; 7: e2420382. <https://doi.org/10.1001/ja- manetworkopen.2024.20382>.
- [97] Katoh Y, Iriyama T, Yano E, Sayama S, Seyama T, Kotajima- Murakami H, *et al*. Increased production of inflammatory cytokines and activation of microglia in the fetal brain of preeclamptic mice induced by angiotensin II. *Journal of Re- productive Immunology*. 2022; 154: 103752. <https://doi.org/10.1016/j.jri.2022.103752>.
- [98] Hayes LN, An K, Carloni E, Li F, Vincent E, Trippaers C, *et al*. Prenatal immune stress blunts microglia reactivity, impairing neurocircuitry. *Nature*. 2022; 610: 327-334. <https://doi.org/10.1038/s41586-022-05274-z>.
- [99] Xia Y, Zhang Z, Lin W, Yan J, Zhu C, Yin D, *et al*. Modulating microglia activation prevents maternal immune activation in- duced schizophrenia-relevant behavior phenotypes via arginase 1 in the dentate gyrus. *Neuropsychopharmacology*. 2020; 45: 1896-1908. <https://doi.org/10.1038/s41386-020-0743-7>.
- [100] Giambone AB, Logue OC, Shao Q, Bidwell GL, 3rd, War- rington JP. Perinatal Micro-Bleeds and Neuroinflammation in E19 Rat Fetuses Exposed to Utero-Placental Ischemia. *Internation- al Journal of Molecular Sciences*. 2019; 20: 4051. <https://doi.org/10.3390/ijms20164051>.
- [101] O'Loughlin E, Pakan JMP, Yilmazer-Hanke D, McDermott KW. Acute in utero exposure to lipopolysaccharide induces inflammation in the pre- and postnatal brain and alters the glial cytoarchitecture in the developing amygdala. *Journal of Neuroinflammation*. 2017; 14: 212. <https://doi.org/10.1186/s12974-017-0981-8>.
- [102] Schaafsma W, Basterra LB, Jacobs S, Brouwer N, Meerlo P, Schaafsma A, *et al*. Maternal inflammation induces immune ac- tivation of fetal microglia and leads to disrupted microglia im- mune responses, behavior, and learning performance in adult- hood. *Neurobiology of Disease*. 2017; 106: 291-300. <https://doi.org/10.1016/j.nbd.2017.07.017>.
- [103] Li WY, Chang YC, Lee LJH, Lee LJ. Prenatal infection affects the neuronal architecture and cognitive function in adult mice. *Developmental Neuroscience*. 2014; 36: 359-370. <https://doi.org/10.1159/000362383>.
- [104] Zhu F, Zheng Y, Liu Y, Zhang X, Zhao J. Minocycline alleviates behavioral deficits and inhibits microglial activa- tion in the offspring of pregnant mice after administration of polyriboinosinic-polyribocytidilic acid. *Psychiatry Research*. 2014; 219: 680-686. <https://doi.org/10.1016/j.psychres.2014.06.046>.
- [105] Sones JL, Davisson RL. Preeclampsia, of mice and women. *Physiological Genomics*. 2016; 48: 565-572. <https://doi.org/10.1152/physiolgenomics.00125.2015>.
- [106] Zhao X, Su F, Kong F, Su J, Yang X, Li L, *et al*. WD repeat domain 5 promotes the development of late-onset preeclampsia by activating nuclear factor kappa B. *Acta Cirurgica Brasileira*. 2023; 38: e386223. <https://doi.org/10.1590/acb386223>.
- [107] Ma RQ, Sun MN, Yang Z. Effects of preeclampsia-like symp- toms at early gestational stage on fetoplacental outcomes in a mouse model. *Chinese Medical Journal*. 2010; 123: 707-712.
- [108] Lawrence AR, Canzi A, Bridlance C, Olivieri N, Lansonneur C, Catale C, *et al*. Microglia maintain structural integrity during fetal brain morphogenesis. *Cell*. 2024; 187: 962-980.e19. <https://doi.org/10.1016/j.cell.2024.01.012>.
- [109] Estes ML, McAllister AK. Maternal immune activation: Impli- cations for neuropsychiatric disorders. *Science*. 2016; 353: 772-777. <https://doi.org/10.1126/science.aag3194>.

- [110] Robinson-Agramonte MDLA, Noris García E, Fraga Guerra J, Vega Hurtado Y, Antonucci N, Semprún-Hernández N, *et al.* Immune Dysregulation in Autism Spectrum Disorder: What Do We Know about It? *International Journal of Molecular Sciences*. 2022; 23: 3033. <https://doi.org/10.3390/ijms23063033>.
- [111] Kaminski VDL, Michita RT, Ellwanger JH, Veit TD, Schuch JB, Riesgo RDS, *et al.* Exploring potential impacts of pregnancy-related maternal immune activation and extracellular vesicles on immune alterations observed in autism spectrum disorder. *Heliyon*. 2023; 9: e15593. <https://doi.org/10.1016/j.heliyon.2023.e15593>.
- [112] Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, *et al.* Chronic inflammation in the etiology of disease across the life span. *Nature Medicine*. 2019; 25: 1822–1832. <https://doi.org/10.1038/s41591-019-0675-0>.
- [113] Lo JO, Roberts VHJ, Schabel MC, Wang X, Morgan TK, Liu Z, *et al.* Novel Detection of Placental Insufficiency by Magnetic Resonance Imaging in the Nonhuman Primate. *Reproductive Sciences*. 2018; 25: 64–73. <https://doi.org/10.1177/1933719117699704>.
- [114] Taylor BD, Ness RB, Klebanoff MA, Zoh R, Bass D, Hougaard DM, *et al.* First and second trimester immune biomarkers in preeclamptic and normotensive women. *Pregnancy Hypertension*. 2016; 6: 388–393. <https://doi.org/10.1016/j.preghy.2016.09.002>.
- [115] Taylor BD, Tang G, Ness RB, Olsen J, Hougaard DM, Skogstrand K, *et al.* Mid-pregnancy circulating immune biomarkers in women with preeclampsia and normotensive controls. *Pregnancy Hypertension*. 2016; 6: 72–78. <https://doi.org/10.1016/j.preghy.2015.11.002>.
- [116] Spann MN, Monk C, Scheinost D, Peterson BS. Maternal Immune Activation During the Third Trimester Is Associated with Neonatal Functional Connectivity of the Salience Network and Fetal to Toddler Behavior. *The Journal of Neuroscience*. 2018; 38: 2877–2886. <https://doi.org/10.1523/JNEUROSCI.2272-17.2018>.
- [117] Ghassabian A, Albert PS, Hornig M, Yeung E, Cherkerzian S, Goldstein RB, *et al.* Gestational cytokine concentrations and neurocognitive development at 7 years. *Translational Psychiatry*. 2018; 8: 64. <https://doi.org/10.1038/s41398-018-0112-z>.
- [118] McGlade A, Whittingham K, Barfoot J, Taylor L, Boyd RN. Efficacy of very early interventions on neurodevelopmental outcomes for infants and toddlers at increased likelihood of or diagnosed with autism: A systematic review and meta-analysis. *Autism Research*. 2023; 16: 1145–1160. <https://doi.org/10.1002/aur.2924>.
- [119] Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. *American Journal of Obstetrics and Gynecology*. 2022; 226: S1108–S1119. <https://doi.org/10.1016/j.ajog.2020.08.045>.
- [120] Sharp A, Cornforth C, Jackson R, Harrold J, Turner MA, Kenny LC, *et al.* Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. *The Lancet. Child & Adolescent Health*. 2018; 2: 93–102. [https://doi.org/10.1016/S2352-4642\(17\)30173-6](https://doi.org/10.1016/S2352-4642(17)30173-6).
- [121] Kalafat E, Sukur YE, Abdi A, Thilaganathan B, Khalil A. Metformin for prevention of hypertensive disorders of pregnancy in women with gestational diabetes or obesity: systematic review and meta-analysis of randomized trials. *Ultrasound in Obstetrics & Gynecology*. 2018; 52: 706–714. <https://doi.org/10.1002/uo.g.19084>.
- [122] Litov L, Petkov P, Rangelov M, Ilieva N, Lilkova E, Todorova N, *et al.* Molecular Mechanism of the Anti-Inflammatory Action of Heparin. *International Journal of Molecular Sciences*. 2021; 22: 10730. <https://doi.org/10.3390/ijms221910730>.
- [123] Zheng L, Xia B, Yuan Y, Wang Y, Wang Y. Low-molecular-weight heparin in addition to low-dose aspirin for preventing preeclampsia and its complications: A systematic review and meta-analysis. *Frontiers in Cardiovascular Medicine*. 2022; 9: 1073148. <https://doi.org/10.3389/fcvm.2022.1073148>.
- [124] Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzias P, Nihoyannopoulos P. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation*. 1999; 100: 793–798. <https://doi.org/10.1161/01.cir.100.8.793>.
- [125] Wooff Y, Man SM, Aggio-Bruce R, Natoli R, Fernando N. IL-1 Family Members Mediate Cell Death, Inflammation and Angiogenesis in Retinal Degenerative Diseases. *Frontiers in Immunology*. 2019; 10: 1618. <https://doi.org/10.3389/fimmu.2019.01618>.
- [126] Jones ML, Mark PJ, Waddell BJ. Maternal omega-3 fatty acid intake increases placental labyrinthine antioxidant capacity but does not protect against fetal growth restriction induced by placental ischaemia-reperfusion injury. *Reproduction*. 2013; 146: 539–547. <https://doi.org/10.1530/REP-13-0282>.
- [127] Chen L, Yang Y, Zhang N, Che H, Wang Z, Han J, *et al.* DHA and EPA alleviate depressive-like behaviors in chronic sleep-deprived mice: Involvement of iron metabolism, oligodendrocyte-lipids peroxidation and the LCN2-NLRP3 signaling axis. *Free Radical Biology & Medicine*. 2024; 225: 654–664. <https://doi.org/10.1016/j.freeradbiomed.2024.10.298>.
- [128] Shukuri M, Uchino M, Sakamaki T, Onoe S, Hosoi R, Todoroki K, *et al.* Ex vivo imaging and analysis of ROS generation correlated with microglial activation in rat model with acute neuroinflammation induced by intrastriatal injection of LPS. *Biochemical and Biophysical Research Communications*. 2021; 584: 101–106. <https://doi.org/10.1016/j.bbrc.2021.11.008>.
- [129] Luo Y, Lv K, Du Z, Zhang D, Chen M, Luo J, *et al.* Minocycline improves autism-related behaviors by modulating microglia polarization in a mouse model of autism. *International Immunopharmacology*. 2023; 122: 110594. <https://doi.org/10.1016/j.intimp.2023.110594>.