

# **Pre-eclampsia and neurodevelopmental outcomes: potential pathogenic roles for inflammation and oxidative stress?**

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**Abbreviations:**

ADHD – Attention-deficit/hyperactivity disorder  
ASD – Autism spectrum disorder  
CP – Cerebral palsy  
CRP – C-reactive protein  
DMN – Default mode network  
DTI – Diffusion tensor imaging  
ETC – Electron transport chain  
FA – Fractional anisotropy  
FC – Functional connectivity  
GPx – Glutathione peroxidase  
HDP – Hypertensive disorder(s) of pregnancy  
HUVECs – Human umbilical vein endothelial cells  
ISSHP – International Society for Studying Hypertension in Pregnancy  
IUGR – Intrauterine Growth Restriction  
LPS – Lipopolysaccharide  
MDA – Malondialdehyde  
MDI – Mental developmental index  
MIA – Maternal immune activation  
mPFC – Medial prefrontal cortex  
MRI – Magnetic resonance imaging  
mROS – Mitochondrial reactive Oxygen Species  
mtDAMPs – Mitochondrial damage-associated molecular patterns  
mtDNA – Mitochondrial DNA  
PE – Pre-eclampsia  
PE-F1 – First generation offspring exposed prenatally to pre-eclampsia  
PPV – Positive predictive value  
ROS – Reactive Oxygen Species  
rsFC – Resting state functional connectivity  
rs-fMRI – Resting-state functional magnetic resonance imaging  
RUPP – Reduced uterine perfusion pressure  
SGA – Small for Gestational Age  
SLF – Superior longitudinal fasciculus  
SOD – Superoxide dismutase

**Abstract:**

Pre-eclampsia (PE) is a common and serious hypertensive disorder of pregnancy that occurs in approximately 3-5% of first-time pregnancies and is a well-known leading cause of maternal and neonatal mortality and morbidity. In recent years, there has been accumulating evidence that *in utero* exposure to PE acts as an environmental risk factor for various neurodevelopmental disorders, particularly autism spectrum disorder and ADHD. At present, the mechanism(s) mediating this relationship are uncertain. In this review, we outline the most recent evidence implicating a causal role for PE exposure in the aetiology of various neurodevelopmental disorders and provide a novel interpretation of neuroanatomical alterations in PE-exposed offspring and how these relate to their sub-optimal neurodevelopmental trajectory. We then postulate that inflammation and oxidative stress, two prominent features of the pathophysiology of PE, are likely to play a major role in mediating this association. The increased inflammation in the maternal circulation, placenta and fetal circulation in PE expose the offspring to both prenatal maternal immune activation – a risk factor for neurodevelopmental disorders, which has been well-characterised in animal models – and directly higher concentrations of pro-inflammatory cytokines, which adversely affect neuronal development. Similarly, the exaggerated oxidative stress in the mother, placenta and fetus induces the placenta to secrete factors deleterious to neurons, and exposes the fetal brain to directly elevated oxidative stress and thus adversely affects neurodevelopmental processes. Finally, we describe the interplay between inflammation and oxidative stress in PE, and how both systems interact to potentially alter neurodevelopmental trajectory in exposed offspring.

**Keywords:**

Pre-eclampsia, Neurodevelopmental Disorder, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Inflammation, Oxidative Stress.

## **1.0 Introduction**

Pre-eclampsia (PE) is a common hypertensive disorder of pregnancy (HDP), characterised by new-onset hypertension on or after 20 weeks' gestation as well as any one of proteinuria, organ dysfunction or uteroplacental dysfunction [1]. PE affects approximately 3-5% of primiparous women worldwide [2–4] and is a leading cause of maternal mortality [5, 6]. Women who have had a pregnancy complicated by PE are also at an increased risk of long-term cardiovascular, renal and metabolic morbidity and mortality [7–10].

Crucially, PE exposure is also a leading cause of perinatal mortality and morbidity. Infants exposed to PE (PE-F1) have an increased risk of neonatal death, neonatal thrombocytopenia, neutropenia, bronchopulmonary dysplasia [11] and hypotension [12], and PE may account for between 1 in 10 and 1 in 4 perinatal deaths [13]. Two meta-analyses reported that children and adolescents exposed to PE *in utero* have higher systolic and diastolic blood pressure and BMI than controls, without major differences in blood glucose or lipid profiles [14, 15]. A study from the Helsinki Birth Cohort Study of children born in Helsinki between 1934 and 1944 followed the offspring for 60 – 70 years after birth and reported that adults who had been exposed to PE *in utero* had a two-fold increased risk of stroke [16].

The largest study concerning long-term morbidity in PE-F1s was conducted by Wu et al., in which the authors used birth records for all singleton live births in Denmark 1978-2004 (N=1,545,443) and matched these with hospitalization records for several diseases until the end of 2004 (0 – 27 years follow-up) [17]. In this study, PE-F1s in every age group had a higher risk of hospitalization, with incidence risk ratios ranging from 1.13 to 1.26. PE-F1s born at term were at increased risk of hospitalization for digestive system diseases, asthma, pneumonia, infectious and parasitic diseases and epilepsy than term controls, while PE-F1s born pre-term (< 37 weeks) had a higher risk of hospitalization for digestive system diseases, skin diseases and genital malformations than term controls.

So, while the effects of PE on the mother are well established, more recently there has been considerable accumulating research characterising the effects of PE exposure on a range of outcomes in the child. Additionally, there has been recent interest in elucidating the mechanisms of this association, particularly using preclinical models of PE [18]. In the following section we review the growing evidence that fetal exposure to PE increases the risk of a range of adverse neurodevelopmental outcomes in the offspring.

## **2.0 Evidence of an Association between PE exposure and Neurodevelopmental Outcome.**

Here we review the evidence for an association between fetal exposure to PE and risk for autism spectrum disorder, attention-deficit/hyperactivity disorder, cerebral palsy, schizophrenia and epilepsy, and alterations in cognitive function in the offspring. We also discuss current limitations and knowledge gaps to understanding these associations. Although PE may also confer an increased risk on exposed offspring for various other brain disorders and deficits throughout the lifespan, the current review will focus on neurodevelopmental disorders.

### ***2.1 Autism Spectrum and Attention Deficit/ Hyperactivity Disorders***

Autism spectrum disorder (ASD) is a group of related neurodevelopmental disorders characterised by social communication deficits and stereotypic behaviours, which affects an estimated 1 – 1.5% of

children [19, 20]; while attention-deficit/hyperactivity disorder (ADHD) is characterised by inattention, hyperactivity and impulsivity, with an estimated prevalence of 1.4 -3% [21]. The role of pre- and perinatal risk factors in the aetiology of these two highly prevalent neurodevelopmental disorders is increasingly well-recognised, and the evidence for an association between PE and offspring neurodevelopmental trajectory is strongest for ASD and ADHD.

Several cohort studies, most commonly retrospective population-based studies, have identified PE exposure as an independent risk factor for ASD [22–26] and ADHD [26–29]. The evidence from case-control studies, however, is less conclusive. While many have reported a positive association between PE exposure and ASD [30–32] or ADHD [33–35], others reported no such association [36–43], while another reported a borderline-significant association with ADHD [44]. This discrepancy may be due to the fact that case-control studies have less control than cohort studies over confounding variables (see section 2.5); their larger proclivity for bias; or smaller sample sizes, as PE incidence was too low in some studies to see an effect – the case-control studies above which reported positive findings typically had much larger samples than those that did not. Other studies which did not specify the type of HDP that offspring were exposed to also noted a similar positive association with ASD [45–48] and ADHD [49, 50].

Recent meta-analyses provide the most convincing evidence that there is a strong association between PE exposure and ASD or ADHD. Four meta-analyses published between 2017 – 2018 all concluded that PE-F1s have a significantly increased relative risk or odds ratio for ASD, ranging from 1.32 to 1.50 [51–54], while one of these [52] reported an odds ratio of 1.28 for ADHD. Interestingly, a recent population-based retrospective cohort study found that offspring exposed to PE both via their mother and intergenerationally via their maternal grandmother are more likely again to be diagnosed with ASD or ADHD than those exposed via only their mother, suggesting an intergenerational association between PE exposure and these disorders [55]. Overall, the emerging literature suggests that PE exposure increases offspring risk of ASD and ADHD.

## ***2.2 Other Common Neurodevelopmental Disorders: Cerebral Palsy, Schizophrenia and Epilepsy***

The term cerebral palsy (CP) is used to describe motor disabilities with cerebral origin that are acquired in prenatal or early postnatal life, with a wide range of aetiology and symptomology [56]. Among studies that do not dichotomize the sample into pre-term- and full-term-born infants, there is no clear relationship between PE exposure and risk for CP: while many studies report a higher risk of CP among PE-F1s [57–61], others report do not [62–64]. Failing to make this distinction may be problematic because pre-term birth is itself a well-recognised risk factor for CP [60, 65]. However, among children born at or after 37 weeks' gestation, there is evidence of a positive association between PE exposure and CP [66–69]. Intriguingly, the opposite is commonly seen among PE-F1s born pre-term, in that PE exposure appears to have a protective effect against CP [17, 70–72]. Illustrating this elusive relationship, one large retrospective population-based cohort study (N = 1,764,509) reported a negative association between PE exposure and CP risk for infants born at 23 – 31 weeks' gestation, no association when born at 32 – 36 weeks, and a positive association when born on or after 37 weeks [69].

Schizophrenia is a complex neurodevelopmental disorder, which comprises psychosis, apathy, social withdrawal and cognitive impairment and has an equally complex aetiology associated with various genetic and environmental risk factors [73]. Interestingly, placentae from pregnancies complicated by PE express higher levels of genes associated with the genomic risk of schizophrenia [74]. PE exposure, however, has long been controversial as a risk factor for schizophrenia and the evidence is mixed. Two large retrospective cohort studies observed a

positive association between PE exposure and schizophrenia [75, 76], while a third reported no increased risk [77], although outcome measures in the latter study included non-schizophrenia psychotic disorders. The evidence is mixed from case-control studies: although some report an increased schizophrenia risk among PE-F1s [78, 79], most do not [80–84]. Meta-analyses from 2002 and 2018 reported significant odds ratios of 1.36 and 1.37, respectively, among PE-F1s for schizophrenia [85, 86], while a more recent and conclusive meta-analysis reported an odds ratio of 1.32, although this did not reach statistical significance ( $p = 0.059$ ) [87]. Overall, the data suggest that PE exposure may be linked to offspring schizophrenia risk, although this is still uncertain.

Epilepsy is a neurological disease characterised by a propensity or predisposition for generating epileptic seizures [88]. Obstetric and perinatal complications, including eclampsia, have been implicated as risk factors for idiopathic childhood epilepsy [89], yet surprisingly few studies have investigated pre-eclampsia as a perinatal risk factor for the disease. Those that have, however, generally report an increased risk of epilepsy among PE-F1s [26, 58, 90]. If the sample is divided into term- and preterm-born offspring, the association is seen specifically for those born at term [27, 91], which suggests that, like CP, the effects of PE on epilepsy in the offspring may be gestational age-dependent.

In summary, the role of PE exposure in the aetiology of other common neurodevelopmental disorders is less certain than it is for ASD and ADHD. It appears, however, to have a gestational age-dependent effect on CP risk; its effect on schizophrenia risk is contentious; and despite the paucity of literature, appears to be positively associated with epilepsy.

### ***2.3 Cognitive Function***

Cognitive function is an individual's capacity to adequately think, learn and remember and is typically measured by one's performance across the domains of perception, reasoning, intuition and creativity [92]. A number of studies have reported poorer cognitive function among PE-F1s compared to controls (for systematic review, see Tuovinen et al., 2014 [93]). In infancy, the Bayley scales is commonly used to determine mental developmental index (MDI), encompassing the infant's current level of cognitive, language, social and personal skill development. Three studies have reported lower MDI scores among exposed offspring [94–96], while one study reported higher scores [97]. However, this latter study measured all pregnancy-induced hypertension, and not PE specifically, as its exposure; additionally, whereas the first three studies measured MDI at 24 months, this study was conducted at 18 months.

Lower IQ has been noted among PE-F1s from 3 to 18 years old [98–101], although one large study observed no association [102]; however, IQ is a very narrow measure of intelligence and all of these studies used different tests to measure offspring IQ. The first study to investigate academic performance among PE-F1s reported poorer verbal reasoning only when compared to unexposed siblings [103], although this reduced the ability to control for confounding variables, such as gestational age, and reduced the sample to PE-F1s with siblings who could be compared to. A more recent cohort study from Iceland found that after controlling for covariates, PE-F1s perform worse than their unexposed peers at 9, 12 and 15 years old on mathematics but not language arts [104]. Two older studies found that PE exposure is a risk factor for intellectual disability in childhood [105, 106]. This has been confirmed by a more

recent population-based cohort study [26] and is in line with reports that children exposed to PE are more likely to avail of special needs services and special education classes than their unexposed peers [101, 107].

The Helsinki Birth Cohort Study has reported that PE-F1s have poorer verbal reasoning skills and total intellectual ability at 20 years old [108]. Interestingly, when subjects were followed up at a mean of age of 69, they exhibited an increased rate of cognitive decline and higher rates of self-reported cognitive dysfunction, suggesting the deleterious effects of PE exposure persist into old age [109–111]. However, to the best of the authors' knowledge, no study so far has implicated prenatal PE exposure as a risk factor for any form of dementia. Taken together, these data suggest that PE may also be associated with impaired cognitive function in exposed offspring.

## ***2.4 Validity and Types of PE Exposure***

Detailed medical birth registries are kept by Denmark, Iceland, Finland, Norway and Sweden and the manner in which these registries are kept is remarkably similar, to the point that their data can even be combined to generate larger cohorts [112]. Many of the studies presented in sections 2.1 – 2.3 which provide some of the most convincing evidence for a causal role of PE in the aetiology of neurodevelopmental disorders, are population-based studies using these Nordic registries [17, 24, 60, 69, 75, 76, 78, 91, 98, 104, 26, 29, 31, 39, 41, 44, 46, 55], so the validity of these registries is an important factor for determining the true relationship between PE and offspring neurodevelopmental disorders. The specificity and positive predictive value (PPV) for Nordic registries varies depending on diagnosis, but is generally very high, although sensitivity can be quite low [113–115]. The PPV for PE in these registries is very high, ranging from 74 – 93%, while specificity is typically ~99% [116–120]; sensitivity of PE diagnosis, however, is only 43 – 69% [117–119], which means that the registries may be missing as many as half of the true PE cases. Increasing the sensitivity of the Nordic registries would mean that a higher proportion of true PE cases are reported in the PE groups, but how this would affect the results from the above-mentioned studies is uncertain. Other cohort studies, such as the Helsinki Birth Cohort Study [77, 108–111] and the Avon Longitudinal Study of Parents and Children [28, 81], as well as many smaller studies set in regional hospitals or clinics, defined PE according to gestational blood pressure and protein urine measurements, or a diagnosis made by a qualified clinician.

Although the International Society for the Study of Hypertension in Pregnancy (ISSHP) does not recommend classifying PE as 'mild' or 'severe' for clinical purposes, the distinction may be useful for research purposes [1, 121]. Surprisingly few studies compare the effects of mild vs. severe PE in their final analysis. Apart from one study measuring IQ [98], all of these studies reported a stronger effect on the offspring's risk of ASD, CP and epilepsy if PE was severe [17, 27, 32, 58]. Wu et al. found that the increased risk for epilepsy among PE-exposed term-born infants was greater when exposed to severe PE; while the protective effect of PE against CP in preterm-born offspring was seen only for severe PE [17]. It is therefore possible that there is a dose-response effect regarding fetal exposure to PE. However, as severe PE is much less common than mild PE, one limitation of making this distinction is to drastically reduce the sample size for the severe PE group, potentially affecting statistical power. Additionally, a few studies grouped eclampsia into the exposure group [25, 104] which is likely to confound the results, as eclamptic seizures are essentially a separate disease exposure for the fetus.

Another distinction that can be made is whether PE is early- (typically <34 weeks' gestation) or late-onset [121]. As with PE severity, however, very few studies subdivide the PE exposure group in this way. The few studies which do this report an increased risk for CP if exposed to early-, but not late-onset PE, and a greater increased risk for epilepsy if exposed to late- rather than early-onset PE [27, 57, 67]. In early-onset PE, there is a greater risk for intra-uterine growth restriction (IUGR) and preterm birth, and a higher involvement of placental pathology [122]. Additionally, in early-onset PE, the fetus is exposed to PE pathophysiology for a longer duration, and during a period in which neurodevelopmental processes are at an earlier and potentially more sensitive stage. Therefore, it would be a valuable contribution to our understanding of the relationship between PE and fetal neurodevelopment if more future studies dichotomize the PE exposure as early- or late-onset.

### ***2.5 Confounding by Parity and Comorbid Obstetric Complications***

Women who suffer from PE in their first pregnancy are less likely to have additional pregnancies, so PE incidence is correspondingly lower in the multiparous population [4, 123]. Importantly, high parity is itself a risk factor for neurodevelopmental disorders [36, 53, 78]. This means it is possible that the effect of PE on offspring neurodevelopment may be smaller than it would otherwise be if pre-eclamptic women progressed to multiparity at the same rate as normotensive women. However, most of the studies in this review control for parity as a potentially confounding variable in their multivariate analysis, while one study [62] restricted their sample to primiparous women only.

PE is also a leading cause of other obstetric complications, most notably pre-term birth, small for gestational age (SGA) birthweight and IUGR, and, importantly, these conditions are recognized as perinatal risk factors for neurodevelopmental disorders [22, 25, 44, 46, 53, 60, 75, 124, 125]. The studies described here generally control well for these and other factors as potentially confounding variables in their analyses, and the associations reported in this review, where possible, are based on adjusted risk figures from multivariate analysis models reported in these studies. PE is particularly associated with preterm births, so a few studies have stratified their sample by gestational age. This has revealed, for example, that PE reduces risk for CP in preterm-born infants compared to unexposed preterm controls, but increases the risk in term infants [68, 69] and that PE may only increase epilepsy risk in children born at term [17]. Similarly, PE may only increase risk for CP among term infants if they are SGA [126]. Although most cohort studies compare the PE group to an unexposed population and then control for confounding variables, some instead compare to unexposed siblings [29, 55, 103]. While this approach has the advantage of controlling for several maternal, paternal, genetic and sociodemographic factors, it can be difficult to control for the lower incidence of preterm birth, SGA and IUGR in unexposed siblings.

Exactly how much of the relationship between PE and offspring neurodevelopmental disorders is attributable to these factors can be difficult to determine. A number of studies restricted their analysis to preterm, SGA or IUGR-exposed populations [71, 72, 100, 127, 128] and in many cases still report an effect of PE on offspring neurodevelopment. One study reported that 50% of the relationship between PE and intellectual disability in the offspring was mediated by SGA; similarly, a recent study used Sobel testing to determine how much of the relationship between PE and cumulative mental disorders in the offspring is mediated by preterm birth or SGA, and in both cases found that the mediation effect was a similar size to the direct effect of



PE [129]. Thus it appears that these comorbid obstetric complications account for some, but not all, of the association between PE and offspring neurodevelopmental trajectory, and that the remaining effect may be attributable to some feature(s) intrinsic to the pathophysiology of PE.

In summary, PE is associated with sub-optimal neurodevelopmental outcome in exposed offspring, but some questions about this relationship remain unanswered – these are, primarily: how strong is the relationship between PE and disorders others than ASD and ADHD in exposed offspring; what proportion of PE is missed by Nordic registries and how may this affect the results from studies using these registries; does the effect of PE on fetal neurodevelopment become more drastic with an increase in PE severity; do early- and late-onset PE affect fetal neurodevelopment differently; and to what extent is the relationship mediated by confounding variables such as comorbid birth complications? Before discussing potential pathogenic mechanisms, we will next describe neuroimaging studies in PE-F1s and relate their results to the evidence provided above in section 2.

### **3.0 Evidence for neuroanatomical alterations in the brains of offspring exposed to Pre-eclampsia**

Few neuroimaging studies have been carried out on PE-F1s, although one group has recently reported neuroanatomical alterations which are congruent with the studies described above [130]. The authors selected 10 children aged 7 – 10 years old who had been exposed to PE, and 10 age-matched controls, using three types of magnetic resonance imaging (MRI) paradigms to investigate regional grey matter volumes, white matter structural connectivity and functional connectivity differences between the groups.

#### ***3.1 Regional Grey Matter Volume***

Although the authors reported no difference in total brain volume, PE-F1s exhibited larger regional corrected volumes of the amygdala, temporal lobe, brainstem and cerebellum. There was, however, a significant difference in birth weight between the groups, which may have confounded the results [130]. Enlarged amygdalae are seen in children with ASD [131, 132] and some cases of temporal lobe epilepsy [133]. Similarly, increased temporal lobe [134] and brainstem [135] volumes have been reported in children with ASD. Unlike the above finding of increased cerebellar volume, however, a smaller cerebellum is seen in patients with ASD [136], ADHD [137, 138] and schizophrenia [139].

#### ***3.2 Structural Connectivity***

Diffusion tensor imaging (DTI) characterizes the diffusion of water molecules in tissues and can be used to map white matter tracts in the brain [140]. This is achieved by measuring fractional anisotropy (FA) as a proxy for white matter microstructural integrity, and axial and radial diffusion to determine the directionality of axons in the white matter tract. Using DTI, the authors reported that PE-F1s have increased white matter volume and fractional anisotropy in the caudate nucleus, increased white matter volume of the superior longitudinal fasciculus (SLF) and increased axial diffusion of the cingulate gyrus [141].

The caudate nucleus is part of the striatum and is involved in learning and memory, motor output and goal-directed behaviour [142]. Autistic children exhibit hyperconnectivity of the

striatum [143] and accelerated growth of caudate grey matter, which correlates with severity of restricted-repetitive behaviours [144]. They also display abnormal processing of social and non-social rewards associated with striatal activity, which may partially underlie their restricted interests [145]. Higher inflow/outflow and structural connectivity of the caudate nucleus have also been reported in Tourette's syndrome and frontal lobe epilepsy [146, 147].

The SLF is a frontoparietal white matter tract with a crucial role in language processing [148]. Language deficits are a prominent feature of ASD [149–151]. However, the literature on connectivity of the SLF in ASD is inconclusive – whereas one study reported increased FA in part of the SLF [152], others found decreased FA [153] or no FA change at all [154]. Similarly, language problems are common in schizophrenia [155], and schizophrenics display reduced FA of the SLF [156], particularly those with auditory hallucinations [157].

The cingulum bundle is a large white matter tract which forms a core part of the limbic system and its roles include episodic memory, pain and emotional processing [158]. In ASD there is increased mean diffusivity of the cingulum [159] and hypoactivity of the associated cingulate gyrus, which correlates with the severity of autistic symptoms [160]. ADHD and schizophrenia are characterised by dysfunctional emotional processing [161, 162] and, importantly, both disorders are associated with reduced FA of the cingulum [163–166].

### ***3.3 Functional Connectivity***

Resting-state functional MRI (rs-fMRI) can be used to measure the degree of functional connectivity (FC) between two brain regions based on the temporal synchronization of their activity [167]. Using rs-fMRI, the authors observed higher connectivity in PE-F1s between the left amygdala and bilateral frontal pole, the right amygdala and left frontal pole and the medial prefrontal cortex (mPFC) and precuneus; and decreased connectivity between the mPFC and the left occipital fusiform gyrus [168].

The amygdala is a deep-brain nucleus involved in emotional learning and memory and fear processing [169], and the frontal pole is the most anterior part of the prefrontal cortex, concerned with goal-engineering processes [170]. In the neurotypical brain, rsFC between the amygdala and frontal pole increases after acute psychosocial stress [171]. Interestingly, increased amygdala-frontal pole rsFC positively correlates with symptom severity in adolescents with generalized anxiety disorder [172] and emotional lability in children with ADHD [173].

The mPFC and precuneus are part of the default mode network (DMN), a group of functionally related brain structures that are highly active at rest and suppressed during most tasks [174]. Increased rsFC between these regions is unusual considering DMN hypoconnectivity is seen at rest in schizophrenia [175], ADHD [176] and ASD with low verbal and cognitive performance [177], wherein the latter study DMN dysconnectivity was negatively correlated with IQ. However, it would be interesting to study DMN FC in PE-F1s during cognitive tasks, as task-related de-activation of the DMN is reduced in ASD and schizophrenia, and this reduction is associated with poorer task performance [178–180].

The fusiform gyrus, continuous between the temporal and occipital lobes, is important for face perception and object recognition [181]. Facial recognition deficits are present in both ASD [182] and schizophrenia [183]. Correspondingly, the fusiform gyrus is smaller in schizophrenia [184] and hypoactive during face recognition tasks in ASD [185, 186].

The main brain regions affected in this study were part of the “social brain”, concerned with empathy, social cognition and social interaction [187]. Social cognition is impaired in both ASD and schizophrenia [188]. For example, children with ASD have reduced activity of social brain areas in response to emotional facial expressions [189]. In fact, the aberrant empathy and overall social brain deficits in schizophrenia have led to the “social brain hypothesis” of schizophrenia which postulates that the disease primarily manifests from social brain dysfunction [190].

Thus the regional volumetric brain changes, white matter structural connectivity and rsFC results from these three studies are congruous with the anatomical and functional brain changes seen in neurodevelopmental disorders. Although these results come from only one small pilot cohort, they suggest that PE-F1s have brain structural and functional alterations which may underlie their increased risk of neurodevelopmental disorders.

#### **4.0 Potential Pathogenic Mediators of Pre-eclampsia that May Alter Fetal Neurodevelopmental Outcomes.**

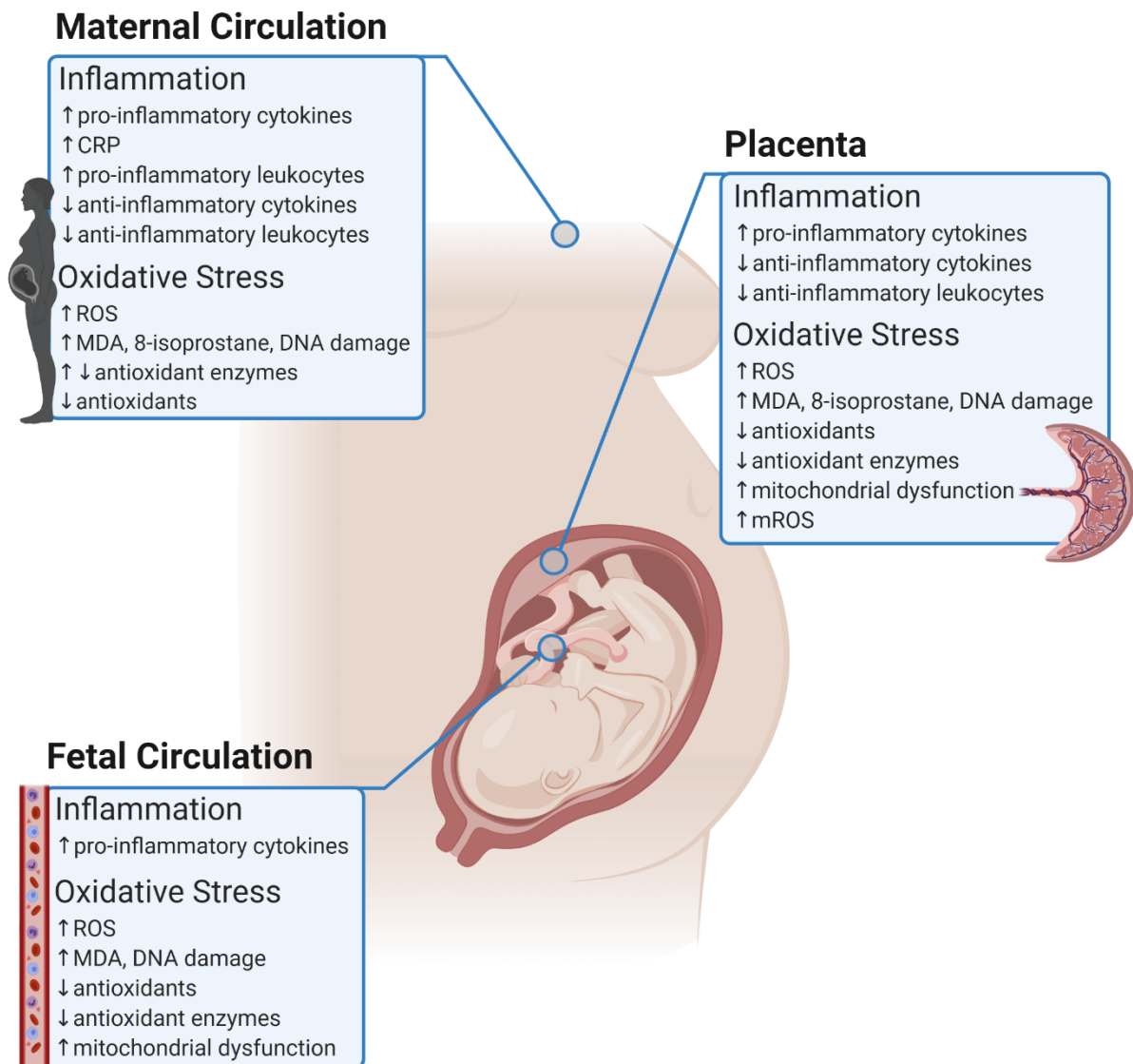
##### **4.1 Inflammation**

Although maternal inflammation is a physiological component of pregnancy [191, 192], PE is characterised by an exaggerated maternal inflammatory response, which can have a deleterious effects on fetal neurodevelopmental trajectories (Figure 1).

##### ***4.1.1 Increased inflammatory response in Pre-eclampsia***

Dysregulated immune activation is a well-recognized feature of PE (reviewed by [193]). Women with PE have higher circulating concentrations of the pro-inflammatory cytokines TNF $\alpha$ , IL-6, IL-8 and IL-16 and C-reactive protein (CRP) [192, 194–198]. They may also have lower levels of anti-inflammatory cytokines, TGF $\beta$  and IL-10, although this is less well characterized [197, 199]. Correspondingly, there is an imbalance of circulating immune cell populations. Pre-eclamptic women have greater numbers of neutrophils, increased neutrophil activation [200] and increased leukocytes [192] compared to normotensive pregnant women. There is also a reduction in regulatory T (T<sub>reg</sub>) cell number [201], and immune cell populations are shifted towards an increased relative abundance of pro-inflammatory T-cells (Th1 > Th2 cells and Th17 > T<sub>reg</sub> cells) [202]. Interestingly, monocytes from women with PE produce higher levels of TNF $\alpha$ , which inhibits proliferation of human trophoblasts [203].

Animal models of PE have elucidated a central role for inflammation in the pathophysiology of the disease. In the reduced uterine perfusion pressure (RUPP) pre-clinical model of pre-eclampsia, RUPP rats have increased levels of circulating TNF $\alpha$  and IL-6 [204, 205]; similarly, IL-6 infusion or transfer of Th-17 cells from RUPP rats to normal pregnant rats induces increased mean arterial pressure (MAP) and other features of PE [205, 206]. Conversely, the raised MAP and additional features of PE in RUPP rats can be ameliorated by injection of exogenous anti-inflammatory IL-4, IL-10 or T<sub>reg</sub> cells, or by stimulating the proliferation of endogenous T<sub>reg</sub> cells [207–210]. Additionally, injection of the bacterial endotoxin lipopolysaccharide (LPS) stimulates an immune response in rodents [211, 212], this pro-inflammatory state results in raised MAP and cardiovascular and renal deficits and is often used as a preclinical model of PE [213–215].



**Figure 1: Overview of markers of inflammation and oxidative stress in PE.** Various biomarkers of inflammation and oxidative stress have been reported in the maternal circulation, placenta and fetal circulation in pregnancies complicated by PE.

Pertinent to fetal development, pre-eclamptic placentae express or secrete significantly increased levels of pro-inflammatory cytokines  $\text{TNF}\alpha$ ,  $\text{IL-1}\beta$ ,  $\text{IL-6}$  and  $\text{IL-16}$  [196, 216, 217] and lower levels of anti-inflammatory cytokines  $\text{IL-4}$  and  $\text{IL-10}$ ; it is also populated by fewer  $\text{T}_{\text{reg}}$  cells when compared with placentae from uncomplicated pregnancies [218–220]. Hypoxia/reoxygenation of human placental explants cultured *ex vivo* induces secretion of  $\text{TNF}\alpha$  and  $\text{IL-1}\beta$  [221, 222]. There is also evidence that these inflammatory mediators reach the developing foetus. In placental vascular disease, which, like PE, is characterised by placental insufficiency, placentae express more  $\text{IL-6}$  and  $\text{IL-8}$  specifically on the fetal side [223]. Importantly,  $\text{IL-6}$  has been shown to cross the placenta and reach the fetal circulation both *in vivo* and *ex vivo* [224, 225]. Umbilical cord blood of PE-F1s have higher concentrations of  $\text{TNF}\alpha$ ,  $\text{IL-6}$  and  $\text{IL-8}$  [226, 227] and while no human studies have investigated cytokine levels in the PE-F1 brain,  $\text{IL-1}\beta$ ,  $\text{IL-6}$  and  $\text{IL-18}$  are found in high concentrations in the brain tissue of pups prenatally exposed to RUPP [228]. These latter findings demonstrate that PE-

FIs are not only prenatally exposed to maternal immune activation (MIA), but also directly to elevated concentrations of pro-inflammatory cytokines.

#### ***4.1.2 Implications of prenatal exposure to inflammation for fetal neurodevelopmental outcome***

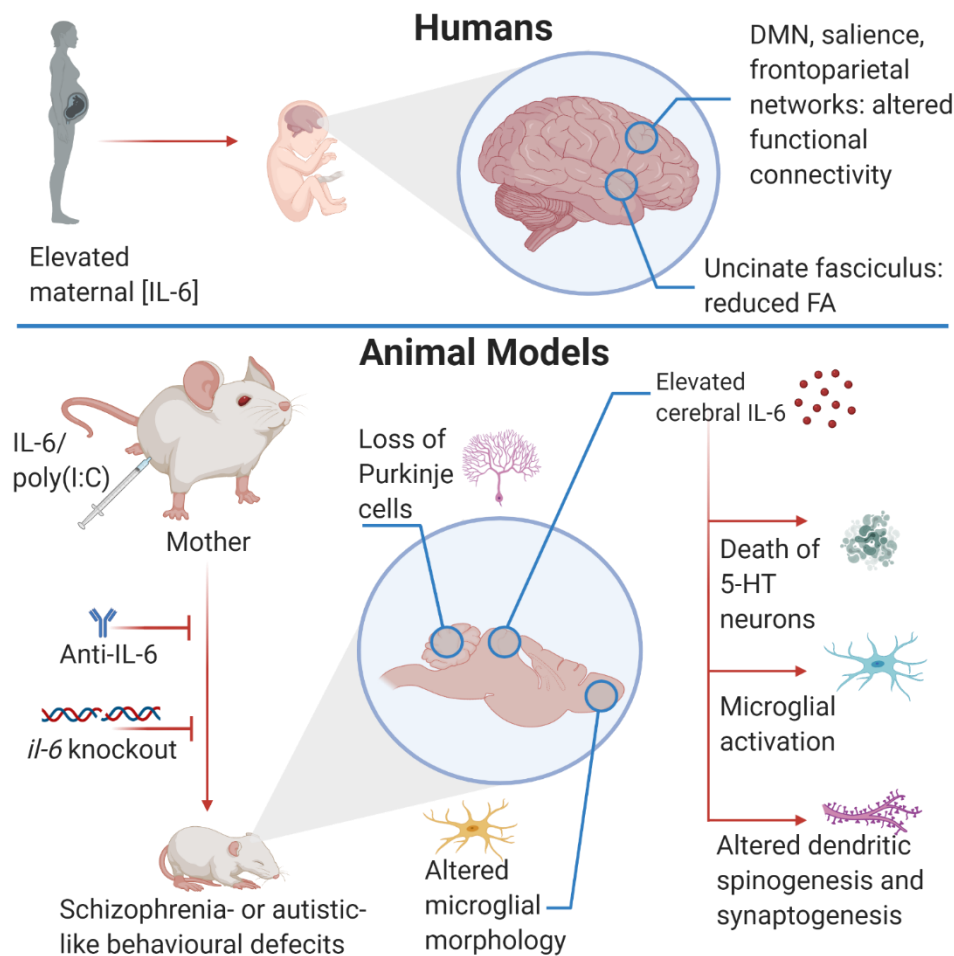
Maternal infection during pregnancy and the consequential induction of inflammation is a major environmental risk factor for ASD and schizophrenia [229, 230] and elevated maternal CRP during pregnancy is associated with a significantly increased risk of ASD [231]. At 7 years of age, children exposed to elevated TNF $\alpha$  during pregnancy have poorer performance on cognitive tests, although, interestingly, exposure to elevated levels of IL-8 improved performance, suggesting divergent roles of different pro-inflammatory cytokines [232]. Similarly, prenatal exposure to MIA can cause alterations in structural and functional brain connectivity. Elevated maternal IL-6 concentrations are associated with reduced neonatal FA in the central portion of the uncinate fasciculus, a frontolimbic tract implicated in neurodevelopmental disorders [233]; while elevated maternal IL-6 and CRP concentrations in the third trimester are associated with altered functional connectivity in the DMN, salience network and frontoparietal networks in exposed offspring [234].

Animal models of MIA provide mechanistic insights into this association. Mice prenatally exposed to the influenza virus develop schizophrenia-like behavioural deficits [235], caused not by the virus itself, but by the MIA it induces, since viral particles are not detected in the foetus, and the same behavioural deficits can be elicited by the viral mimetic compound poly(I:C) [236]. Prenatal poly(I:C)-induced behavioural deficits have been replicated in rats and can be attenuated by treatment with anti-psychotic drugs [237, 238]. Prenatal poly(I:C) exposure in mice also leads to dopamine and serotonin imbalances, mimicking the neurochemical alterations seen in schizophrenia [239, 240]. Prenatal exposure to LPS can have different effects on offspring depending on the timing of exposure: early exposure (GD12) in rats alters reward-seeking behaviour, whereas late exposure (GD16) causes motor deficits, without affecting the number of midbrain dopaminergic neurons postnatally [241].

One potential mechanism for this association is the influence of MIA on offspring microglia. Mouse offspring exposed to MIA have behavioural deficits accompanied by increased activation of microglia, reduced microglial expression of BDNF and an altered microglial methylome and transcriptome [242–244]. Interestingly, the areas of increased methylation are associated with inflammatory pathways, such as IL-4, IL-6, and IL-8 signalling [243]. This is particularly pertinent to neurodevelopment, considering the central role microglia play in regulating cortical neurogenesis and early postnatal synaptic pruning [245, 246]. As such, microglial alterations have been implicated in the pathogenesis of neurodevelopmental disorders such as ASD [247].

Neurodevelopmental alterations may also result from high concentrations of cytokines in the fetal brain. Rats exposed to LPS have higher levels of IL-1 $\beta$  in the placenta and TNF $\alpha$ , IL-1 $\beta$  and IL-6 in the amniotic fluid [248, 249]. Cytokines are known to cross the blood-brain barrier (BBB) [250], and, consequently, elevated concentrations of TNF $\alpha$ , IL-1 $\beta$  and IL-6 are found in the brains of MIA-exposed rats and mice [251, 252]. This aligns with observations of neuroinflammation in individuals with ASD and schizophrenia [253, 254]. One example of a pro-inflammatory cytokine with deleterious effects on neurodevelopment is IL-1 $\beta$ , which inhibits proliferation of neural progenitor cells and neurite growth of superior cervical ganglion

neurons via the IL-1R1 receptor [255, 256]. *In vivo*, IL-1 $\beta$  has been shown to activate microglia (which in turn secrete more IL-1 $\beta$ ) and initiate BBB breakdown, increasing the brain's permeability to additional peripherally circulating cytokines [257, 258].



**Figure. 2 The role of IL-6 in mediating adverse neurodevelopmental outcome of offspring exposed to MIA.** Elevated maternal IL-6, as seen in PE, leads to neurodevelopmental deficits in humans and animal models of MIA. High [IL-6] from the placenta reaches the fetal brain, where it can have various deleterious consequences for developing neurons. The effects of prenatal IL-6 exposure on offspring brain and behaviour have been attenuated in animal models by anti-IL-6 antibody or *il-6* knockout.

Perhaps the strongest candidate for a pathogenic mediator linking MIA and poor fetal neurodevelopmental outcome is IL-6 (Figure 2). The schizophrenia-like behaviours in mice prenatally exposed to poly(I:C) were shown to be IL-6-dependent [259]. In these experiments, maternal IL-6 or poly(I:C) administration induced similar behavioural deficits; however, poly(I:C) failed to affect offspring behaviour in *il-6*<sup>-/-</sup> mice or mice co-administered with an anti-IL-6 antibody [259]. Similarly, mice prenatally exposed to poly(I:C) have a transient increase in *il-6* expression in the brain, in addition to autistic-like behaviours and a loss of cerebellar Purkinje neurons, which are attenuated by maternal knockout of *il-6* or conditional knockout of *il-6* specifically in the placenta [260]. Chronic maternal administration of IL-6 also causes altered microglial morphology in exposed offspring, which is prevented by maternal IL-6 blockade [261]. These studies point to a primary role for IL-6 in facilitating structural and neurochemical brain changes in MIA-exposed offspring; furthermore, cerebral IL-6, similar to IL-1 $\beta$ , is increased in MIA and RUPP models, with detrimental effects on

neurodevelopment. IL-6 inhibits the survival of serotonergic neurons and, like IL-1 $\beta$ , increases microglial activity resulting in increased IL-6 secretion [262, 263]. In mice, elevated concentration of IL-6 in the brain leads to multiple behavioural deficits; increased excitatory synaptogenesis and reduced inhibitory synaptogenesis; and alterations in dendritic spine length and morphology [264]. Intriguingly, another study showed that serum from pre-eclamptic women increased neurite number, length and branching in primary cortical neurons, and found a trend towards higher IL-6 in the PE sera compared to controls, suggesting a potential mechanistic role for IL-6 in this study [48].

## **4.2 Oxidative Stress**

Oxidative stress is the relative increase in intracellular reactive oxygen species (ROS) production and corresponding relative reduction in antioxidant levels. Elevated levels of ROS are a normal feature of gestation and play important physiological roles in the establishment of a healthy pregnancy, including regulation of endometrial changes, fertilization, implantation and placental and embryonic growth [265, 266]. Excessively high levels of ROS, however, have been associated with the pathophysiology of various pregnancy disorders, including PE, gestational diabetes mellitus and spontaneous abortion [267], and this may also contribute to the sub-optimal neurodevelopmental trajectory of PE-F1s.

### ***4.2.1 Evidence for increased oxidative stress in Pre-eclampsia***

Compared to those of normotensive pregnant women, circulating blood and erythrocyte samples from women with PE reveal increased ROS production [268–270]; higher levels of the oxidative stress markers malondialdehyde (MDA), 8-isoprostane and leukocyte DNA damage [271–274]; lower levels of the antioxidants glutathione, lycopene, vitamin C and vitamin E [268, 271, 275, 276]; and altered activity of the antioxidant enzymes superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) [268, 269, 271, 277]. Although ROS are produced by both endothelial and circulating blood cells during pregnancy, the dominant source in PE is the placenta. Pre-eclamptic placentae exhibit increased ROS production [278, 279]; elevated levels of MDA, 8-isoprostane and oxidative DNA damage [280–282]; low levels of glutathione [283]; and reduced expression and activity of SOD, GPx, thioredoxin and thioredoxin reductase [271, 279, 283–285]. Correspondingly, rats exposed to RUPP have higher placental MDA and 8-isoprostane levels and reduced SOD activity, and RUPP-induced hypertension is attenuated by the antioxidant tempol [286]. Collectively, these studies suggest that exaggerated oxidative stress is a prominent feature of PE.

Mitochondria are the primary source of ROS, and mitochondrial electron transport chain (ETC) deficits have been shown to increase ROS production [265, 287]. Notably, mitochondrial dysfunction in the placenta has been implicated as the major source of oxidative stress in PE. Mitochondria in pre-eclamptic placentae show extensive degeneration and apoptosis and have an altered metabolome [288] and mitochondrial protein expression profile, including downregulation of ETC complex V (ATP synthase) expression [289] and reduced expression and activity of ETC complex III (cytochrome c reductase) [290]. Correspondingly, mitochondria exhibit increased lipid peroxidation and MDA levels, which are markers of oxidative stress [291, 292]. Interestingly, mitochondria are not only a source of ROS, but also a target – dysfunctional mitochondria release ROS which can induce dysfunction and

consequent ROS release from neighbouring mitochondria, amplifying cellular oxidative stress [293].

In a large clinical trial, supplementation with the dietary antioxidants vitamin C and vitamin E failed to reduce the risk of PE [294]. One potential explanation for this is that the antioxidants failed to target the source of the problem – *mitochondrial* ROS (mROS). This hypothesis has led to a recent increase in the development of mitochondrial-targeted antioxidants as a potential therapeutic strategy with encouraging data emerging from pre-clinical models: RUPP exposure in pregnant rats leads to reduced ETC activity and respiratory rate and increased mROS production in placental mitochondria, and RUPP-induced hypertension was attenuated by the mitochondria-specific antioxidants MitoQ or MitoTEMPO [295]; RUPP-induced hypertension and increased sFlt1 levels were ameliorated by the nutraceutical mitochondrial antioxidant L-ergothioneine, effects that were mediated in part by specifically reducing mROS production [296]. There is further evidence of the potential therapeutic benefit of specifically targeting mitochondria in other models of hypertension, including angiotensin-II-induced hypertension in mice, which was significantly reduced following administration of mitoTEMPO, but, importantly, not by tempol, which lacks mitochondrial specificity [297]. Interestingly, the antioxidant trace element selenium is reduced in women with PE [298] and clinical trials implementing selenium supplementation have successfully reduced the risk of developing PE [299]. This may be because, unlike vitamins C and E, selenium exerts an antioxidant effect directly on placental mitochondria [300, 301].

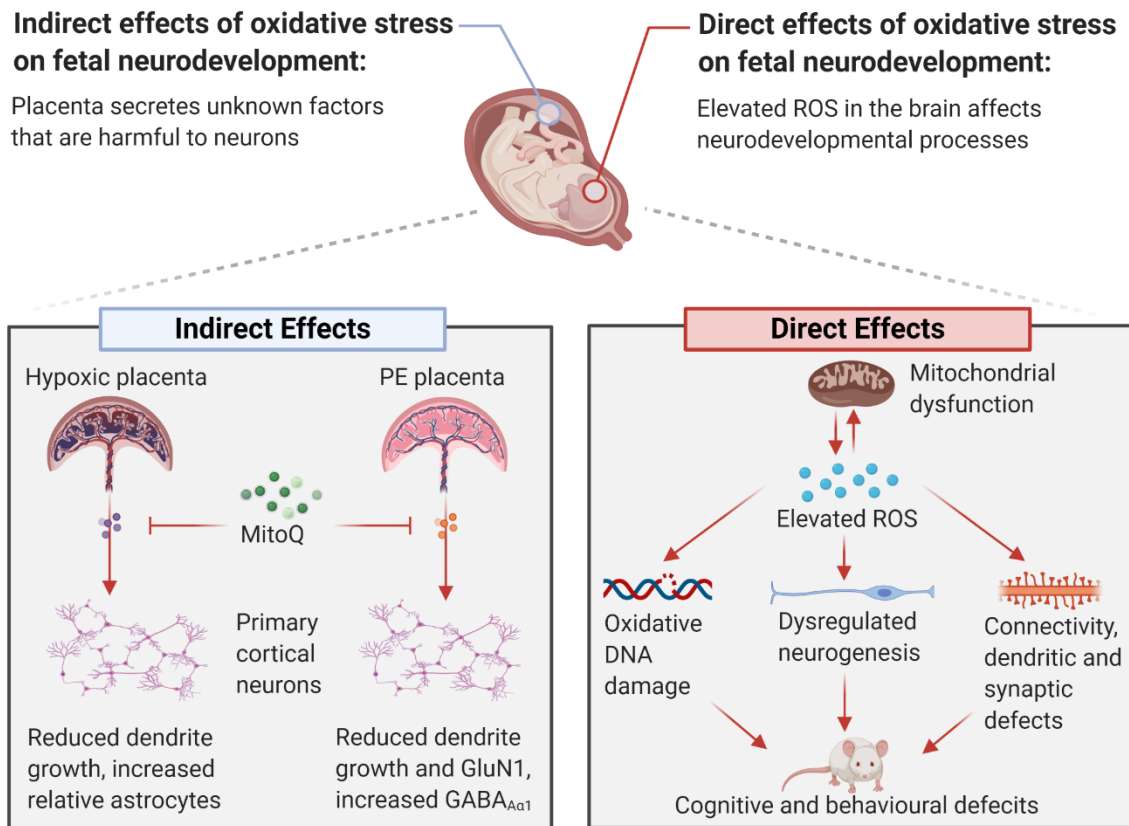
Oxidative stress in PE is present not only in the maternal, but also fetal circulation. PE-F1 umbilical vein blood is characterised by increased ROS, MDA and leukocyte DNA damage, GPx hypoactivity and decreased levels of vitamin C and selenium [274, 276, 298]. Additionally, there is significant mitochondrial dysfunction in human umbilical vein endothelial cells (HUVECs) [302]. Collectively these data show that while women with PE have multiple features that are indicative of exaggerated oxidative stress, these changes can also be seen in neonatal PE-F1s (Figure 1).

#### ***4.2.2 The implications of prenatal exposure to oxidative stress for fetal neurodevelopmental programming***

Firstly, placental oxidative stress, as seen in PE, may affect fetal neurodevelopment indirectly by inducing the placenta to secrete various factors into the fetal circulation capable of affecting the developing nervous system. This is illustrated by a series of elegant experiments, whereby the authors exposed the placental cell line BeWo or placental explants to hypoxia in order to induce oxidative stress. BeWo- or placenta-conditioned media contained increased concentrations of TNF $\alpha$ , which, when added to human embryonic stem cells, caused DNA damage and apoptosis – the latter effect blocked by an anti- TNF $\alpha$  antibody [222]. Conditioned medium from both BeWo cells and placental explants exposed to oxidative stress was next added to primary cortical neurons resulting in reduced dendritic growth and increased relative abundance of astrocytes. In a rat model of gestational hypoxia, exposed rats exhibited placental oxidative stress and offspring brains displayed similar neuronal deficits as seen *in vitro*. In both cases, these neuronal deficits were prevented by therapeutic targeting of the placenta with MitoQ [303]. Finally, using conditioned media from placental explants from women with PE, these authors established that when added to primary cortical neurons, there was reduced dendritic growth, decreased GluN1 expression and increased GABA $_{A\alpha 1}$  expression in an astrocyte-dependent manner, effects that were diminished by *ex vivo* treatment of explants with



MitoQ [304]. Therefore, oxidative stress stimulates the release of factors from the placenta which are harmful to neurons.



**Figure 3: The influence of placental and fetal brain oxidative stress on fetal neurodevelopment.** The exaggerated oxidative stress reported in PE may adversely impact fetal neurodevelopment both indirectly, via the release of factors from the placenta that are harmful to neurons; and directly, via the influence of ROS on neurodevelopmental processes.

Secondly, the high oxidative status of PE-F1s is particularly pertinent due the direct impact of ROS on neuronal development. Highly regulated concentrations of ROS modulate many neurodevelopmental processes, including neural progenitor cell proliferation and differentiation, apoptosis, dendritic growth and axonal guidance [305–309]. The brain, however, is particularly vulnerable to the deleterious effects of hyperphysiological oxidative stress and this has been illustrated by a number of animal studies. Mice with genetic impairments in the repair of oxidative DNA damage, for example, have memory deficits which can be recovered by antioxidant treatment [310]. Offspring of rats exposed to the L-NAME (N $\omega$ -nitro-L-arginine methyl ester) preclinical model of PE have reduced neurogenesis at birth, decreased numbers of oligodendrocytes in the cortex, delayed development of sensorimotor reflexes and reactions and impaired spatial learning [300-302] and it has recently been shown that rats prenatally exposed to this model also exhibit raised levels of oxidative stress markers in the cortex and cerebellum [303]. Similarly, in a mouse model of DiGeorge/22q11 deletion syndrome, a developmental disorder which includes widespread neurodevelopmental deficits, layer 2/3 cortical neurons had mitochondrial damage and oxidative stress concurrent with defects in connectivity, synapse integrity and dendritic growth and branching, which manifested as cognitive behavioural deficits in the mice. These mitochondrial, dendritic and behavioural alterations were ameliorated by antioxidant treatment [311]. Finally, in a rat model

of MIA, male, but not female, offspring exhibit oxidative stress in the hippocampus and corresponding spatial learning deficits, which were rescued by maternal treatment with antioxidants, suggesting that some of the effects of MIA on offspring behaviour in males are mediated by oxidative stress [312]. In line with these observations, high levels of markers of oxidative stress are reported in those with ASD, ADHD, epilepsy and schizophrenia [313–316]. This has been most extensively investigated in ASD, where there is prominent mitochondrial dysfunction and oxidative stress in the brain [317–319]. Overall, these data suggest that the oxidative stress reported in PE-F1s may contribute to their sub-optimal neurodevelopmental trajectory via the direct effects of exaggerated ROS concentrations on neurodevelopmental processes (Figure 3).

#### ***4.2.3 The interplay between oxidative stress and inflammation***

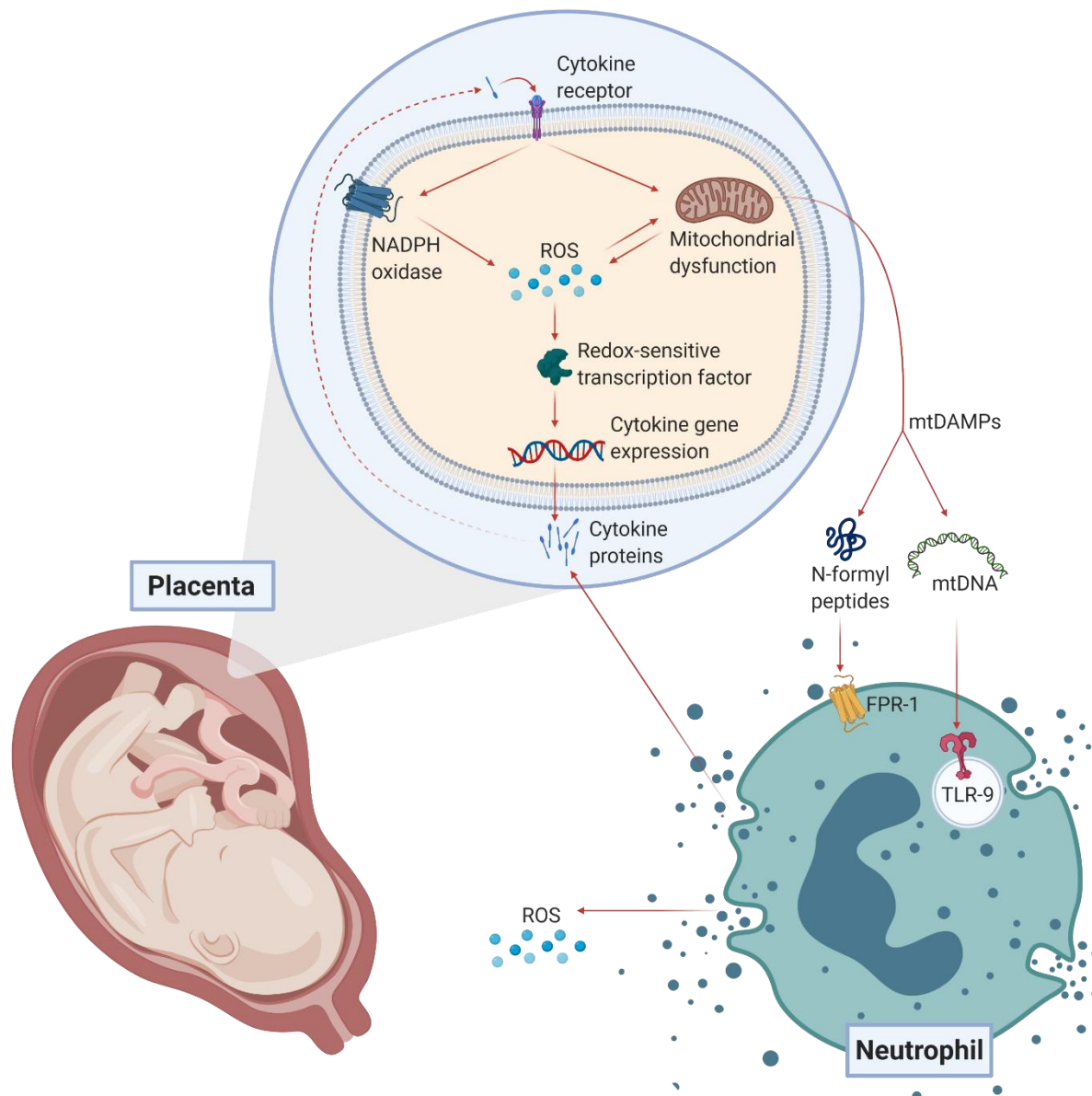
Oxidative stress and inflammation are inextricably linked and cannot be viewed as independent systems in the context of PE. Placental oxidative stress is one of the earliest events in PE and this causes the placenta to secrete various factors into the maternal circulation, ultimately leading to the hyperinflammatory and oxidative state that characterises the disease [320]. Markers of both oxidative stress and inflammation can be detected in advance of the onset of clinical symptoms and circulating levels of IL-6 are highly correlated with protein carbonylation, an oxidative stress marker, in PE [272, 273, 321, 322].

Oxidative stress activates redox-sensitive transcription factors, particularly NF- $\kappa$ B, upregulating cytokine gene expression [323, 324]. In the human placenta, hypoxia/reoxygenation activates p38, NF- $\kappa$ B and MAPK signalling pathways, increasing expression of downstream TNF $\alpha$  and IL-1 $\beta$ , an effect that is blocked by vitamins C or E [325]. Similarly, mitochondrial dysfunction in trophoblasts stimulates IL-6 secretion, which is blocked by vitamin E or the antioxidant, deferoxamine [326]. Activation of T-cell receptors induces intracellular ROS and downstream IL-2 and IL-4 production, which can be prevented by inhibition of ETC complex I [327]. Complex IV inhibition alters leukocyte response to LPS, increasing IL-6 and decreasing TNF $\alpha$  production; also, in healthy adults, leukocyte complex IV activity is correlated with IL-6 levels [328].

Another mechanism by which oxidative stress can promote inflammation in PE is the production of mitochondrial damage-associated molecular patterns (mtDAMPs) [329]. Oxidative stress induces the release of mtDNA and N-formyl peptides, both of which act as mtDAMPs and bind TLR-9 or FPR-1 receptors, respectively, on neutrophils to activate and drive them towards a pro-inflammatory phenotype [330]. This may have implications for PE, due to increased circulating levels of mtDNA and increased TLR-9 expression and activity in dendritic cells and placenta [200, 331–333]. Similarly, PE serum induces mROS and TLR-9 expression in HUVECs, an effect which is attenuated by MitoTEMPO [334]. Thus, oxidative stress in PE, via activation of redox-sensitive transcription factors and mtDAMPs, induces the release of cytokines both from the placenta and from immune cells.

The reverse is also true, in that inflammation promotes oxidative stress, by stimulating mitochondrial and non-mitochondrial (primarily via NADPH oxidase activity) ROS production [267]. Injection of IL-17 or Th17 cells from RUPP rats into normal pregnant rats induces placental oxidative stress [206, 335]; conversely, RUPP-induced placental oxidative stress is diminished by injection of IL-10, TNF $\alpha$  blocker or T<sub>reg</sub> cells [207, 209, 336]. Endogenous natural killer (NK) cells also contribute to RUPP-induced placental oxidative stress, while NK

cell depletion mitigates these effects [337]. When stimulated by N-formyl peptides, neutrophils from pre-eclamptic women release higher levels of ROS than those from normotensive controls resulting in increased endothelial cell damage, suggesting that, in PE, there is a heightened sensitivity to inflammation-induced oxidative stress [338].



**Figure 4: The interplay between oxidative stress and inflammation in the context of PE.** Exaggerated oxidative stress and maternal immune activation are well-characterised features of PE and both systems interact such that increases in one induce a corresponding increase in the other. This is particularly well-characterised in the placenta and circulating immune cells such as neutrophils, resulting in the constant maintenance of an adverse *in utero* microenvironment, which is likely to have deleterious consequences for fetal neurodevelopment.

Thus, the roles of inflammation and oxidative stress are convergent and interconnected. Upregulation of one leads to increases in the other, in a self-perpetuating cycle that culminates in a highly oxidative and inflammatory microenvironment for the developing foetus (Figure 4). This adverse *in utero* environment persists throughout gestation and may have deleterious consequences for fetal neurodevelopmental outcome.

## **5.0 Conclusion:**

The association between PE and offspring neurodevelopmental outcome is becoming increasingly well recognized. Recent evidence has established *in utero* exposure to PE as a risk factor for ASD and ADHD and may also confer an increased risk upon offspring for poor cognitive function, CP, epilepsy, schizophrenia and neuroanatomical alterations similar to those seen in these disorders. Currently, however, the associative mechanisms are yet to be fully elucidated, and this review proposes inflammation and oxidative stress as potential leading candidates. Although inflammation and oxidative stress have been discussed independently in this review for the purpose of clarity, it is important to recognize that these systems are intricately interconnected and increases in one lead, via positive feedback, to augmentation of the other.

Both inflammation and oxidative stress are prominent features of PE pathophysiology, creating a sub-optimal *in utero* environment. Persistent exposure to this inflammatory and oxidative milieu, as well as fetal inflammation and oxidative stress, are likely to affect neurodevelopmental programming in exposed offspring via the mechanisms provided in section 4 of this review. On these premises, targeting maternal immune activation, particularly IL-6, and maternal oxidative stress, particularly mROS in the placenta, are predicted to improve the neurodevelopmental outcome of exposed offspring. Although, to the best of our knowledge, no study to date has attempted both interventions simultaneously, several animal studies, as discussed above, have significantly improved offspring neurodevelopmental outcome using one therapeutic approach or the other. These studies are encouraging and suggest that similar interventions in humans may ameliorate the increased risk of neurodevelopmental disorders seen in PE-F1s.

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### ***Competing Interests***

The authors declare that they have no competing interests.

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