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In-utero exposure to air pollution and early-life neural development and cognition

Chenju Yi [a,*,#], Qi Wang [a,#], Yibo Qu [b], Jianqin Niu [c], Brian G Oliver [d,e], Hui Chen [d]

a. Research Centre, The Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen, 518107, China;

b. Guangdong-Hongkong-Macau Institute of CNS Regeneration, Ministry of Education CNS Regeneration Collaborative Joint Laboratory, Jinan University, Guangzhou 510632, China;

c. Department of Histology and Embryology, Chongqing Key Laboratory of Neurobiology, Brain and Intelligence Research Key Laboratory of Chongqing Education Commission, Third Military Medical University, Chongqing 400038, China

d. School of Life Sciences, Faculty of Science, University of Technology Sydney, NSW 2007, Australia;

e. Respiratory Cellular and Molecular Biology, Woolcock Institute of Medical Research, NSW 2037, Australia

# These authors contributed equally to this work.

* Corresponding author:

Associate Professor Chenju Yi, The Seventh Affiliated Hospital of Sun Yat-sen University, 628 Zhenyuan Rd, Guangming District, Shenzhen, China, 518107

Email address: yichj@mail.sysu.edu.cn

Abstract

Air pollution remains one of the major health threats around the world. Compared to adults, foetuses and infants are more vulnerable to the effects of environmental toxins. Maternal exposure to air pollution causes several adverse birth outcomes and may lead to life-long health consequences. Given that a healthy intrauterine environment is a critical factor for supporting normal foetal brain development, there is a need to understand how prenatal exposure to air pollution affects brain health and results in neurological dysfunction. This review summarised the current knowledge on the adverse effects of prenatal air pollution exposure on early life neurodevelopment and subsequent impairment of cognition and behaviour in childhood, as well as the potential of early-onset neurodegeneration. While inflammation, oxidative stress, and endoplasmic reticulum are closely involved in the physiological response, sex differences also occur. In general, males are more susceptible than females to the adverse effect of in-utero air pollution exposure. Considering the evidence provided in this review and the rising concerns of global air pollution, any efforts to reduce pollutant emission or exposure will be protective for the next generation.

Keywords

Particulate matter, maternal exposure, brain health, neurological dysfunction

Abbreviation

APOE: Apolipoprotein E; CNS: Central Nervous System; CO_x: Carbon Oxides; ER: endoplasmic reticulum; IQ: intelligence quotient; NTD: Neural Tube Defect; NOx: Nitrogen Oxides; O_3: Ozone; OR: odds ratio; PAH: Polycyclic Aromatic Hydrocarbon;

1. Introduction

Air pollution refers to chemicals or particles in the air coming from anthropogenic or natural sources that are hazardous to the health of living creatures (Landrigan et al., 2018). Increasing emissions from the fast-growing modern industry, urbanisation, and road traffic, in addition to the traditional biomass fuel, have been affecting the air quality in both developed and developing countries (Bell and Davis, 2001). According to the World Health Organization (WHO), more than 90 percent of the global population breathes air that does not meet WHO standards, and seven million people die each year as a result of the negative health effects of polluted air (Fowler et al., 2020).

Increasing evidence has shown that air pollutants can cause systemic oxidative stress resulting in inflammatory and hemodynamic responses, causing multiple organ dysfunctions, including the brain (Araujo, 2010; Brook, 2005). It has been found that air pollution is associated with several neurological disorders, especially in children and the aging population (Cacciottolo et al., 2017; Chen and Schwartz, 2009; Lopuszanska and Samardakiewicz, 2020; Oliveira et al., 2019; Tallon et al., 2017). Such adverse impacts are not restricted to those who directly breathe in the pollutants, but also affect the growing foetuses whose mothers are exposed to polluted air. In-utero exposure to air pollutants can cause myriad adverse birth outcomes and increase the susceptibility to the development of certain diseases later in life (Gluckman et al., 2008). However, studies on early-life brain development and cognitive defects due to prenatal exposure to air pollutants are still limited.

This review summarised the current discoveries on how in-utero exposure to air pollutants influences early-life neural development and cognitive functions, and how sex affects the responses. We also discussed the potential mechanisms involved in this process.

2. The sources of air pollution and the major health impacts

Air pollution, particularly outdoor air pollution, has gained more and more attention in the past decades, which poses significant public health risks. The global increase in morbidity and mortality due to polluted air has brought substantial social and economic

costs (Costa, 2018; Lelieveld et al., 2015; Lelieveld et al., 2019). Pollutants emitted primarily by traffic and industrial fuel combustion contain a complex mixture of various substances, depending on the source and area, including several noxious gases (nitrogen oxides (NO_x), sulphur dioxide (SO_2), carbon oxides (CO_x), ozone (O_3), liquids, and particulate matters (PMs) (Costa et al., 2019). Because of the increased consumption of fossil fuels in both developed and developing countries, air pollution has become a major concern in both industrial areas and major cities, as global industrialisation and urbanisation have increased. (Bell and Davis, 2001; Mannucci and Franchini, 2017).

Tiny airborne particles in the polluted air, particularly solid PMs, can reach the lung alveoli where gas exchange occurs. Based on where they can reach in the respiratory tract, PM is classified according to the size, such as PM_{10} (particles less than 10 micrometres in diameter, thoracic particles) which deposits in the nose and throat, $PM_{2.5}$ (particles less than 2.5 micrometres in diameter, fine particles) which can enter the bronchial regions, and PM_1 (particles less than 1 micrometres in diameter, ultrafine particles) which goes even deeper into the alveoli (Brown et al., 2013; Franck et al., 2011; Xing et al., 2016). The fine and ultrafine particles are associated with the most significant burden on human health.

Following the exposure to heavily polluted air, respiratory responses, such as coughing and dyspnoea, are common, which became the primary focus of the early studies. However, fine and ultrafine particles can enter the bloodstream in the alveoli and exert direct adverse effects on the cardiovascular system, making air pollution one of the top risk factors for cardiovascular and cerebrovascular diseases (Lee et al., 2014). In addition, a growing body of studies has also linked air pollution to other adverse impacts, such as cancers and metabolic disorders (Clementi et al., 2019; Eze et al., 2015; Turner et al., 2020). Furthermore, increasing evidence from human and animal studies shows that air pollutants indirectly affect the central nervous system (CNS) by two means; 1) local inflammatory response in the lung tissues, which release pro-inflammatory cytokines to induce systemic inflammation to affect the brain (Block and Calderon-Garciduenas, 2009); 2) small size particles crossing the blood-air barrier in the alveoli and later blood-brain barrier via circulation to access glial cells and neurons in the brain. In humans, it has also been suggested that the inhaled pollutants can directly enter the brain through nasal olfactory bulbs before reaching the deep lung

sections due to their small sizes and migrate to remote brain regions (Balasubramanian et al., 2013; Cheng et al., 2016; Garcia et al., 2015; Hopkins et al., 2014; Lucchini et al., 2012). There, pollutants cause the inflammatory responses in resident inflammatory cells, such as perivascular macrophages microglia, releasing pro-inflammatory cytokines to affect nearly neurons (Kraft and Harry, 2011; Mumaw et al., 2016; Xu et al., 2013). The indirect and direct effects of pollutants on the brain can induce inflammatory responses and impair brain function (Babadjouni et al., 2017; Costa et al., 2020).

3. Foetal exposure to air pollution

Air pollution is particularly detrimental during pregnancy by harming the foetus resulting in poor birth outcomes, increasing the risk of lower respiratory tract infections, and in extreme cases, infant mortality (Goshen et al., 2020; Padula et al., 2020; Yang et al., 2020). Evidence has shown an increased risk of preterm birth associated with increased concentrations of air pollutants. However, two studies have shown that even exposure to low-level air pollution in the week before delivery can cause preterm birth (Ghosh et al., 2021; Siddika et al., 2020). In addition, two recent publications have also indicated that there is no safe level of PM exposure to human health (Danesh Yazdi et al., 2021; Khomenko et al., 2021). Therefore, any level of $PM_{2.5}$ pollution can be harmful to pregnant women and their unborn children.

The effects of exposure to air pollution at different stages of fetal development can vary, although, in humans, such exposure often occurs throughout the whole pregnancy as pregnant women unlikely to move houses during this period. According to human cohort studies, exposure to polluted air in the first trimester can interrupt placental formation leading to foetal underdevelopment, and increase the risks of pre-eclampsia and preterm birth (Michikawa et al., 2017). PM exposure during this stage may also affect later cognitive functions, since it is a critical window for neurogenesis, which needs to be examined in future studies. Exposure to polluted air in the second trimester may increase the risk of asthma, while exposure in the third trimester is associated with small for gestational age babies (Percy et al., 2019), allergic rhinitis (Deng et al., 2016; Lavigne et al., 2018). An animal study suggested PM exposure during the human equivalent of the third trimester impaired learning and short-term memory functions,

with males more affected than the females (Allen et al., 2014). In other studies, male rodents also showed increased depression-like, aggression, and deficits in social communication in response to continuous in-utero PM exposure, akin to observations in humans (Davis et al., 2013; Sobolewski et al., 2018; Yokota et al., 2016). Therefore, exposure to polluted air in all three trimesters is associated with adverse birth outcomes. How in-utero air pollution exposure influences foetal development is not fully understood, with two routes proposed, the direct and indirect impacts.

Recent studies have suggested that ambient fine PMs can cross the human placental barrier from the maternal circulation (Bongaerts et al., 2020; Bove et al., 2019). PMs presented in the foetal side of the placenta suggest their potential to circulate in foetal blood and directly affect all foetal organ systems (Bongaerts et al., 2020; Bove et al., 2019). On the other hand, inhaled air pollutants depositing in the mother's lung can induce oxidative stress and inflammatory response in the placenta to affect its functions (Kannan et al., 2006; Seltenrich, 2016; van den Hooven et al., 2012). As such, oxygen and nutrient transport to the foetus can be impaired to cause foetal underdevelopment and low birth weight (Cao et al., 2019; Rich et al., 2015; Zhao et al., 2021). The inflammatory cytokines in the maternal circulation may also be transported to the foetal blood to cause foetal systemic inflammatory responses, delaying foetal development (Kannan et al., 2006; Seltenrich, 2016; van den Hooven et al., 2012).

4. In-utero exposure to air pollution and brain health

The foetal period, as the very beginning of life, is a critical window for brain development. Adverse in-utero and early-life environmental conditions can significantly increase the susceptibility to certain neurological diseases later in life (Gluckman et al., 2008). Human epidemiological studies and animal studies strongly suggest that exposure to air pollution is associated with structural damage and functional impairment to the CNS (Costa et al., 2019). Epidemiologic studies have shown that prenatal exposure to certain air pollutants is associated with brain developmental and cognitive disorders (**Table 1**). Studies on several birth cohorts in New York City found that exposure to Polycyclic Aromatic Hydrocarbon (PAH)s during pregnancy is associated with a 6.8% reduction in body weight and a 3% reduction in head circumference at birth, and reduced white matter surface of the left

hemisphere in childhood (Perera et al., 2003; Perera et al., 2005). These developmental disorders in the brain resulted in a lower mental Development Index at age 3, lower intelligence quotient (IQ) scores at age 5, slower processing speed at age 7, as well as symptoms of anxiety, depression, and inattention at age 6-7 (Perera et al., 2006; Perera et al., 2012; Peterson et al., 2015). Another cohort study in Poland also reported that prenatal exposure to PAHs is associated with decreased IQ scores at age 5 and the abovementioned abnormal neurocognitive behaviours in the New York City cohort studies (Edwards et al., 2010; Jedrychowski et al., 2015; Perera et al., 2013). Animal models of prenatal PAH exposure are consistent with these human observations (Saunders et al., 2002; Wormley et al., 2004).

Exposure to polluted air is positively linked to the development of Autism Spectrum Disorder, a neurodevelopmental disorder characterised by impaired communication and social ability (Geschwind, 2011). Several epidemiological studies reported the association between prenatal air pollution exposure and the risk of developing Autism. In a case-controlled study named "Childhood Autism Risks from Genetics and the Environment (CHARGE)", exposure to traffic-related air pollution, NO_2 (odds ratio (OR): 1.81), PM_{10} (OR: 2.17) and $PM_{2.5}$ (OR: 2.08) during pregnancy was strongly associated with the pathogenesis of Autism compared to the control group (Kerin et al., 2018; Volk et al., 2013). Another cohort study recruited 148,722 birth information and regional air quality data in 1995-2006, found that risks of Autism were increased with pregnancy exposures to most toxins in polluted air, including butadiene, meta/para-xylene, lead and perchloroethylene, which provided population-based evidence that in-utero exposure to air pollution is linked to the increased risk of Autism (von Ehrenstein et al., 2014).

Air pollution is also a risk for other neurological disorders. A Korean Mother and Children Environmental Health (MOCEH) study found that prenatal exposure to high levels of PM_{10} was linked to abnormal Mental Developmental Index, and NO_2 exposure was linked to the impairment of psychomotor development between 1-2 years of age (Kim et al., 2014). In a Spanish study, maternal exposure to NO_2 during pregnancy adversely affected infant mental development, with impaired attention function at 4-5 years of age (Guxens et al., 2012; Sentis et al., 2017). Maternal exposure to $PM_{2.5}$ in the 3rd trimester has been shown to decrease corpus callosum volume, which is

associated with hyperactivity in children (Mortamais et al., 2019). Animal studies also confirmed that in-utero $PM_{2.5}$ exposure decreased the volumes of both lateral ventricle and corpus callosum in mice (Allen et al., 2017; Klocke et al., 2017). Studies in China found that maternal exposure to higher ambient PM_{10} levels in the first trimester can cause neural tube defects (OR: 1.57), and increase the risk of anencephaly if the exposure occurs three months before and after the conception (OR: 1.74) (Xia et al., 2020; Zhang et al., 2020). This suggests a critical window to ensure normal early neural development.

While molecular changes in the brain caused by in-utero exposure to air pollution is difficult to obtain in human, animal studies shed some light on the potential mechanisms leading to impaired motor-cognitive functions. Prenatal exposure to diesel exhaust particles in mice altered the expression of pro-inflammatory cytokines and N-methyl-D-aspartate receptor subunit in the hippocampus, associated with increased anxiety and spatial memory dysfunction in adult male offspring (Ehsanifar et al., 2019). Maternal exposure to a high dose of $PM_{2.5}$ impaired the development of the cerebral cortex in mice (Zhang et al., 2018). Prenatal exposure to low level $PM_{2.5}$ also caused aberrant hyperactivity of the dopamine pathway and suppression of the glycine pathway in the brain, which correlated with the hyper-activities in those mice (Cui et al., 2019). In rabbits, prenatal exposure to diesel exhaust PMs interrupted the homeostasis of neuromodulators in olfactory tissues, which impaired their smell function (Bernal-Meléndez et al., 2019).

5. Sex differences in response to in-utero exposure to air pollution

Sex dimorphism is commonly observed in many neurological disorders. Studies have shown that boys are more susceptible to the adverse effects of prenatal exposure to air pollution (especially in the 3rd trimester) on cognitive and behavioural disorders, such as the development of Autism (Jo et al., 2019; Raz et al., 2015). Animal studies also confirmed this male preference for Autism-like behaviours in response to in-utero exposure to air pollution (Church et al., 2018; Li et al., 2018). Another study on prenatal exposure to traffic-related black carbon showed that boys' memory function and learning ability are more affected than girls (Cowell et al., 2015).

Animal studies have also provided evidence on the possible risk of other neurological conditions. A recent study in mice showed depressive behaviour and decreased neurogenesis in the dentate gyrus of the hippocampus in male mice with in-utero PM exposure (Haghani et al., 2020). The male-specific neurodevelopmental disorder and cognitive impairment have been associated with transcriptome changes in serotonin signalling, endocytosis, Gαi, cAMP signalling, as well as inflammatory pathways (Haghani et al., 2020). In-utero exposure to high levels of PMs can also impair motor coordination and cause impulsive behaviour in males, by affecting several neurotransmitters in various brain regions, including dopamine, serotonin, and noradrenaline levels (Yokota et al., 2009; Yokota et al., 2013).

However, females are not unaffected by direct exposure to air pollution, especially in those genetically susceptible to certain neurological disorders. A Mexican cohort study showed that when exposing healthy children to high levels of ozone and $PM_{2.5}$, young girls with Apolipoprotein E (APOE) 4 heterozygous allele were at the highest risk of having low IQ scores (Calderon-Garciduenas et al., 2016). The limitation of this study is that it was unable to separate the prenatal and postnatal exposure, which may interact with each other to exaggerate the effects on cognitive function. The sex difference in response to air pollution may also be pollutant-type dependent. According to a study on acute respiratory disorders, ozone, NO_2, and $PM_{2.5}$ impact differently on females and males (Shin et al., 2021). Males are more affected by NO_2 and $PM_{2.5}$, and females are more susceptible to the adverse effects of ozone on respiratory disorders (Shin et al., 2021). However, how individual pollutant affects brain development and cognitive function is unclear in the setting of in-utero exposure, which can be focused on in future studies.

6. The potential mechanisms

Fine particles, especially PMs, can damage the blood-placental barrier to access foetal organs. In an animal study, following maternal exposure to a low dose of carbon black nanoparticle, the brain resident macrophages in perivascular areas were reduced, and the end-feet of astrocytes were swelling, which can impair the protective function of the blood-placental barrier, allowing PMs to enter the foetal brain (Onoda et al., 2014). In addition, in response to in-utero PM exposure, the expression of genes involved in

angiogenesis, cell migration, proliferation, chemotaxis, and growth factor production was changed in the brain of male mice offspring at 6 weeks of age (Onoda et al., 2017b). In adult mice offspring's brains, protein levels of presynaptic protein synaptophysin were also increased, associated with impaired spatial memory function (Kulas et al., 2018).

The potential mechanisms of how maternal air pollution exposure during pregnancy influences brain development and cognitive performance remain largely unknown. However, limited animal studies have identified inflammation, oxidative stress, and endoplasmic reticulum (ER) stress as potential mechanisms, which are also involved in other types of intrauterine toxins, such as tobacco cigarette smoke (Chen et al., 2021).

Neuroinflammation has been recognised as a leading risk factor associated with neurological diseases (Block et al., 2007). As a multifaced environmental toxin, inhaled air pollutants, such as PMs, by the mothers during pregnancy can induce both foetal systemic inflammatory response and neuroinflammation in the developing brain. The source of systemic inflammation may arise from the foetal lung, liver or cardiovascular system, which can be transferred into the brain (Block and Calderon-Garciduenas, 2009; Morris et al., 2021). Due to immature or impaired blood-brain barrier function, PM itself can enter the foetal brain to activate the inflammatory responses in the astrocytes and microglia, which subsequently release proinflammatory cytokines locally and activate the classical inflammatory pathways (Gomez-Budia et al., 2020; Kulas et al., 2018; Zheng et al., 2018), such as JNK and NF-κB (Kulas et al., 2018; Zheng et al., 2018). Inflammatory responses in the astrocytes and microglia can further impair oligodendrocytes to damage myelination in the white matter, leading to reduced white matter size (Allen et al., 2017; Klocke et al., 2017; Klocke et al., 2018; van Tilborg et al., 2016). Such responses can directly affect normal neural development, by inducing apoptosis, reducing neural density, affecting pruning, and impairing synaptic budding and plasticity (Ferro et al., 2021; Jiang et al., 2018; Sanz and Garcia-Gimeno, 2020; Szepesi et al., 2018).

In addition, the complex chemical composition of PM makes it possess strong oxidative potentials, which can induce the production of reactive oxygen species (ROS) in the mother's lungs and remote organs where they travel via circulation, including foetal organs (Daellenbach et al., 2020). Without a mature immune system and endogenous

antioxidant defence mechanism, direct PM exposure through foetal circulation is likely to induce oxidative stress responses in the foetal brain, resulting in abnormal neural development in certain brain regions, such as the hippocampus that affects learning and memory functions (Lee et al., 2018; Perrone et al., 2010). Both *in vivo* and *in vitro* studies have confirmed increased brain levels of reactive oxygen species in different cell types following exposure to air pollutants (Costa et al., 2017; Costa et al., 2020; Morris et al., 2021). The vulnerability of foetal and neonatal brains to oxidative stress has been well-reviewed in the literature, due to their high demand in energy turnover that generates a large amount of free radicals and immature redox signalling that counteracts increased oxidants (Buonocore et al., 2011; Cobley et al., 2018; Ikonomidou and Kaindl, 2011). Furthermore, oxidative stress can trigger inflammatory responses in astrocytes and microglia, which subsequently release proinflammatory cytokines locally and activate the inflammatory pathways (Gomez-Budia et al., 2020; Kulas et al., 2018; Zheng et al., 2018). On the other hand, neuroinflammation can further exacerbate oxidative stress. Thus, oxidative stress may play a vital role in the adverse impact of in-utero PM exposure on the development of neurological disorders.

As PMs are potent oxidants, the endogenous antioxidants produced by the mothers may not be sufficient to protect the unborn child (Daellenbach et al., 2020). A cohort study compared antioxidant levels in antecubital blood and cord blood from healthy pregnant women, which showed similar antioxidant capacity between maternal blood and cord blood (1.97 ± 0.50 vs 1.76 ± 0.50 mmol Trolox equiv/L, respectively) (Erdem et al., 2012). PM induced systemic oxidative stress in the mothers may overconsume their endogenous antioxidants (Wang et al., 2021). Indeed, another study demonstrated that maternal exposure to $PM_{2.5}$ can reduce the antioxidant capacity in foetal blood, making the foetus more vulnerable to $PM_{2.5}$ in foetal circulation (Lee et al., 2020). As such, increased inflammatory response and oxidative stress were also observed in the offspring with prenatal $PM_{2.5}$ exposure (Wang et al., 2021). Thus, maternal circulating antioxidants during pregnancy may not be sufficient to protect the foetus. While antioxidant treatment can reduce mitochondrial dysfunction related oxidative stress by PM exposure *in vitro* (Wang et al., 2021), no study has investigated whether such an approach during pregnancy can protect foetal brain development and promote normal neurocognitive behaviours in those with in-utero exposure to air pollution. A Brazilian study assessed the correlation between antioxidant intake (based on β-carotene,

vitamins (A, C, E), and trace minerals (zinc, magnesium, selenium)) during pregnancy and prenatal $PM_{2.5}$ exposure induced wheezing frequency (Chiu et al., 2022). While higher maternal intake of such micronutrients during pregnancy led to reduced wheezing numbers after birth, such practice cannot prevent prenatal PM exposure-associated asthma risks, but only reduce the severity (Chiu et al., 2022). Therefore, further investigation is needed to determine which antioxidant and at what dose range can prevent adverse health outcomes due to prenatal PM exposure, especially the neurocognitive effects.

ER stress is also considered one of the potential mechanisms of brain impairment following prenatal exposure to air pollution. ER stress is mainly induced by the accumulation of misfolded proteins in the ER membranes, which are unable to be cleared by the autophagy process. Protein misfolding is common with neuroinflammation. Inflammation leads to abnormal clearance of these misfolded proteins in the ER membrane, which in turn induces more inflammation and oxidative stress in glial cells (Onoda et al., 2020). One study found increased accumulation of β-sheet protein, mostly consisting of misfolded proteins, in the brain perivascular area with astrogliosis and denaturation of macrophages, suggesting impaired clearance (Onoda et al., 2017a). The increase in ER stress-related markers is also found in the macrophages and astrocytes in this brain area, which has been suggested as a risk of neurodegeneration in later life (Onoda et al., 2020). However, it is unclear whether ER stress also occurs in the neurons to directly damage their integrity. Nevertheless, long-term exposure to high levels of air pollutants, including $PM_{2.5}$, NO_2/NO_x, and CO, has been suggested as a strong risk factor for the development of dementia (Peters et al., 2019). An animal study also suggests that chronic exposure to even low-level PMs can be harmful to the brain by exacerbating Alzheimer's disease-related brain injury (Lee et al., 2021). In vitro study also confirmed that PM induced ER stress can also activate CHOP/Caspase12/DR5/Caspase8 pathway to induce apoptosis and neuronal death (Zhang et al., 2022). Future studies can investigate whether prenatal PM exposure can accelerate cognitive decline and early onset of dementia and neurodegenerative disorders in adulthood, such as Alzheimer's disease.

Direct PM exposure has been shown to impair the learning ability and memory function in both school-age children and elderlies aged 60 and above (Clifford et al., 2016).

However, no human or animal study has reported the potential intergenerational effects on neurodevelopmental and cognitive outcomes. An animal study using rabbits showed intergenerational effects of in-utero exposure to traffic pollution on the metabolic disorder in the 3rd generation (Valentino et al., 2016). Although without direct evidence, it can be postulated that epigenetic regulation may play a role in PM exposure caused intergenerational effects. $PM_{2.5}$ exposure is known to cause DNA methylation and histone acetylation (Ferrari et al., 2019; Ji and Khurana Hershey, 2012; Real et al., 2021). Several epigenome-wide analyses in cord blood from newborns with prenatal PM_{10} and $PM_{2.5}$ exposure found DNA methylation of genes involved in cell cycle, apoptotic, embryogenesis, postnatal development, neurotransmitter transport, ER stress, tumour suppression, lung function, and risk of asthma (Gruzieva et al., 2019; Isaevska et al., 2022; Park et al., 2022). Such study design can exclude the impact of postnatal direct inhalation of PMs by the newborns to more accurately reflect the prenatal/maternal effects. Nevertheless, DNA methylation at this early stage of life can affect foetal and postnatal development and be passed to the next generation via maternal nuclei or/and mitochondrial DNA to affect neurodevelopment and cognitive outcomes in future generations. However, there is no direct evidence linking epigenetic changes by prenatal PM exposure to abnormal brain function, representing a significant knowledge gap, in addition to the molecular mechanism of the intergenerational effects, which need to be addressed in future studies.

7. Conclusion and future perspectives

Air pollution is a significant threat to developing brains at the very beginning of life, even at low levels. Prenatal exposure to air pollutants adversely affects foetal neurodevelopment, with male offspring more susceptible to cognitive and behavioural disorders. Current guidelines for pregnant women still focus on nutrition balance and avoiding toxins like alcohol and tobacco cigarettes, without mentioning air quality. While policy-makers need to develop strategies to protect our air quality, health professionals and educators also need to raise public awareness of the importance of air quality to unborn children.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that influence the work in this paper.

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Table 1. Summary of human cohort studies on the effects of prenatal air pollution exposure

Pollutants	Location	Participants	Major conclusion	Reference
PAHs	New York, USA	Pregnant African and Dominican-American women	Prenatal exposure to PAHs adversely affects children's IQ scores, and is associated with slower processing speed, attention-deficit/hyperactivity disorder by disrupting the development of left hemisphere white matter.	(Perera et al., 2003) (Perera et al., 2005) (Perera et al., 2006) (Perera et al., 2009) (Peterson et al., 2015)
PAHs	Krakow, Poland	A cohort of pregnant Caucasian women enrolled in Krakow study	Prenatal exposure to high levels of PAHs is associated with decreased IQ scores at 5 years of age. The combination of prenatal exposure to high levels of PAHs and maternal demoralisation adversely affects children's behaviours. Breastfeeding (for at least 6 months) shows a protective effect against prenatal PAH exposure.	(Edwards et al., 2010) (Perera et al., 2013) (Jedrychowski et al., 2015)
Woodsmoke, CO	Rural western highland, Guatemala	39 mother-child dyads participated in RESPIRE/CRECER study From March to June 2010	Maternal CO exposures in the 3rd trimester is associated with child neuropsychological performance inversely	(Dix-Cooper et al., 2012)
NO_2, Benzene	Spain	Pregnant women from the INMA cohort	Prenatal exposure to air pollutants adversely affects mental development in infants.	(Guxens et al., 2012)

			The exposure to NO_2 is associated with impaired attentional function in children at 4-5 years of age.	(Sentis et al., 2017)
TRAP, NO_2, PMs	California, USA	ASD and control children from CHARGE study	Prenatal exposure to traffic-related air pollution, NO_2, and PMs is associated with Autism. NO_2 and PM_{10} exposure is associated with cognitive and adaptive functions in Autism patients.	(Volk et al., 2013) (Kerin et al., 2018)
PM_{10}, NO_2	Korea	520 mother–child pairs from MOCEH study in 2008	Prenatal exposure to air pollution results in delayed neurodevelopment in early childhood.	(Kim et al., 2014)
BC, $PM_{2.5}$	Eastern Massachusetts, USA	1,109 mother–child pairs in Project Viva cohort between 1999–2002	Prenatal exposure to traffic-related pollution negatively influences the performance across a range of cognitive domains in the age of 6.6-10.9 (mean, 8.0) years	(Harris et al., 2015)
NO_2, PMs	Rome, Italy	719 newborns in the GASPII project enrolled in 2003–2004	Prenatal exposure to NO_2 and traffic intensity was inversely associated with the verbal development	(Porta et al., 2016)
Air pollutants	Mexico	718 Mexican mother-child pairs	Prenatal exposure to air pollution is associated with impaired cognitive development trajectories in the first 7 years of life. Indoor environmental pollutants cause more adverse effects on cognitive development.	(Gonzalez-Casanova et al., 2018)
$PM_{2.5}$	Barcelona, Spain	Children enrolled in the BREATHE project	Prenatal exposure to $PM_{2.5}$ may be associated with decreased volumes of lateral ventricles and corpus callosum in children	(Mortamais et al., 2019)
$PM_{2.5}$	Southern California, USA	246420 mother-child pairs from pregnancy cohort study in California	Prenatal $PM_{2.5}$ exposure-associated Autism risk is stronger in boys	(Jo et al., 2019)
PM_{10}	Liaoning, China	Infants registered in Maternal and Child Health Certificate	PM_{10} exposure is positively associated with the risk of neural tube deformation and anencephaly during both	(Xia et al., 2020)

	Registry of Liaoning Province	preconception and early pregnancy	(Zhang et al., 2020)

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