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Review article

The influence of environmental particulate matter exposure during late gestation and early life on the risk of neurodevelopmental disorders: A systematic review of experimental evidences

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ABSTRACT

Particulate matter (PM) is a major component of ambient air pollution (AAP), being widely associated with adverse health effects. Epidemiological and experimental studies point towards a clear implication of AAP on the development of central nervous system (CNS) diseases. In this sense, the period of most CNS susceptibility is early life, when the CNS is maturing. In humans the last trimester of gestation is crucial for brain maturation while in rodents, due to the shorter gestational period, the brain is still immature at birth, and early postnatal development plays a significant role. The present systematic review provides an updated overview and discusses the existing literature on the relationship between early exposure to PM and neurodevelopmental outcomes in experimental studies. We included 11 studies with postnatal exposure and 9 studies with both prenatal and postnatal exposure. Consistent results between studies suggest that PM exposure could alter normal development, triggering impairments in short-term memory, sociability, and impulsive-like behavior. This is also associated with alterations in synaptic plasticity and in the immune system. Interestingly, differences have been observed between sexes, although not all studies included females. Furthermore, the developmental window of exposure seems to be crucial for effects to be observed in the future. In summary, air pollution exposure during development affects subjects in a time- and sex-dependent manner, the postnatal period being more important and being males apparently more sensitive to exposure than females. Nevertheless, additional experimental investigations should prioritize the examination of learning, impulsivity, and biochemical parameters, with particular attention provided to disparities between sexes.

1. Introduction

Ambient air pollution (AAP) is one of the major sources of harmful environmental toxicity in the modern world. Globally, in 2012, 3 million deaths were attributable to AAP (WHO, 2016). Among different types of air pollutants, particulate matter (PM) is receiving much attention because of its detrimental effects on human health. PM consists of a complex mixture of solid and liquid particles of organic and inorganic substances suspended in the air, which can be from natural sources (e.g. volcanoes and fires) or man-made sources (e.g. diesel usage, road traffic and industrial activities) (Costa et al., 2019). The major components of PM are sulfates, nitrates, elemental and organic carbon, organic compounds (such as polycyclic aromatic hydrocarbons), biological compounds and metals (such as iron and copper) (Kim et al., 2015).

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PM is classified according to its aerodynamic diameter; PM_{10} comprises coarse particles with a diameter <10 μm, $PM_{2.5}$ comprises fine particles with a diameter <2.5 μm and $PM_{0.1}$ comprises ultrafine particles with a diameter <0.1 μm (Kim et al., 2015). Both size and composition determine the route of entry and distribution throughout the body.

Inhalation is the main route of exposure for air pollutants (Costa et al., 2019), although they can also enter the human body through ingestion and dermal absorption (Thompson, 2018). Fine and ultrafine particles can enter by the olfactory epithelium or nerves, respectively, arriving at different brain regions, such as the cerebral cortex and the cerebellum, among others. On the other hand, PM deposited in the lungs, can be translocated into the blood and from there to the brain (Costa et al., 2019). Generally, the smaller a particle is, the deeper it will penetrate. For this reason, the fine and ultrafine particles are the ones that may cause major adverse effects. In fact, $PM_{2.5}$ has been the mostly studied air pollutant associated with increased mortality and morbidity (Arias-Pérez et al., 2020).

Numerous epidemiological studies in humans and in animal models evidenced that air pollution contributed to the development of pulmonary, cardiovascular and metabolic diseases (Feng et al., 2016). What is important is that the negative impact of AAP on the central nervous system (CNS) and its implication on CNS diseases is supported by a growing amount of experimental and epidemiological evidence, especially when the exposure to this pollution takes place in the first phases of its development. Among others, it may contribute to microglial activation and neuroinflammation, which will lead to the onset of neurodevelopmental and/or neurodegenerative diseases, such as autism spectrum disorder and Parkinson's disease, respectively (Cory-Slechta et al., 2023).

The development of the CNS is a period of great vulnerability to insults, in which cell proliferation, migration and differentiation contribute to the formation of the distinct brain structures. During this period, in which crucial processes are taking place, toxic exposure may lead to structural and functional effects that persist and produce a long-life impact on the subject (Costa et al., 2019).

Currently, air quality is measured periodically at different stations across different countries. The data obtained, which is known as Air Quality Index (AQI), allows the population to know the contamination levels that they are exposed to. In Europe, the AQI is based on the concentration of five key pollutants, including PM_{10}, $PM_{2.5}$, ozone, nitrogen dioxide and sulfur dioxide ("European Air Quality Index — European Environment Agency," 2021). However, it is difficult to establish a direct relationship between the level of environmental contamination, the levels of exposure to the same and harmful effects in humans. In this sense, experimental studies with animal models may contribute to establishing the risk of exposure and to identify biological targets and pathways implicated in adverse outcomes.

Given all the above, we conclude that the developing brain is much more sensitive to toxic insults than the mature one. For this reason, in this review we focus on biochemical, structural and behavioral effects derived from the impact of AAP on the nervous system generated by the postnatal and both prenatal and postnatal exposure to PM in mice or rats.

2. Material and methods

2.1. Search strategy

The bibliographical search for this systematic review was completed in September 2022 based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement (Shamseer et al., 2015). The following databases were consulted in order to find relevant studies published to date: Scopus, Web of Science and PubMed. The keywords used for the search were "particulate matter", "mouse or rat", "neuro" and "postnatal exposure". Reviews and human studies were excluded. The search formula in Scopus was: (TITLE-ABS-KEY ("particulate matter") AND ALL (mouse) OR ALL (rat) AND ALL (neuro*) AND ALL (postnatal AND exposure) AND NOT TITLE-ABS-KEY (human) AND (EXCLUDE (DOCTYPE,"re"). The symbol * in the previous formula is used to search all terms that begin with a word, allowing for the retrieval of any terms that share the same prefix. Furthermore, a hand-searching was performed from the referenced articles of the selected studies. This review and its protocol were registered on the PROSPERO database (Registration Code: CRD42023418043).

2.2. Eligibility criteria

The purpose of this review was to gather the experimental data published in relation to postnatal exposure to PM and its effects on CNS development; studies including both prenatal and postnatal exposure were also reviewed. Articles written in languages other than English were excluded, as were reviews. Articles studying the effects of PM exposure on other organs, such as the kidneys, lungs and heart, and not including the CNS, were excluded. Study subjects could be mice or rats; studies on humans or other animal models were excluded. Exposure had to include early postnatal development (preweaning), which is equivalent to human third trimester of gestation and 2–3 years old, being a crucial period for CNS development (Semple et al., 2013). Studies involving chronic exposure until adulthood or an exposure beyond weaning were excluded. Moreover, we also included those articles that used diesel particulate material for the exposure, because it is an important component of PM. Articles studying exposure to cigarette smoke were excluded.

2.3. Study selection and data extraction

Two independent reviewers analyzed all the identified articles in order to avoid bias thanks to the IT tool "Rayyan" (Ouzzani et al., 2016). Any disagreements were discussed until achieving consensus. In the first screening, titles and abstracts were read in order to exclude those articles that didn't meet our interest criteria. Then, the articles included in this first selection were analyzed in depth.

2.4. Quality assessment

The quality of individual studies was evaluated using SYRCLE'S Risk of Bias Tool (Hooijmans et al., 2014), an adapted version of the Cochrane risk of bias tool, whose aim is to assess methodological quality and consider aspects of bias that play an important role in animal experiments.

In this regard, the SYRCLE'S Risk of Bias tool consists of six quality parameters: selection, performance, detection, attrition, reporting and other biases. It assigns a maximum of six points for selection, four points for performance, four points for detection, four points for attrition, four points for reporting and four points for others (for a total of 26 points). Therefore, the total quality index score was ranked as follows: 0 to 8, 9 to 17 and 18 to 26, these being low (L), medium (M) and high (H) quality, respectively.

3. Results

3.1. Selection of studies and bias assessment

The whole search strategy is represented in the following flow diagram (Fig. 1). First, we identified 176 articles with the three databases used. In addition, 9 articles were added by hand-searching. After removing duplicates, a total of 151 articles were screened according to the title and abstract of each one. At this point, we also applied different selection filters (see eligibility criteria of material and methods section for explanation in detail). Then, 68 articles were read thoroughly and, finally, 20 articles were selected for this review: 11 correspond to

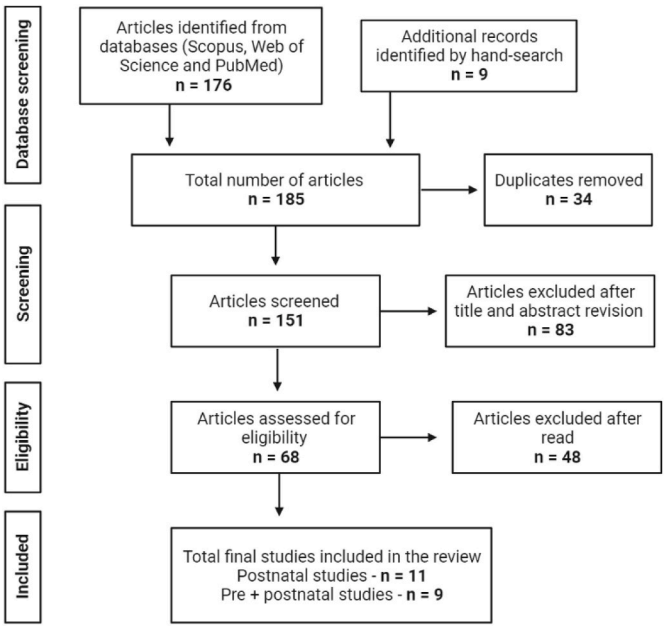

Fig. 1. PRISMA flow diagram.

postnatal exposure and 9 include both pre and postnatal exposures.

Regarding bias assessment (see Tables 1 and 2), 36% of the articles included in the postnatal section had low bias and 64% had medium bias, while in the prenatal and postnatal section 33% of the articles showed low bias and 67% had medium bias. None of the articles in either section presented a high bias score.

3.2. Effects of postnatal exposure to PM

Eleven articles were selected to review the effect of postnatal exposure to PM: eight of them used mice (Allen et al., 2013, 2014a, 2014b; Cory-Slechta et al., 2018, 2019; Morris-Schaffer et al., 2019a, 2019b; Sobolewski et al., 2018) as animal model and the rest used rats (Li et al., 2018; Liu et al., 2019; Zhou et al., 2021). Next, we describe the results, focusing on developmental milestones, behavioral, cognitive, biochemical and molecular variables.

3.2.1. Studies in mice

The same group, led by Cory-Slechta at the University of Rochester (New York), conducted all the studies in mice included in this section. All studies used C57BL/6J as mice model and the period of exposure was from postnatal day (PND) 4 to PND7 and from PND10 to PND13 (4 h/day) in whole-body exposure chambers. Seven articles work with ultrafine ambient particulate matter ($PM_{0.1}$), six of them obtained by the Harvard University Concentrated Ambient Particle System (HUCAPS) (Allen et al., 2013, 2014a, 2014b; Cory-Slechta et al., 2018, 2019; Sobolewski et al., 2018), and the other one used ultrafine elemental carbon particles (UFCP) produced in an argon-filled chamber (Morris--Schaffer et al., 2019a); only one article used isolated diesel particulate material (Morris-Schaffer et al., 2019b). Diesel exhaust (DE) is an important component of $PM_{2.5}$ and $PM_{0.1}$ (Costa et al., 2019). It is important to point out that the exposure doses vary considerably between studies, ranging from 15 to 240 $\mu g/m^3$/day.

Differences in body weight (BW) were analyzed in four different articles. Generally, they didn't observe differences in BW after postnatal PM exposure (Allen et al., 2014b; Morris-Schaffer et al., 2019a; Sobolewski et al., 2018); only the article using diesel particulate material found lower BW in exposed males at adolescence (Morris-Schaffer et al., 2019b). Also, ventriculomegaly was evaluated in four studies. In one study (Allen et al., 2014a) it was observed at PND14 and PND55 in males but not in females. Moreover, two studies noticed ventriculomegaly in adult males (PND270) (Allen et al., 2014a; Cory-Slechta et al., 2019). This effect was detected after postnatal exposure to $PM_{0.1}$ at doses above 96 $\mu g/m^3$/day. The other two studies did not notice ventriculomegaly at PND14, after an exposure dose of UFCP of 50 $\mu g/m^3$/day or after diesel particulate material exposure (Morris-Schaffer et al., 2019a, 2019b).

Cognitive function was tested using young mice in six articles. Only two studies reported delayed learning during the initial phase of acquisition in operant chambers at doses higher than 44 $\mu g/m^3$/day (Cory-Slechta et al., 2018, 2019); the remaining articles did not observe treatment-related differences at doses between 15 and 240 $\mu g/m^3$/day (Allen et al., 2013, 2014b; Morris-Schaffer et al., 2019a, 2019b). Impairments in short-term memory assessed in the Novel Object Recognition (NOR) test were seen in three studies: in one of them (Allen et al., 2014b), males and females were affected, while the other two studies only reported deficits in males (Cory-Slechta et al., 2018, 2019). Finally, only one study did not find any differences (Morris-Schaffer et al., 2019a).

Locomotor activity was evaluated in five studies. For the most part, no significant treatment-related differences were found in locomotor activity (Allen et al., 2013; Morris-Schaffer et al., 2019b); only Cory-Slechta et al. (2018) reported male-specific locomotor alterations. Two different studies noticed a female-specific decrease in vertical activity (Allen et al., 2014b) and a steeper slope (Morris-Schaffer et al., 2019a) in an Open Field (OF) test. Impulsivity was examined in four studies: two of them with a fixed interval schedule conducted in operant chambers and the other two with different reinforcement schedules (DRL). Three studies showed impulsive-like behavior (Allen et al., 2013, 2014b; Cory-Slechta et al., 2018). However, one study (Morris-Schaffer et al., 2019a) failed to find treatment-related differences in the DRL. Anxiety was only studied in two articles with the Elevated Plus Maze (EPM) test, in which no differences were observed (Morris-Schaffer et al., 2019a; Sobolewski et al., 2018).

Two articles assessed social behavior with a social conditioned place preference (SCPP) test, in which no differences were observed (Morris-Schaffer et al., 2019a; Sobolewski et al., 2018). Moreover, one of them (Sobolewski et al., 2018) underwent a Three-Chamber Social Test (3CST) and they found male-specific alterations in sociability as well as in social novelty preference.

Apart from studying PM exposure in the postnatal period, Allen et al. (2013, 2014b) studied the effects of a re-exposure at adulthood in previously exposed mice in the postnatal period. They reported that there is an additional vulnerability when there are cumulative exposures. In the first study, they did not include females in the experiment, but in the second they did. Interestingly, they concluded that males showed greater sensitivity to early postnatal exposures in the fixed interval schedule, while females are more sensitive to adult exposures.

Different biochemical and molecular changes in different brain sections and in serum were analyzed in six studies. They focused mainly on inflammation, astrocyte and microglial activation, and neurotransmitters profile. They found changes in the inflammatory profile (interleukin 1-beta (IL-1β), tumor necrosis factor alpha (TNFα) and IL-6), and alterations in neurotransmitters, such as dopamine (DA), norepinephrine (NE), serotonin (5-HT), glutamate (Glu), glutamine (Gln) and γ-aminobutyric acid (GABA), among others.

Five studies included immunostaining techniques to assess brain tissue structure and cellular organization. In order to determine the astrocyte and microglial status, two studies analyzed glial fibrillary acidic protein (GFAP) and ionized calcium-binding adapter molecule 1 (IBA1), respectively, in different brain sections at different periods of age: at PND14 and PND55 (Allen et al., 2014a) and at PND270 (Allen et al., 2014b). A persistent microglial activation was observed in the white matter of males at the periods mentioned above (Allen et al., 2014a, 2014b), while astrogliosis was observed in females at PND14 (Allen et al., 2014a) and at PND270 (Allen et al., 2014b), but not at PND55. Moreover, two other articles studied GFAP immunostaining at

Table 1
Summary of exposure protocol and results observed in mice and rats postnatally exposed to PM. Bias assessment included: low bias studies highlighted in green (L) and medium bias studies highlighted in yellow (M).

Reference & Bias	Exposure protocol			Results
	Animal model & age at exposure	Molecule size & origin	Doses, exposure via & experimental groups	Developmental milestones (DEV) Behavioral and cognitive variables (BEH) Biochemical and molecular variables (BCH)
Allen et al. (2013) Bias → M	Mice (C57BL/6J). **PND4-7 + PND10-13** *Reexposed in 2 groups at PND56 for 4 days.	$PM_{0.1}$ Ambient UFP concentrated by HUCAPS.	96,4 μg/m³/day. WBI (4h/day). FA/FA (n= 8) FA/CAPS (n= 8) CAPS/FA (n= 7) CAPS/CAPS (n= 7)	**DEV.** No reference. **BEH.** Operant behavior (PND71): No differences in learning. CAPS-mice presented impulsive behavior relative to free but delayed rewards. More evident in CAPS/CAPS mice. No differences in locomotor activity as a measure of hyperactivity. **BCH.** No reference. *Females not included.
Allen et al. (2014b) Bias → L	Mice (C57BL/6J). **PND4-7 + PND10-13** *Reexposed in 2 groups at PND56 for 4 days.	$PM_{0.1}$ Ambient UFP concentrated by HUCAPS.	15-240 μg/m³/day. WBI (4h/day). FA/FA (n= 9M/8F) FA/CAPS (n= 9M/8F) CAPS/FA (n= 12M/12F) CAPS/CAPS (n= 12M/11F)	**DEV.** No differences in BW. **BEH.** Activity (PND71-78): CAPS/FA females ↓ vertical activity compared to FA/FA females. No differences in males. FI-schedule in operant chambers (PND93-240): CAPS-mice showed impulsive behavior; males showed more sensitivity to early postnatal exposure, while females to adult exposures. NOR (PND180): CAPS/FA mice had short-term memory impairments. **BCH.** PND60: CAPS/FA males ↓ serum corticosterone levels than FA/FA males. PND270: All CAPS-treated males ↓ corticosterone and CAPS females ↑ corticosterone levels. FC → (CAPS/FA). Males and females: ↓ NE, and ↑ Glu, Gln and GABA; Males: ↓ Gln:Glu ratio. HPC → (CAPS/FA). Males: ↑ Glu; Females: ↑ NE and Gln:Glu ratio. STR → (CAPS/FA). Males: ↑ DOPAC and DA TO, and ↓ NE, 5-HT, DA, HVA and 5-HIAA; Females: ↑ NE. IBA1: ↑ in FC and CC of CAPS-males; no differences in females. GFAP: ↑ in FC of CAPS-females; no differences in males.
Allen et al. (2014a) Bias → M	Mice (C57BL/6J). **PND4-7 + PND10-13**	$PM_{0.1}$ Ambient UFP concentrated by HUCAPS.	96 μg/m³/day. WBI (4h/day). FA sacrificed PND14 (n= 8-12) FA sacrificed PND55 (n= 8-12) CAPS sacrificed PND14 (n= 8-12) CAPS sacrificed PND55 (n= 8-12)	**DEV.** Ventriculomegaly in CAPS-males, but not in females (confirmed at PND14, PND55, and at PND270 in mice form another group). **BEH.** No reference. **BCH.** Males → PND14: ↑ Glu (HPC) and DA TO (MB, FC); PND55: ↑ Glu (HPC), DA TO (MB, FC) and NE (FC). Females → PND14: ↓ GABA (HPC) and DA TO (MB), ↑ HVA and DA (MB), DA TO and 5-HT (HPC); PND55: ↓ GABA (HPC), ↑ HVA and DA (MB), 5-HT (HPC) and NE (FC). No differences in OB or hypothalamus. Males → PND14: ↓ GFAP in CC and HPC, ↑ IBA1 in AC; PND55: ↓ GFAP in CC, ↑ IBA1 in AC (persistent microglial response in white matter) and HPC. Females → PND14: ↑ GFAP in CC, HPC and AC (transient astrocytic response). Males → PND14: ↓ IL-6 (HPC), IL-1β and TNFα (STR), IL-1β and TNFα (MB); PND55: ↓ IL-6 (HPC), IL-1β and TNFα (STR), ↑ IL-1β and TNFα (MB). Females → PND14: ↓ IL-6 (STR) (IL-6 in FC not detected), ↑ IL-1β and TNFα (MB); PND55: ↓ IL-6 (FC), ↑ IL-6, IL-1β and TNFα (MB). No differences in OB or cerebellum.
Sobolewski et al. (2018) Bias → M	Mice (C57BL/6J). **PND4-7 + PND10-13**	$PM_{0.1}$ Ambient UFP concentrated by HUCAPS.	45 μg/m³/day. WBI (4h/day). FA (n= 8-12/sex) UFP (n= 8-12/sex)	**DEV.** No differences in BW. **BEH.** 12 months. Male-specific alterations in 3CST. No differences in EPM and SCPP. **BCH.** PND14: UFP-males ↓ testosterone levels than FA-males. No differences between females. PND120: No differences. No differences in corticosterone concentrations.
Cory-Slechta et al. (2018) Bias → L	Mice (C57BL/6J). **PND4-7 + PND10-13**	$PM_{0.1}$ Ambient UFP concentrated by HUCAPS.	45 μg/m³/day. WBI (4h/day). FA (n= 10-12/sex) CAPS (n= 10-12/sex)	**DEV.** No reference. **BEH.** From 1 to 8 months. Male-specific deficits in NOR, memory and learning impairments in early acquisition in multiple schedule of repeated learning; DRL deficits in the first sessions (transient impulsive behavior). Male-specific locomotor alterations. **BCH.** No reference.
Morris-Schaffer et al. (2019b) Bias → L	Mice (C57BL/6J). **PND4-7 + PND10-13**	Diesel particulate material (NIST Standard	100 μg/m³/day. WBI (4h/day). FA (n= 16/sex) NIST (n= 16/sex)	**DEV.** NIST-males ↓ BW during adolescence; no differences in females. Ventriculomegaly not present (PND14). **BEH.** PND60. No treatment-related differences in locomotor activity and FI schedule.

Abbreviations: Anterior commissure (AC), Aluminum (Al), Body weight (BW), Brain-derived neurotrophic factor (BDNF), Concentrated ambient particles (CAPS), Corpus callosum (CC), Differential reinforcement of low rate (DRL), 3,4-Dihydroxyphenylacetic acid (DOPAC), Dopamine turnover (DA TO), Elevated plus maze (EPM), Filtered air (FA), Iron (Fe), Fixed interval (FI), Forced swimming (FS), Frontal cortex (FC), Glial fibrillary acidic protein (GFAP), Glutamate (Glu), Glutamine (Gln), Growth associated protein-43 (GAP43), Harvard University Concentrated Ambient Particle System (HUCAPS), Hippocampus (HPC), 5-Hydroxyindoleacetic acid (5-HIAA), Homovanillic acid (HVA), Interleukin (IL), Ionized calcium-binding adapter molecule 1 (IBA1), Midbrain (MB), Norepinephrine (NE), Novel object recognition (NOR), Nucleus accumbens (NAc), Olfactory bulb (OB), Particulate matter (PM), Phosphorylated cAMP response element binding protein (p-CRB), Postnatal day (PND), Postsynaptic density-95 protein (PSD95), Serotonin (5-HT), Social conditioned place preference (SCPP), Social novelty preference (SNP), Striatum (STR), Synaptophysin protein (SYP), Three-chamber social test (3CST), Tumor necrosis factor (TNF), Ultrafine elemental carbon particles (UFCP), Ultrafine particle (UFP), Whole-body inhalation (WBI), Zinc (Zn).

PND14. One of them did not find any differences in GFAP at a UFCP exposure dose (50 μg/m³) below those used in the previous articles (100 μg/m³) (Morris-Schaffer et al., 2019a). The other article exposed mice to diesel particulate material and reported a decrease of GFAP in the hippocampus of females, and an increase in the frontal cortex and corpus callosum of males (Morris-Schaffer et al., 2019b). The myelination pattern was assessed in two studies by immunostaining the myelin basic protein. One study, only performed in males, showed a reduction in

Table 2
Summary of exposure protocol and results observed in mice and rats prenatal and postnatally exposed to PM. Bias assessment included: low bias studies highlighted in green (L) and medium bias studies highlighted in yellow (M).

Reference & Bias	Exposure protocol			Results
	Animal model & age at exposure	Molecule size & origin	Doses, exposure via & experimental groups	Developmental milestones (DEV) Behavioral and cognitive variables (BEH) Biochemical and molecular variables (BCH)
Win-Shwe et al. (2016) Bias → L	Mice (Balb/C). **GD14-PND21**	DE and DE-SOA. DE generated by 81-diesel engine; DE-SOA generated mixing DE with ozone.	113,19 ± 19,5 μg/m^3/day (DE) and 130,90 ± 31,2 μg/m^3/day (DE-SOA). WBI (5h/day, 5 days/week). FA (n= 12) DE (n= 12) DE-SOA (n= 12)	**DEV.** No differences in BW and brain weight. **BEH.** PND22. DE and DE-SOA mice showed decreased sociability and poor social novelty preference (3CST) and social interaction impairments. No anxiety-like behavior observed in light and dark test. **BCH.** PND23-24. Hypothalamus → In DE and DE-SOA, ↑ glutamate secretion. In DE-SOA, ↓ estrogen receptor α (compared to FA) and oxytocin receptor (compared to DE) mRNA; ↑ COX2 and HO1 mRNA compared to FA. No differences in IL-1β and TNFα mRNA. *Females not included.
Nway et al. (2017) Bias → M	Mice (C3H/HeN and C3H/HeJ). **GD14-PND10**	DE and DE-SOA. DE generated by 81-diesel engine; DE-SOA generated mixing DE with ozone.	85,57 ± 9,17 μg/m^3/day (DE) and 106,84 ± 12,70 μg/m^3/day (DE-SOA). WBI (5h/day, 5 days/week). FA (n= 8*) DE (n= 8*) DE-SOA (n= 8*) *litter/sex/genotype	**DEV.** No reference. **BEH.** PND11. Mice exposed to DE or DE-SOA showed deficits in spatial learning in an olfactory-based spatial learning test. No differences in odor discrimination and motor function test. **BCH.** PND11. In HPC. C3H/HeN male exposed to DE and DE-SOA ↑ NMDA receptor subunits NR1 and NR2B, COX2 and IBA1 mRNA compared to FA and C3H/HeJ males. No differences in TNFα and HO1 mRNA. No differences in females.
Church et al. (2018) Bias → M	Mice ($B_6C_3F_1$). **GD0.5-17 + PND2-10**	$PM_{2.5}$ Collected by Versatile Aerosol	135,8 ± 13,17 μg/m^3/day. WBI (GD 6h/day, PND 2h/day).	**DEV.** No differences in litter size, growth and BW. **BEH.** 20-week-old. In 3CST, CAPS mice showed reductions in social approach, but not in social recognition. Male-specific reduction in RSIT. ↑ repetitive grooming behavior in males, not in females. No treatment-
		Concentration Enrichment System.	FA (n= 13M/13F) CAPS (n= 15M/16F)	effect on anxiety behavior (EPM). No treatment-related differences in motor activity (OF). **BCH.** No reference.
Chang et al. (2018) Bias → M	Mice (C57BL/6J). **GD0-PND21**	DE. Generated by Yanmar YDG5500 diesel generator.	250-300 μg/m^3/day. WBI (6h/day, 5 days/week). FA (n= 16-9M/16-8F) DE (n= 14-9M/13-7F)	**DEV.** No differences in BW or size. DE-males showed ↓ USV compared to FA-males; DE-mice emitted more unstructured calls (PND6). **BEH.** 6-8 weeks old. In 3CST, no differences in sociability, but females showed inability to differentiate social novelty. Male-specific reduction in RSIT. In olfactory habituation/ dishabituation test, DE mice failed to habituate to the repeated presentation of odor. Repetitive behavior in DE-mice observed in T-maze and MBT. **BCH.** No reference.
Chang et al. (2019) Bias → M	Mice (C57BL/6J). **GD0-PND21**	DE. Generated by Yanmar YDG5500 diesel generator.	250-300 μg/m^3/day. WBI (6h/day, 5 days/week). FA (n= 5-10) DE (n= 5-10)	**DEV.** No reference. **BEH.** No reference. **BCH.** PND3. ↑ IL-6 mRNA; ↑ signal transducer and activator of transcription 3 activation and DNA methyltransferase 1 mRNA, and ↓ reelin mRNA. No differences in reelin at PND21 or PND60. PND60. immunohistochemical analysis revealed an altered cortical lamina organization. Generally, males ↑ sensitive to the effects of DE exposure.
Emam et al. (2020) Bias → M	Rats (Wistar). **GD0-PND21**	$PM_{2.5}$ Echo $PM_{2.5}$ Low Volume Sampler (TCR Tecora Italy).	43,82 ± 21,12 μg/m^3/day. WBI (12h/day, 5 days/week). FA (n= 8-10) PGE (n= 8-9) GE (n= 8-13)	**DEV.** No reference. **BEH.** PND29-46. No differences in locomotor activity (OF). PGE rats showed ↓ social novelty (3CST). Repetitive behavior and/or restricted behavioral patterns observed in PGE and GE rats (Y-maze and MBT). **BCH.** PND22. PGE rats ↓ catalase activity, glutathione and oxytocin receptor levels in all brain regions (AMG, CBM, HPC and FC). GE rats ↓ catalase activity in HPC and FC, glutathione in AMG and CBM, and oxytocin receptor in all brain regions. *Females not included.
Nephew et al. (2020) Bias → L	Rats (Sprague Dawley). **GD0-PND21**	$PM_{2.5}$ Collected from a Boston highway tunnel	173,0 ± 27,9 μg/m^3/day. WBI (5h/day, 5 days/week).	**DEV.** No differences in dam or pup BW, litter size and milk intake. **BEH.** PND32-40. PM rats exhibited higher anxiety (EPM), impaired cognition (nest building performance) and decreased social behavior. No differences in MBT.

Abbreviations: Amygdala (AMG), Body weight (BW), Cerebellum (CBM), Concentrated ambient particles (CAPS), Cyclooxygenase 2 (COX2), Diesel engine exhaust (DE), DE origin secondary organic aerosol (DE-SOA), Elevated plus maze (EPM), Filtered air (FA), Frontal cortex (FC), Gaseous pollutants (GE), Gestational day (GD), Glial fibrillary acidic protein (GFAP), Heme-oxygenase 1 (HO1), Hippocampus (HPC), Interleukin (IL), Ionized calcium-binding adapter molecule 1 (IBA1), Marble burying test (MBT), Novel object recognition test (NOR), N-methyl-D-aspartate (NMDA), Open field (OF), Particulate matter (PM), PM and GE (PGE), Postnatal day (PND), Reciprocal social interaction task (RSIT), Three-chamber social test (3CST), Tumor necrosis factor (TNF), Total suspended particles (TSP), Ultrasonic vocalizations (USV), Whole-body inhalation (WBI).

myelination when the concentration of $PM_{0.1}$ was greater than 96 μg/m^3/day (Cory-Slechta et al., 2019). However, no effects were observed at 50 μg/m^3/day of UFCP in either males or females (Morris-Schaffer et al., 2019a).

Three articles analyzed the neurotransmitter profile in different brain sections, and they found an imbalance in the physiological levels of the main excitatory and inhibitory neurotransmitters, which was different between articles and between different brain sections (see Table 1 for detailed results). Thus, treatment-related alterations were reported in the levels of Glu, Gln, GABA, NE, DA and 5-HT, mainly in the

frontal cortex, hippocampus and midbrain. It is worth mentioning that they observed sex-dependent variations. The inflammatory profile was studied only in one article (Allen et al., 2014a), indicating altered levels of IL-1β, TNFα and IL-6 at both PND14 and PND55 in the striatum, hippocampus, midbrain and cortex, which was also different between sexes.

Serum determinations were done in two articles to test endocrine function: both analyzed serum corticosterone and one of them included testosterone levels. In the first one, no differences were found in corticosterone concentrations either at PND14 or at 12 months of age (Sobolewski et al., 2018); in the other study, exposed males had persistent lower corticosterone levels (PND60 and PND270), while exposed females had higher levels at PND270 (Allen et al., 2014b). Regarding testosterone (T) levels, a significant drop was found in exposed males at PND14 (Sobolewski et al., 2018).

Brain metal dyshomeostasis was assessed in one study (Cory-Slechta et al., 2019). Elevated levels of iron (Fe), sulfur (S), copper, calcium and aluminum and low levels of manganese and zinc were found in brains of postnatal PM-exposed mice. Moreover, male-specific increases in the levels of serum oxidized glutathione (GSSG) and in the number of dead cells in the nucleus accumbens (NAc) were reported.

3.2.2. Studies in rats

The remaining studies used rats and differed in the method of exposure to $PM_{2.5}$. Two of them used intranasal instillation, the exposure period being from PND3 to PND15 (Liu et al., 2019) and from PND8 to PND22 (Li et al., 2018); and the other used inhalation of outdoors air in acrylic cages from PND1 to PND21 (Zhou et al., 2021). Another difference between the studies is that the first two used Sprague Dawley rats and the last one Wistar rats. Although all studies worked with $PM_{2.5}$ collected from AAP, they were collected from different cities in China. The intranasal instillation in both cases was made with two doses: low-dose (2 mg/kg bw) and high-dose (10 and 20 mg/kg bw, respectively). The doses were estimated according to the average concentrations of $PM_{2.5}$ of their cities, which are calculated by measuring the $PM_{2.5}$ concentration levels in a very busy street over a period of 4–5 months approximately. As regards the low-dose exposed groups, in both studies the $PM_{2.5}$ dose corresponds to 41–43 μg/day. Meanwhile, the exposure levels for whole body exposures in the acrylic cages were 100 $\mu g/m^3$/day, approximately.

Two authors who studied differences in BW observed different results: on the one hand, a transient decrease of average BW was found in the high-dose group during the developmental period (Liu et al., 2019); on the other hand, no treatment-related differences were seen (Zhou et al., 2021). Moreover, Li et al. (2018) measured ultrasonic vocalizations (USV) at PND16 and found a decrease in the number of vocalizations in PM-exposed pups, with a dose-dependent relationship.

Cognitive endpoints were evaluated in two studies. Impaired spatial learning and memory, as evaluated in the Morris Water Maze (MWM) test, were observed in immature (PND28) rats exposed at high dose, but not in mature (PND60) ones (Liu et al., 2019). Moreover, Li et al. (2018) also found impairments in short-term memory in immature rats measured with the NOR test.

In terms of behavioral outcomes, Liu et al. (2019) noticed anxiety-like symptoms in an EPM test in immature and mature rats exposed to low and high doses of PM, and depressive-like symptoms in the Forced Swimming (FS) test in mature rats exposed at high dose. Finally, two studies assessed social behavior in the 3CST in immature rats. One of them reported poor social interaction and social novelty impairments in high-dose exposed males (females were not studied) (Li et al., 2018), while the other only reported social novelty impairments in both sexes (Zhou et al., 2021).

In addition to behavioral testing, these three articles also studied different proteins and gene expression related to astrocyte and microglial activation, synaptic plasticity and inflammatory profile. Li et al. (2018) reported astrocyte and microglial activation in a dose-dependent manner, by means of gene expression and protein levels of GFAP and IBA1, respectively.

With regard to the number and structure of synapses, the three studies that analyzed this aspect agreed that damage is caused by PM exposure. One study reported a decreased number of synapses and impaired synaptic ultrastructure in the hippocampal region, being more evident in immature than in mature rats (Liu et al., 2019). This study also noticed a decrease in the levels of several synaptic proteins. In this sense, Zhou et al. (2021) studied epigenetic changes and found alterations in the methylation pattern of genes that codify for proteins related to synaptic functions. They reported an increased methylation of MeCP2 and Shank3 genes in immature exposed rats, which correlated with a decreased expression of both genes and protein levels. This was corroborated in other article that analyzed Shank3 expression and protein level (Li et al., 2018). It was also observed that females had lower levels of tri-methylation of lysine 27 on histone H3 (H3K27me3) associated with transcriptional repression (Zhou et al., 2021).

Finally, Li et al. (2018) also analyzed different proinflammatory cytokines at PND22. IL-1β and TNFα were elevated in the hippocampus and frontal cortex of low and high exposed groups, while IL-6 was only elevated in the high-dose group.

3.3. Effects of a prenatal and postnatal exposure to PM

Nine articles were selected to review the effects of prenatal and postnatal exposure to PM. Five of them used mice (Chang et al., 2018, 2019; Church et al., 2018; Nway et al., 2017; Win-Shwe et al., 2016) as animal model and the rest used rats (Berg et al., 2020; Emam et al., 2020; Nephew et al., 2020; Patten et al., 2020). In this case, all studies worked with inhaled $PM_{2.5}$ collected from environmental pollution or generated DE and exposed in whole-body exposure chambers.

3.3.1. Studies in mice

Studies in mice encompassed a period of exposure between gestational day (GD) 0 and PND21 and the majority worked with generated DE, with doses between 80 and 300 $\mu g/m^3$/day; just one worked with collected environmental $PM_{2.5}$ (Church et al., 2018), with doses above 130 $\mu g/m^3$/day. It is worth mentioning that there is heterogeneity between the mice models used, which were Balb/C (Win-Shwe et al., 2016), C3H/HeN (TLR4 intact) and C3H/HeJ (TLR4 mutated) (Nway et al., 2017), $B_6C_3F_1$ (Church et al., 2018) and C57BL/6J (Chang et al., 2018, 2019).

Regarding developmental effects, no differences were found in BW in any of the three studies that analyzed it (Chang et al., 2018; Church et al., 2018; Win-Shwe et al., 2016). Only Chang et al. (2018) studied USV at PND6 and observed fewer USV in males exposed to DE compared to control males, while DE-exposed mice of both sexes emitted less frequency-step calls and more unstructured calls.

As regards social behavior, only three studies assess this aspect with 3CST, and their findings were very similar. Impaired sociability and poor social novelty preference were observed in exposed male mice (females were excluded from this study) evaluated at PND22 (Win-Shwe et al., 2016) and at twenty weeks of age (Church et al., 2018). On the other hand, Chang et al. (2018) observed female-specific deficits in social novelty and male-specific reduction in reciprocal social interaction task at the age of 6–8 weeks. This study also observed repetitive behavior in a T maze and a Marble Burying Test (MBT) in both sexes. No treatment-related differences were observed in locomotor activity (Church et al., 2018) and anxiety-like behavior (Church et al., 2018; Win-Shwe et al., 2016), assessed with the EPM test and with the light and dark test, respectively. Furthermore, one study evaluated an olfactory-based spatial learning. Males and females of both genotypes (C3H/HeN and C3H/HeJ) showed deficits; no differences in odor discrimination and motor function test were found (Nway et al., 2017).

Gene expression was assessed in brain samples extracted at PND3 (Chang et al., 2019), PND11 (Nway et al., 2017) and PND23-24

(Win-Shwe et al., 2016). At the same time, it was shown that estrogen receptor α and oxytocin receptor (OXTR) mRNA were significantly decreased in the DE-derived secondary organic aerosol (SOA) exposed group; while cyclo-oxygenase 2 (COX2) and heme-oxygenase 1 (*Ho1*) mRNA were upregulated (Win-Shwe et al., 2016). In addition, some NMDA receptor subunits, *Cox2* and *Iba1* mRNA were increased in C3H/HeN males exposed to DE and DE-SOA; but no differences were found on *Ho1* mRNA or TNFα (Nway et al., 2017). Moreover, IL-6 and DNA methyltransferase 1 (DNMT1) mRNA levels were increased in exposed neonatal pup brains, while reelin mRNA levels were decreased (Chang et al., 2019). Signal transducer and activator of transcription 3, a modulator of DNMT1, was more active in exposed mice compared to control. No differences were found in inflammatory cytokine (IL-1β and TNFα) expression. Moreover, Glu secretion increased remarkably in mice exposed to DE or DE-SOA (Win-Shwe et al., 2016).

3.3.2. Studies in rats

Two of the four studies using rats made the exposure from GD0 to PND21 in whole-body exposure chambers and differed in their concentration of $PM_{2.5}$: Nephew et al. (2020) worked with a concentration of 200 μg/m^3/day, while Emam et al. (2020) worked with a considerably lower concentration of approximately 44 μg/m^3/day. These investigations had sex bias, due to the fact that in the first one only males were evaluated, while in the other study females were excluded from behavioral testing. On the other hand, the two remaining studies are based on the same study protocol but with different results published in each one, and they made the exposure from GD14 to PND47/51 in a major freeway tunnel system (Berg et al., 2020; Patten et al., 2020). Something to keep in mind is that the two latest studies used an exposure beyond weaning, and including adolescence.

Regarding developmental milestones, no differences were found in pup weight (Berg et al., 2020; Nephew et al., 2020), litter size and milk intake (Nephew et al., 2020) between exposed and control groups. Curiously, Berg et al. (2020) had a control group located in the laboratory and they found differences between this group and the exposed and control groups located in the tunnel system, not only in body weight, but also in early physical development and neurological reflexes, which were delayed. Moreover, they discovered that exposed males showed less USV at PND5 (Berg et al., 2020).

Three studies conducted behavioral testing between PND29 and PND48. No differences in locomotor activity were found in the OF test (Berg et al., 2020; Emam et al., 2020). Normal sociability, but decreased social novelty preference, was observed in the 3CST (Emam et al., 2020), and similarly, deficits in social behavior were observed when assessing the rat's behavior (Nephew et al., 2020). Surprisingly, Berg et al. (2020) evidenced altered social interaction in both control and exposed groups in the tunnel system with a reciprocal social interaction task. They also observed normal novel object preference, assessed with NOR, and normal learning and memory, assessed in Pavlovian fear conditioning (Berg et al., 2020). In one study, repetitive behavior was noticed in exposed rats in the MBT and the Y-maze test (Emam et al., 2020); while in the other study, no differences were detected in the MBT (Nephew et al., 2020). Moreover, increased anxiety and impaired cognition were also observed in those animals exposed to high doses of PM, assessed in EPM and in nest building performance tests, respectively (Nephew et al., 2020).

Some cytokine and growth factor levels were analyzed in serum at PND21 by Nephew et al. (2020). However, they only reported a significant decrease in basal levels of IL-18 and vascular endothelial growth factor in exposed rats. Oxidative stress was assessed by Emam et al. (2020) by measuring the antioxidant catalase (CAT) activity and glutathione (GSH) in different brain regions. OXTR was also assessed. Rats exposed to $PM_{2.5}$ and gaseous pollutants showed decreased CAT activity, GSH and OXTR levels in all brain regions analyzed. Meanwhile, GE rats presented a decreased CAT activity (hippocampus and frontal cortex), GSH (amygdala and cerebellum) and OXTR levels (all brain regions) (Emam et al., 2020). Patten et al. (2020) observed enhanced IBA1-marked cells and less GFAP immunoreactivity at PND51-55 in hippocampus samples of exposed rats. Moreover, only exposed females showed increased IL-10 levels and reduced lateral ventricular volume. Regarding proliferation and differentiation of neurons in the granule cell layer, exposed males showed increased doublecortin, an immature neuronal marker, while exposed females showed increased nuclei, a mature neuronal marker.

4. Discussion

All the articles included in this review were specifically focused on exposure to PM during the postnatal period. In rodent models, exposure during PND1 to PND21 could be equivalent to the third trimester of gestation and the first 2–3 years of age in humans (Semple et al., 2013), which indeed are the most sensitive periods when it comes to exposure to air pollution (Rice and Barone, 2000). Numerous studies demonstrate that neural development extends from the embryonic period to adolescence. Interestingly, in rodents, the maturation of the nervous system occurs principally during postnatal development, while in humans, the most important period is the prenatal. Depending on the specific temporal window of exposure to environmental pollution during development, processes such as proliferation, migration, differentiation or synaptogenesis, could be disrupted, leading to different functional, biochemical or morphological signs of neurotoxicity (Rice and Barone, 2000).

We included a total of 20 articles from 10 different laboratories studying endpoints related to CNS biochemistry, morphology and function. It is worth mentioning that all the studies corresponding to postnatal exposure in mice were carried out by the same group from the University of Rochester (New York), with some discrepancies in the results between studies. Curiously, the exposure period in this group was from PND4-7 and PND10-13, meaning that they included a break in exposure during the developmental period, which was not the case in the rest of studies reviewed.

As regards the doses evaluated, these ranged between 15 and 300 μg/m^3/day for whole-body exposure and between 2 and 20 mg/kg bw for intranasal instillation. These doses were calculated based on the average concentration of PM in the cities in question. Therefore, these doses will show meaningful results that could be extrapolated to what is expected to be observed in humans. It is worth noting that, for postnatal exposures in mice, all studies used $PM_{0.1}$, except for one that works with diesel particulate material alone and one that works with UFCP (a primary constituent of ambient $PM_{0.1}$); while all studies in rats administered $PM_{2.5}$ or DE. However, no noticeable differences were found with regards to the type of pollutant used in the studies.

Even though there are some studies that excluded females from the experiment, most studies that analyzed both males and females suggest that males are more sensitive to PM exposure, but there are still some endpoints that have not been tested in females. Accordingly, a prospective cohort study made in children reported that boys seem to be more susceptible to air pollution in terms of cognitive development, although both boys and girls were affected (Sunyer et al., 2015a).

Epidemiological studies in humans suggest that there is a relationship between AAP exposure during pregnancy (Kim et al., 2016, 2016r, 2016met al., 2005) and/or during the first year of age (Kim et al., 2016) and BW, which tends to be lower when exposure to $PM_{2.5}$ occurs during the postnatal period. Furthermore, some studies showed a positive association between weight and $PM_{2.5}$ exposure in infants and toddlers up to 2 years of age, where predominantly boys, but also girls, exhibit more rapid postnatal weight gain (Fleisch et al., 2015; Vanoli et al., 2022). In our review only one study reported a tendency towards low BW at PND28 in rats postnatally exposed intranasally to high doses of $PM_{2.5}$ (Liu et al., 2019); but no differences were reported for rats (Zhou et al., 2021) or mice (Allen et al., 2014b; Sobolewski et al., 2018) upon whole-body exposure, with the exception of one study that found a

decrease in BW of male mice in adolescence (Morris-Schaffer et al., 2019b). In this last study they used exposure with just diesel particulate material, which cannot be compared to the other studies in the same way.

It must be noted that epidemiological studies included the whole period of development (pre and postnatal), but none of the 5 studies that evaluated BW in the whole developmental period found changes in BW (Berg et al., 2020; Chang et al., 2018; Church et al., 2018; Nephew et al., 2020; Win-Shwe et al., 2016). Thus, based on discrepancies between studies, it must be indicated that studies in rodents don't fit in with epidemiological studies in humans. This is of concern, as it may be the case that these animal models might not be sensitive enough to study this hallmark. This is an important point to consider regarding the validity of the model if we are going to extrapolate data to humans.

Ventriculomegaly is the enlargement of at least one of the two cerebral ventricles and when it is severe it may be accompanied by poor neurodevelopment outcomes (Laskin et al., 2009). Two out of four articles that studied the presence of ventriculomegaly in mice after postnatal exposure, found a persistent ventriculomegaly at doses above 96 $\mu g/m^3$/day in males (Allen et al., 2014a; Cory-Slechta et al., 2019). However, no differences were observed in mice exposed at lower doses of UFCP (Morris-Schaffer et al., 2019a) or with diesel particulate material alone (Morris-Schaffer et al., 2019b). Reported data suggests that males are more sensitive than females and there is a dose-dependent effect of PM for this endpoint. To date, there is no reference in the general population linking exposure to PM and ventriculomegaly.

In the articles reviewed, behavioral test in rats were done in young immature animals, while in mice they were conducted when they were adult, from PND60 approximately. Functional endpoints evaluated correspond to communication, anxiety, activity, social behavior, impulsivity, learning and memory. To contextualize, a rat brain at PND28 (immature rat) is comparable to the brain of a 2-year-old child, and a rat brain at PND60 (mature rat) is comparable to the brain of a sexually mature human (Williams et al., 1999).

Epidemiological studies in humans suggested that high exposure to air pollutants during development is associated with severe behavioral problems (Ni et al., 2022; Shin et al., 2022). A systematic review in humans has clearly demonstrated a correlation between $PM_{2.5}$ exposure in early postnatal periods and autism spectrum disease (Lin et al., 2022), which is mainly characterized by deficits in social recognition and communication, as well as repetitive behavior patterns (Lord et al., 2018). Moreover, air pollution exposure during fetal life is associated with an impaired inhibitory control, meaning that children may behave impulsively (Guxens et al., 2018). In this sense, ultrasonic vocalizations were measured in three studies to assess social communication and they found less vocalizations in male rats (females excluded) postnatally exposed to PM (Li et al., 2018) and also in male mice (Chang et al., 2018) and male rats (Berg et al., 2020) prenatal and postnatally exposed. Furthermore, in our review some studies found an impairment in sociability and no preference for social novelty in rats (Li et al., 2018; Zhou et al., 2021) and male mice (Sobolewski et al., 2018) postnatally exposed to $PM_{2.5}$ or $PM_{0.1}$, respectively, with a 3CST. When the exposure occurred in the prenatal and postnatal period, sociability alterations were also observed in male mice mostly (Chang et al., 2018; Church et al., 2018; Win-Shwe et al., 2016) and male rats (Emam et al., 2020; Nephew et al., 2020), because in most of the studies females were excluded. Repetitive behavior was also noticed with prenatal and postnatal exposure in mice (Chang et al., 2018; Church et al., 2018) and male rats (Emam et al., 2020); only one study did not find any differences (Nephew et al., 2020). Furthermore, impulsive-like behavior was observed in most of the studies that analyzed this parameter (Allen et al., 2013, 2014b; Cory-Slechta et al., 2018), although one study did not find differences, probably because the exposure was with UFCP and with a relatively low dose (Morris-Schaffer et al., 2019a). In humans, impulsivity has been associated with a disrupted myelination pattern in white matter (Zhu et al., 2023), which is important to note as decreased myelination was found in mice after postnatal $PM_{0.1}$ exposure (Cory-Slechta et al., 2019). Something interesting to mention here is that two authors that used prenatal and postnatal exposure found decreased levels of OXTR in exposed mice (Win-Shwe et al., 2016) and rats (Emam et al., 2020). Curiously, oxytocin levels impact different aspects of social behavior (Kirsch, 2015) and it has been demonstrated that disturbed levels of OXTR may considerably contribute to the development of autism spectrum disorder (Pierzynowska et al., 2023) and impulsive behavior (Bozorgmehr et al., 2020). This is another fact that could explain the impaired social behavior and should be further investigated in relation to postnatal exposure of PM.

Locomotor activity, as a hyperactivity measure, was not affected by postnatal or both prenatal and postnatal exposure (Allen et al., 2013, 2014b; Berg et al., 2020; Church et al., 2018; Emam et al., 2020; Morris-Schaffer et al., 2019a, 2019b; Nephew et al., 2020). Only one study found male-specific locomotor alterations in mice postnatally exposed (Cory-Slechta et al., 2018). However, epidemiological evidence in humans indicated that $PM_{2.5}$ exposure during the 7th month of pregnancy to early life after birth is related with hyperactive behavior in 3 year-old children (Liu et al., 2022) and attention deficit and hyperactivity disorder in children, being boys more affected than girls, although it failed to reach significance (Chang et al., 2022).

A recently published review reported an association between air pollution and affective disorders or suicide in children and adolescents, but not a direct causality (Xie et al., 2023). Experimental studies reviewed are not conclusive about the impact of air pollution on anxiety as there is heterogeneity between the results observed. Two studies observed anxiety in immature and mature exposed rats (Liu et al., 2019; Nephew et al., 2020), but other articles did not observe any differences in exposed mice (Church et al., 2018; Morris-Schaffer et al., 2019a; Sobolewski et al., 2018; Win-Shwe et al., 2016). Regarding depression, only one study assessed reported increased depressive-like behaviors in the FS test in mature rats exposed at high-dose (Liu et al., 2019). For this reason, these behaviors deserve to further analysis in future investigations.

A growing number of epidemiological studies in humans point towards a relationship between high levels of traffic-related air pollutants and children's cognitive development (Basagaña et al., 2016; Ni et al., 2022; Sunyer et al., 2015b). Experimental studies assessing learning and memory in specific tests found impairments in spatial learning in rats postnatally exposed (MWM test) (Liu et al., 2019) and in mice prenatal and postnatally exposed (olfactory-based spatial learning test) (Nway et al., 2017); only the study carried out in the major freeway tunnel system did not find any differences in learning and memory using the Pavlovian fear conditioning test (Berg et al., 2020).

In addition, impairments in short-term memory (NOR test) were found in treated male mice (Allen et al., 2014b; Cory-Slechta et al., 2018, 2019) and male rats (females excluded) (Li et al., 2018) postnatally exposed. Moreover, in the MWM test, memory deficits were also noticed in rats postnatally exposed (Liu et al., 2019). Only two studies did not report differences in mice postnatally exposed (Morris-Schaffer et al., 2019a) and in rats prenatal and postnatally exposed (Berg et al., 2020), but in both cases exposure doses were relatively low compared with the other studies. What may be extracted from these data is that PM exposure at high doses may alter learning and memory. Thus, more studies are required, with specific behavioral tests, such as MWM, using both males and females at different doses to corroborate these findings, as epidemiological studies in humans evidenced cognitive impairments.

Thus, even at low-level concentrations of PM (45 $\mu g/m^3$) cognitive alterations are seen; specifically, males presented affectations in learning and memory functions, while females presented motivational shifts (Cory-Slechta et al., 2018). In this sense, a multi-cohort study carried out on children also suggested that behavioral problems were more pronounced in girls, while cognitive impairments were only observed in males (Ni et al., 2022). Nonetheless, in general terms it can be observed that these alterations are dose-dependent: the higher the

dose, the more severe the effects (Cory-Slechta et al., 2019; Li et al., 2018; Liu et al., 2019). Moreover, Allen et al. (2013, 2014b) observed that there is additional vulnerability when there is re-exposure to PM in adulthood. In fact, it has been seen that males are more affected in the postnatal period, while females are more affected in adulthood. Therefore, evidence proves that PM exposure affects subjects in a sex and time-dependent manner.

In order to elucidate which are the mechanisms implicated in PM neurotoxicity, numerous biochemical and molecular studies were performed on brain tissues, primarily, but also on serum samples.

The hippocampus is one of the most highly connected areas of the brain and it is emerging as a brain connector of cognition and emotion. In fact, impaired hippocampal function is associated with cognitive alterations in depressed patients (Femenía et al., 2012). In the same way, anxiety and depression are related with damaged hippocampal synaptic plasticity (Bannerman et al., 2014; Lu et al., 2019). In this sense, Liu et al. (2019) analyzed a representative area of the hippocampus and found impaired synaptic ultrastructure and reduced synaptic plasticity in exposed rats, with more damage in immature than in mature ones. Parallel, anxiety-like symptoms were seen in exposed immature and mature rats, whereas depressive-like symptoms were observed in high-exposed mature rats. Furthermore, high-dose exposed immature rats presented an impairment of spatial learning and memory, which was not observed in mature rats. Thus, these results suggest that after a long period of separation from $PM_{2.5}$ exposure, cognitive abilities and synaptic plasticity may be restored or compensated. In the same way, Zhou et al. (2021) found epigenetic alterations affecting proteins related to normal synaptic function in female rats, where the expression of genes that promotes synaptic functions were reduced. Li et al. (2018) also found a downregulation of the *Shank3* gene in male rats, which codifies the Shank3 protein and plays an important role in the synaptic process (Uchino and Waga, 2013). To sum up, there is strong evidence indicating an altered synaptic plasticity induced by postnatal exposure to PM.

Evidence suggests that ultrafine particles generate a chronic microglial stimulation and an altered innate immune response (Sunyer et al., 2015b). Microglia are the resident immune cells of the CNS and play an important role in the regulation of neuronal activity and synaptic plasticity, but also in learning and memory in the mature brain. Proinflammatory cytokines have variable effects on plasticity: overexpression of TNFα triggers long term potentiation of synaptic plasticity, meanwhile IL-1β impairs it in the CA1 region (Cornell et al., 2022). Further, astrocytes are glial cells that play essential roles in synapse development and plasticity, and they are crucial for neurological function and behavior (Sofroniew, 2020).

In the reviewed articles, PM exposure (doses above 96 $\mu g/m^3$/day) induces a persistent microglial response in white matter and astrocytic disfunction in males postnatally exposed to high doses of PM, in both mice and rats (Allen et al., 2014a, 2014b; Li et al., 2018). When exposure occurred during the prenatal and postnatal periods, microgliosis was also observed in mice (Nway et al., 2017) and rats (Patten et al., 2020). Moreover, a transient astrocytic response to PM was observed in females at doses above 96 $\mu g/m^3$/day (Allen et al., 2014a, 2014b), but no differences were observed at 50 $\mu g/m^3$/day (Morris-Schaffer et al., 2019a). Although Morris-Schaffer et al. (2019b) found contrary results in their study, they did an exposure with isolated diesel particulate alone and they concluded that it was not sufficient to induce protracted adverse outcomes. In the same way, two studies (Nway et al., 2017; Win-Shwe et al., 2016) assessed COX2, which is a key enzyme implicated in pro-inflammatory activities in the brain (Minghetti, 2004), and they found an upregulation of it in brain samples of mice prenatal and postnatally exposed. Thus, most of the studies evaluated points towards an altered neuroinflammatory response, which in turn can also interfere with myelination, which was also observed after PM exposure (Cory-Slechta et al., 2019).

Under normal conditions, serum corticosterone increased with age in males and females. Allen et al. (2014a) found that males postnatally exposed to PM had lower serum corticosterone levels, meanwhile treated females had generally higher levels. Although Sobolewski et al. (2018) did not find any differences in corticosterone levels, we must consider that in this study the exposure doses were relatively low compared with other studies. However, the possible effects on this system deserve further investigation, specially to assess corticosterone levels under different conditions, such as stress, and at different moments during the day, as corticosterone levels follow a circadian rhythm (Jones et al., 2021).

Cory-Slechta et al. (2019) observed increased levels of Fe and S in the brains of mice postnatally exposed to PM (samples were obtained on PND14) and also male-specific increases in GSSG. Meanwhile, one study with prenatal and postnatal exposure observed decreased levels of glutathione in some brain tissues (Emam et al., 2020). These findings point towards oxidative stress and ferroptosis as possible mechanisms implicated in brain damage. Ferroptosis is a type of Fe-dependent cell death characterized by a large amount of Fe accumulation and lipid peroxidation during this process. Recent studies have elucidated that ferroptosis plays an important role in the development of multiple diseases, such as nervous system diseases (Li et al., 2020). In fact, a recent study suggests that ferroptosis could be responsible for inducing toxic effects in neuronal cells exposed to $PM_{2.5}$ (Xiong et al., 2022). Moreover, during the detoxification of lipid peroxides, glutathione is oxidized (Griffith, 1999). These results jointly suggest an increment of oxidative stress, and are in accordance with previous studies in humans, which already demonstrated that prenatal exposure to air pollution may alter fetal neurodevelopment by inducing oxidative stress and inflammation (Ni et al., 2022).

We have to keep in mind that most of the articles work with different PM samples concentrated from the local area where the researchers live. Thus, some differences between studies can be related to the different compositions of PM, which depend on the characteristics of each area.

In general, when comparing the results observed in studies with postnatal exposure with those from studies with prenatal and postnatal exposure, no major differences are observed. This could point to the fact that the postnatal period could be the most important period when it comes to the neurotoxic effects observed under exposure to PM.

5. Conclusion

Collectively, the evidence from these experimental studies points towards a clear impact of early PM exposure on brain development and behavior, with protracted effects in adulthood and with susceptibility to developing neurodevelopmental disorders. Among the effects found, the main ones were impaired social novelty, impulsive-like behavior and short-term memory impairments. Furthermore, synaptic plasticity and immune response were also affected. We can also conclude that the impact of PM exposure differs depending on the specific developmental window of exposure in which it occurs, and that it is sex dependent. This last fact is especially relevant as too few studies considered it; therefore, more research including both sexes is required. However, the clearest conclusion we can reach is that further investigation is needed in order to elucidate the molecular mechanisms by which exposure to ambient air pollutants contributes to the development of certain neurodevelopmental and neurodegenerative diseases with the aim to be able to introduce specific therapeutic interventions that could palliate the detrimental effects.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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References

Allen, J.L., Conrad, K., Oberdörster, G., Johnston, C.J., Sleezer, B., Cory-Slechta, D.A., 2013. Developmental exposure to concentrated ambient particles and preference for immediate reward in mice. Environ. Health Perspect. 121, 32–38. https://doi.org/10.1289/EHP.1205505.

Allen, J.L., Liu, X., Pelkowski, S., Palmer, B., Conrad, K., Oberdörster, G., Weston, D., Mayer-Pröschel, M., Cory-Slechta, D.A., 2014a. Early postnatal exposure to ultrafine particulate matter air pollution: persistent ventriculomegaly, neurochemical disruption, and glial activation preferentially in male mice. Environ. Health Perspect. 122, 939–945. https://doi.org/10.1289/EHP.1307984.

Allen, J.L., Liu, X., Weston, D., Prince, L., Oberdörster, G., Finkelstein, J.N., Johnston, C. J., Cory-Slechta, D.A., 2014b. Developmental exposure to concentrated ambient ultrafine particulate matter air pollution in mice results in persistent and sex-dependent behavioral neurotoxicity and glial activation. Toxicol. Sci. 140, 160–178. https://doi.org/10.1093/toxsci/kfu059.

Arias-Pérez, R.D., Taborda, N.A., Gómez, D.M., Narvaez, J.F., Porras, J., Hernandez, J.C., 2020. Inflammatory effects of particulate matter air pollution. Environ. Sci. Pollut. Control Ser. 27 (34 27), 42390–42404. https://doi.org/10.1007/S11356-020-10574-W, 2020.

Bannerman, D.M., Sprengel, R., Sanderson, D.J., Mchugh, S.B., Rawlins, J.N.P., Monyer, H., Seeburg, P.H., 2014. Hippocampal synaptic plasticity, spatial memory and anxiety. Nat. Rev. Neurosci. 15 (3 15), 181–192. https://doi.org/10.1038/nrn3677, 2014.

Basagaña, X., Esnaola, M., Rivas, I., Amato, F., Alvarez-Pedrerol, M., Forns, J., López-Vicente, M., Pujol, J., Nieuwenhuijsen, M., Querol, X., Sunyer, J., 2016. Neurodevelopmental deceleration by urban fine particles from different emission sources: a longitudinal observational study. Environ. Health Perspect. 124, 1630–1636. https://doi.org/10.1289/EHP209.

Berg, E.L., Pedersen, L.R., Pride, M.C., Petkova, S.P., Patten, K.T., Valenzuela, A.E., Wallis, C., Bein, K.J., Wexler, A., Lein, P.J., Lein, P.J., Silverman, J.L., 2020. Developmental exposure to near roadway pollution produces behavioral phenotypes relevant to neurodevelopmental disorders in juvenile rats. Transl. Psychiatry 10. https://doi.org/10.1038/s41398-020-00978-0.

Bozorgmehr, A., Moayedi, R., Sadeghi, B., Ghadirivasfi, M., Joghataei, M.T., Shahbazi, A., 2020. A novel link between the oxytocin receptor gene and impulsivity. Neuroscience 444, 196–208. https://doi.org/10.1016/J.NEUROSCIENCE.2020.07.033.

Chang, Y.C., Chen, W.T., Su, S.H., Jung, C.R., Hwang, B.F., 2022. PM2.5 exposure and incident attention-deficit/hyperactivity disorder during the prenatal and postnatal periods: a birth cohort study. Environ. Res. 214, 113769 https://doi.org/10.1016/J.ENVRES.2022.113769.

Chang, Y.C., Cole, T.B., Costa, L.G., 2018. Prenatal and early-life diesel exhaust exposure causes autism-like behavioral changes in mice. Part. Fibre Toxicol. 15 https://doi.org/10.1186/S12989-018-0254-4.

Chang, Y.C., Daza, R., Hevner, R., Costa, L.G., Cole, T.B., 2019. Prenatal and early life diesel exhaust exposure disrupts cortical lamina organization: evidence for a reelin-related pathogenic pathway induced by interleukin-6. Brain Behav. Immun. 78, 105. https://doi.org/10.1016/J.BBI.2019.01.013.

Church, J.S., Tijerina, P.B., Emerson, F.J., Coburn, M.A., Blum, J.L., Zelikoff, J.T., Schwartzer, J.J., 2018. Perinatal exposure to concentrated ambient particulates results in autism-like behavioral deficits in adult mice. Neurotoxicology 65, 231. https://doi.org/10.1016/J.NEURO.2017.10.007.

Cornell, J., Salinas, S., Huang, H.Y., Zhou, M., 2022. Microglia regulation of synaptic plasticity and learning and memory. Neural Regen. Res. 17, 705. https://doi.org/10.4103/1673-5374.322423.

Cory-Slechta, D.A., Allen, J.L., Conrad, K., Marvin, E., Sobolewski, M., 2018. Developmental exposure to low level ambient ultrafine particle air pollution and cognitive dysfunction. Neurotoxicology 69, 217–231. https://doi.org/10.1016/j.neuro.2017.12.003.

Cory-Slechta, D.A., Sobolewski, M., Marvin, E., Conrad, K., Merrill, A., Anderson, T., Jackson, B.P., Oberdorster, G., 2019. The impact of inhaled ambient ultrafine particulate matter on developing brain: potential importance of elemental contaminants. Toxicol. Pathol. 47, 976–992. https://doi.org/10.1177/0192623319878400.

Cory-Slechta, D.A., Merrill, A., Sobolewski, M., 2023. Air pollution–related neurotoxicity across the life span. Annu. Rev. Pharmacol. Toxicol. 63, 143. https://doi.org/10.1146/ANNUREV-PHARMTOX-051921-020812.

Costa, L.G., Cole, T.B., Dao, K., Chang, Y.C., Garrick, J.M., 2019. Developmental impact of air pollution on brain function. Neurochem. Int. 131, 104580 https://doi.org/10.1016/J.NEUINT.2019.104580.

Emam, B., Shahsavani, A., Khodagholi, F., Zarandi, S.M., Hopke, P.K., Hadei, M., Behbahani, H., Yarahmadi, M., 2020. Effects of $PM_{2.5}$ and gases exposure during prenatal and early-life on autism-like phenotypes in male rat offspring. Part. Fibre Toxicol. 17 https://doi.org/10.1186/s12989-020-0336-y.

European Air Quality Index — European Environment Agency, 2021. https://www.eea.europa.eu/themes/air/air-quality-index accessed 8.25.22.

Femenía, T., Gómez-Galán, M., Lindskog, M., Magara, S., 2012. Dysfunctional hippocampal activity affects emotion and cognition in mood disorders. Brain Res. 1476, 58–70. https://doi.org/10.1016/J.BRAINRES.2012.03.053.

Feng, S., Gao, D., Liao, F., Zhou, F., Wang, X., 2016. The health effects of ambient PM2.5 and potential mechanisms. Ecotoxicol. Environ. Saf. 128, 67–74. https://doi.org/10.1016/J.ECOENV.2016.01.030.

Fleisch, A.F., Rifas-Shiman, S.L., Koutrakis, P., Schwartz, J.D., Kloog, I., Melly, S., Coull, B.A., Zanobetti, A., Gillman, M.W., Gold, D.R., Oken, E., 2015. Prenatal exposure to traffic pollution: associations with reduced fetal growth and rapid infant weight gain. Epidemiology 26, 43. https://doi.org/10.1097/EDE.0000000000000203.

Griffith, O.W., 1999. Biologic and pharmacologic regulation of mammalian glutathione synthesis. Free Radic. Biol. Med. 27, 922–935. https://doi.org/10.1016/S0891-5849(99)00176-8.

Guxens, M., Lubczyńska, M.J., Muetzel, R.L., Dalmau-Bueno, A., Jaddoe, V.W.V., Hoek, G., van der Lugt, A., Verhulst, F.C., White, T., Brunekreef, B., Tiemeier, H., el Marroun, H., 2018. Air pollution exposure during fetal life, brain morphology, and cognitive function in school-age children. Biol. Psychiatr. 84, 295–303. https://doi.org/10.1016/j.biopsych.2018.01.016.

Hooijmans, C.R., Rovers, M.M., de Vries, R.B.M., Leenaars, M., Ritskes-Hoitinga, M., Langendam, M.W., 2014. SYRCLE's risk of bias tool for animal studies. BMC Med. Res. Methodol. 14 https://doi.org/10.1186/1471-2288-14-43.

Jones, J.R., Chaturvedi, S., Granados-Fuentes, D., Herzog, E.D., 2021. Circadian neurons in the paraventricular nucleus entrain and sustain daily rhythms in glucocorticoids. Nat. Commun. 12 https://doi.org/10.1038/S41467-021-25959-9.

Kim, E., Park, H., Park, E.A., Hong, Y.C., Ha, M., Kim, H.C., Ha, E.H., 2016. Particulate matter and early childhood body weight. Environ. Int. 94, 591–599. https://doi.org/10.1016/J.ENVINT.2016.06.021.

Kim, K.H., Kabir, E., Kabir, S., 2015. A review on the human health impact of airborne particulate matter. Environ. Int. 74, 136–143. https://doi.org/10.1016/J.ENVINT.2014.10.005.

Kirsch, P., 2015. Oxytocin in the socioemotional brain: implications for psychiatric disorders. Dialogues Clin. Neurosci. 17, 463. https://doi.org/10.31887/DCNS.2015.17.4/PKIRSCH.

Laskin, M.D., Kingdom, J., Toi, A., Chitayat, D., Ohlsson, A., 2005. Perinatal and neurodevelopmental outcome with isolated fetal ventriculomegaly: A systematic review. The Journal of Maternal-Fetal & Neonatal Medicine 18 (5), 289–298. https://doi.org/10.1080/14767050500329775.

Li, J., Cao, F., Yin, Hl., Huang, Zj., Lin, Zt., Mao, N., Sun, B., Wang, G., 2020. Ferroptosis: past, present and future. Cell Death Dis. 11 (2 11), 1–13. https://doi.org/10.1038/s41419-020-2298-2, 2020.

Li, K., Li, L., Cui, B., Gai, Z., Li, Q., Wang, S., Yan, J., Lin, B., Tian, L., Liu, H., Liu, X., Xi, Z., 2018. Early postnatal exposure to airborne fine particulate matter induces autism-like phenotypes in male rats. Toxicol. Sci. 162, 189–199. https://doi.org/10.1093/TOXSCI/KFX240.

Lin, L.Z., Zhan, X.L., Jin, C.Y., Liang, J.H., Jing, J., Dong, G.H., 2022. The epidemiological evidence linking exposure to ambient particulate matter with neurodevelopmental disorders: a systematic review and meta-analysis. Environ. Res. 209, 112876 https://doi.org/10.1016/J.ENVRES.2022.112876.

Liu, B., Fang, X., Strodl, E., He, G., Ruan, Z., Wang, X., Liu, L., Chen, W., 2022. Fetal exposure to air pollution in late pregnancy significantly increases ADHD-risk behavior in early childhood. Int. J. Environ. Res. Publ. Health 19. https://doi.org/10.3390/IJERPH191710482/S1.

Liu, J., Yang, C., Yang, J., Song, X., Han, W., Xie, M., Cheng, L., Xie, L., Chen, H., Jiang, L., 2019. Effects of early postnatal exposure to fine particulate matter on emotional and cognitive development and structural synaptic plasticity in immature and mature rats. Brain Behav. 9 https://doi.org/10.1002/brb3.1453.

Lord, C., Elsabbagh, M., Baird, G., Veenstra-Vanderweele, J., 2018. Autism spectrum disorder. Lancet 392, 508. https://doi.org/10.1016/S0140-6736(18)31129-2.

Lu, K., Jing, X.B., Xue, Q., Song, X.J., Wei, M.D., Wang, A.G., 2019. Impaired fear memory extinction during adolescence is accompanied by the depressive-like behaviors. Neurosci. Lett. 699, 8–15. https://doi.org/10.1016/J.NEULET.2019.01.039.

Minghetti, L., 2004. Cyclooxygenase-2 (COX-2) in inflammatory and degenerative brain diseases. J. Neuropathol. Exp. Neurol. 63, 901–910. https://doi.org/10.1093/JNEN/63.9.901.

Morris-Schaffer, K., Merrill, A., Jew, K., Wong, C., Conrad, K., Harvey, K., Marvin, E., Sobolewski, M., Oberdörster, G., Elder, A., Elder, A., Cory-Slechta, D.A., 2019a. Effects of neonatal inhalation exposure to ultrafine carbon particles on pathology and behavioral outcomes in C57BL/6J mice. Part. Fibre Toxicol. 16 https://doi.org/10.1186/s12989-019-0293-5.

Morris-Schaffer, K., Merrill, A.K., Wong, C., Jew, K., Sobolewski, M., Cory-Slechta, D.A., 2019b. Limited developmental neurotoxicity from neonatal inhalation exposure to diesel exhaust particles in C57BL/6 mice. Part. Fibre Toxicol. 16 https://doi.org/10.1186/s12989-018-0287-8.

Nephew, B.C., Nemeth, A., Hudda, N., Beamer, G., Mann, P., Petitto, J., Cali, R., Febo, M., Kulkarni, P., Poirier, G., King, J., Durant, J.L., Brugge, D., 2020. Traffic-related particulate matter affects behavior, inflammation, and neural integrity in a developmental rodent model. Environ. Res. 183, 109242 https://doi.org/10.1016/J.ENVRES.2020.109242.

Ni, Y., Loftus, C.T., Szpiro, A.A., Young, M.T., Hazlehurst, M.F., Murphy, L.E., Tylavsky, F.A., Mason, W.A., Lewinn, K.Z., Sathyanarayana, S., Barrett, E.S., Bush, N. R., Karr, C.J., 2022. Associations of pre-and postnatal air pollution exposures with child behavioral problems and cognitive performance: a U.S. Multi-cohort study. Environ. Health Perspect. 130, 35–38. https://doi.org/10.1289/EHP10248.

Nway, N.C., Fujitani, Y., Hirano, S., Mar, O., Win-Shwe, T.T., 2017. Role of TLR4 in olfactory-based spatial learning activity of neonatal mice after developmental exposure to diesel exhaust origin secondary organic aerosol. Neurotoxicology 63, 155–165. https://doi.org/10.1016/J.NEURO.2017.10.001.

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 5, 1–10. https://doi.org/10.1186/S13643-016-0384-4/FIGURES/6.

Patten, K.T., González, E.A., Valenzuela, A., Berg, E., Wallis, C., Garbow, J.R., Silverman, J.L., Bein, K.J., Wexler, A.S., Lein, P.J., 2020. Effects of early life exposure to traffic-related air pollution on brain development in juvenile Sprague-Dawley rats. Transl. Psychiatry 10 (1 10), 1–12. https://doi.org/10.1038/s41398-020-0845-3, 2020.

Pierzynowska, K., Gaffke, L., Żabińska, M., Cyske, Z., Rintz, E., Wiśniewska, K., Podlacha, M., Węgrzyn, G., 2023. Roles of the oxytocin receptor (OXTR) in human diseases. Int. J. Mol. Sci. 24, 3887. https://doi.org/10.3390/IJMS24043887.

Rice, D., Barone, S., 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ. Health Perspect. 108, 511. https://doi.org/10.1289/EHP.00108S3511.

Semple, B.D., Blomgren, K., Gimlin, K., Ferriero, D.M., Noble-Haeusslein, L.J., 2013. Brain development in rodents and humans: identifying benchmarks of maturation and vulnerability to injury across species. Prog. Neurobiol. 106 (107), 1–16. https://doi.org/10.1016/J.PNEUROBIO.2013.04.001.

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., Altman, D.G., Booth, A., Chan, A.W., Chang, S., Clifford, T., Dickersin, K., Egger, M., Gøtzsche, P.C., Grimshaw, J.M., Groves, T., Helfand, M., Higgins, J., Lasserson, T., Lau, J., Lohr, K., McGowan, J., Mulrow, C., Norton, M., Page, M., Sampson, M., Schünemann, H., Simera, I., Summerskill, W., Tetzlaff, J., Trikalinos, T.A., Tovey, D., Turner, L., Whitlock, E., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 350. https://doi.org/10.1136/BMJ.G7647.

Shin, J., Park, H., Kim, H.S., Kim, E.J., Kim, K.N., Hong, Y.C., Ha, M., Kim, Y., Ha, E., 2022. Pre- and postnatal exposure to multiple ambient air pollutants and child behavioral problems at five years of age. Environ. Res. 206, 112526 https://doi.org/10.1016/j.envres.2021.112526.

Sobolewski, M., Anderson, T., Conrad, K., Marvin, E., Klocke, C., Morris-Schaffer, K., Allen, J.L., Cory-Slechta, D.A., 2018. Developmental exposures to ultrafine particle air pollution reduces early testosterone levels and adult male social novelty preference: risk for children's sex-biased neurobehavioral disorders. Neurotoxicology 68, 203–211. https://doi.org/10.1016/j.neuro.2018.08.009.

Sofroniew, M.v., 2020. Astrocyte reactivity: subtypes, states and functions in CNS innate immunity. Trends Immunol. 41, 758. https://doi.org/10.1016/J.IT.2020.07.004.

Šrám, R.J., Binková, B., Dejmek, J., Bobak, M., 2005. Ambient air pollution and pregnancy outcomes: a review of the literature. Environ. Health Perspect. 113, 375. https://doi.org/10.1289/EHP.6362.

Sunyer, J., Esnaola, M., Alvarez-Pedrerol, M., Forns, J., Rivas, I., López-Vicente, M., Suades-González, E., Foraster, M., Garcia-Esteban, R., Basagaña, X., Viana, M., Cirach, M., Moreno, T., Alastuey, A., Sebastian-Galles, N., Nieuwenhuijsen, M., Querol, X., 2015a. Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study. PLoS Med. 12 https://doi.org/10.1371/JOURNAL.PMED.1001792.

Sunyer, J., Esnaola, M., Alvarez-Pedrerol, M., Forns, J., Rivas, I., López-Vicente, M., Suades-González, E., Foraster, M., Garcia-Esteban, R., Basagaña, X., Viana, M., Cirach, M., Moreno, T., Alastuey, A., Sebastian-Galles, N., Nieuwenhuijsen, M., Querol, X., 2015b. Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study. PLoS Med. 12, 1–24. https://doi.org/10.1371/journal.pmed.1001792.

Thompson, J.E., 2018. Airborne particulate matter: human exposure and health effects. J. Occup. Environ. Med. 60, 392–423. https://doi.org/10.1097/JOM.0000000000001277.

Uchino, S., Waga, C., 2013. SHANK3 as an autism spectrum disorder-associated gene. Brain Dev. 35, 106–110. https://doi.org/10.1016/j.braindev.2012.05.013.

Vanoli, J., Coull, B.A., Ettinger de Cuba, S., Fabian, P.M., Carnes, F., Massaro, M.A., Poblacion, A., Bellocco, R., Kloog, I., Schwartz, J., Laden, F., Zanobetti, A., 2022. Postnatal exposure to PM2.5 and weight trajectories in early childhood. Environ. Epidemiol. 6, E181. https://doi.org/10.1097/EE9.0000000000000181.

Williams, L., Philadciphin, W., Jiang, W., Duong, T.M., de Lanerolle, N.C., 1999. The neuropathology of hyperthermic seizures in the rat. Epilepsia 40, 5–19. https://doi.org/10.1111/J.1528-1157.1999.TB01982.X.

Win-Shwe, T.-T., Kyi-Tha-Thu, C., Moe, Y., Fujitani, Y., Tsukahara, S., Hirano, S., 2016. Exposure of BALB/c mice to diesel engine exhaust origin secondary organic aerosol (DE-SOA) during the developmental stages impairs the social behavior in adult life of the males. Front. Neurosci. 9 https://doi.org/10.3389/fnins.2015.00524.

World Health Organization, 2016. Ambient Air Pollution: a Global Assessment of Exposure and Burden of Disease. World Health Organization. https://apps.who.int/iris/handle/10665/250141. accessed 5.31.22.

Xie, H., Cao, Y., Li, J., Lyu, Y., Roberts, N., Jia, Z., 2023. Affective disorder and brain alterations in children and adolescents exposed to outdoor air pollution. J. Affect. Disord. 331, 413–424. https://doi.org/10.1016/J.JAD.2023.03.082.

Xiong, Q., Tian, X., Xu, C., Ma, B., Liu, W., Sun, B., Ru, Q., Shu, X., 2022. PM2.5 exposure-induced ferroptosis in neuronal cells via inhibiting ERK/CREB pathway. Environ. Toxicol. 37, 2201–2213. https://doi.org/10.1002/TOX.23586.

Zhou, Q., Tian, Y., Xu, C., Wang, J., Jin, Y., 2021. Prenatal and postnatal traffic pollution exposure, DNA methylation in Shank3 and MeCP2 promoter regions, H3K4me3 and H3K27me3 and sociability in rats' offspring. Clin. Epigenet. 13 https://doi.org/10.1186/S13148-021-01170-X.

Zhu, T., Simonetti, A., Ouyang, M., Kurian, S., Saxena, J., Soares, J.C., Saxena, K., Huang, H., 2023. Disrupted white matter microstructure correlates with impulsivity in children and adolescents with bipolar disorder. J. Psychiatr. Res. 158, 71–80. https://doi.org/10.1016/J.JPSYCHIRES.2022.12.033.