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Review

Impact of air pollution and occupational inhalation exposures on neurodegenerative disorders: An epigenetic perspective

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SUMMARY

Neurodegenerative disorders (NDs) are highly prevalent conditions with genetic and environmental causes. Recently, air pollution has emerged as an important contributor to NDs, causing oxidative stress and neuronal damage in the brain. Identifying early molecular alterations mediating the effects of air pollution on ND pathogenesis would be crucial for implementing personalized medicine approaches, especially for the monitoring of specific categories of highly exposed workers. Epigenetic modifications might be suitable candidates in that sense, since they are highly responsive to environmental stressors, they modulate the expression of multiple ND-related genes, and offer technical advantages as they can be studies in peripheral tissues and are relatively stable in biological samples after collection.

In this review, we summarize the current knowledge regarding the association between air pollution inhalation, epigenetics, and NDs. This work will particularly emphasize research gaps, aiming to provide directions for future research with applications in occupational and preventive medicine.

INTRODUCTION

Neurodegenerative disorders (NDs) include a series of chronic pathological conditions characterized by the loss of specific groups of neurons in the central nervous system (CNS) or in the peripheral nervous system (PNS), resulting in major impairments in memory and cognitive performances, mental health, and physical capacities. The most prevalent NDs are dementia, with 55 million cases worldwide, of which approximatively 60%–70% being diagnosed with Alzheimer's disease (AD),[1] and movement disorders, with around 8.5 million individuals affected by Parkinson's disease (PD).[2] The burden of NDs has risen steeply over the past two decades and is projected to grow further in the next years, mainly due to the progressive aging of the global population[3]; however, 20%–30% of PD and 40%–55% of dementia cases have been estimated to be attributable to modifiable risk factors,[4,5] thus highlighting the importance of implementing primary prevention strategies. Preventable risk factors for NDs include lifestyle-related exposures (such as diet, smoking, and physical activity), socioeconomic factors (such as education and income), and environmental exposures (such as pesticide exposure and inhalation of airborne pollutants).[6,7]

Air pollution is a highly diverse mixture of airborne solid, liquid, and gaseous molecules, which can derive from natural sources (wildfires, volcanic ash, and airborne sea salt) or from anthropic activities (traffic, industrial processes, agricultural activities, and domestic fuel burning). In general, solid and liquid components of air pollution are collectively referred to as particulate matter (PM), which can be classified into three main groups depending on its aerodynamic diameter: coarse PM (or $PM_{10\text{-}2.5}$, i.e., particles ranging from 2.5 μm to 10 μm), fine PM (or $PM_{2.5}$, i.e., particles smaller than 2.5 μm), and ultrafine particles (UFPM or $PM_{0.1}$, i.e., particles smaller than 0.1 μm).[8] These particles include inorganic and organic non-viable molecules, such as heavy metals and black carbon, but also pollen, spores, viruses, and bacteria.[8] Besides PM, air pollution also comprises inorganic gaseous molecules (such as carbon, sulfur and nitrogen oxides, and ozone) and volatile organic compounds (VOCs, such as benzene, toluene, and formaldehyde).[9,10]

Air pollution is nowadays considered a major threat to human health, ranking second as the most detrimental risk factor in terms of death burden and disability-adjusted life years (DALYs).[11,12] Indeed, more than 90% of the global population is exposed to concentrations or airborne pollutants exceeding safety thresholds.[13] Although chronic exposure to air pollution has been mainly associated to cardiovascular and respiratory conditions, it is becoming increasingly evident that it may also damage seemingly less exposed organs, including the brain. In particular, certain categories of workers might be particularly

Table 1. Occupational inhalation exposures and ND-related outcomes

Air pollutant	Exposed workers	Brain health outcome	References
Heavy metals (such as manganese and lead)	Miners, metalworkers, waste recycling workers, construction workers	↑risk of PD and manganism (PD-like condition)	Caudle[17]
Nanoplastics	Production and processing workers of plastics, office/teleworkers and custodial staff, workers using respiratory protection equipment, workers using 3D printers	↑systemic inflammation (potentially involving the brain)	Murashov et al.[18]
VOCs (such as toluene, benzene and formaldehyde)	Workers employed in chemical, pharmaceutical, automotive, wood, paint, hairdressing, coatings and food industries	↑risk of AD and PD	Pathak and Sriram[19]
Traffic-related air pollutants (TRAP) (such as NO_2, O_3 and black carbon)	Commuters, professional drivers, gas station attendants and motor mechanics	↑risk of AD and PD	Fu et al.[20]; You et al.[21]

at risk of developing adverse brain health outcomes, as many of the 188 airborne compounds that have been classified as hazardous by the U.S. Environmental Protection Agency[14] are enriched in specific occupational settings[15,16] and are neurotoxic (Table 1).

In this review, we recapitulate the current knowledge regarding the role of air pollution-induced epigenetic changes in ND pathogenesis. Specifically, we focus on DNA methylation, non-coding RNA (ncRNA), and histone modifications, being the most studied epigenetic marks. This study will hopefully provide an updated epigenetic perspective on the effect of air pollution on NDs, which might be helpful to highlight the current gaps in the literature and direct future studies concerning occupational risks of NDs due to inhalable substances.

EFFECTS OF AIR POLLUTION ON THE BRAIN: DIRECT AND INDIRECT PATHWAYS

Over the past decades, growing epidemiological evidence has suggested a link between air pollution exposure and common NDs, such as AD and PD.[22,23] Air pollution can affect brain physiology via two different routes, subsequently referred to as "direct pathway" and "indirect pathway" (Figure 1).

The direct pathway is mediated by UFPM and some gaseous pollutants, which can first handedly alter brain physiology via two different mechanisms. On one hand, once inhaled, UFPM can enter the bloodstream and reach the blood-brain barrier (BBB), potentially compromising its integrity and the capacity to protect the brain from noxious compounds; on the other hand, it might travel by retrograde transportation along the olfactory nerve and reach the olfactory bulb, causing inflammation and neuronal damage.[24] Similarly, some gaseous pollutants are likely to exert a direct action on the brain, due to the capacity of their derivatives to penetrating the BBB. When entering biological fluids, small gases can undergo spontaneous reactions; therefore, their effect on the brain is rather exerted by their derivatives: for instance, NO_2 is converted into NO, a pleiotropic signaling molecule which regulates cerebral blood flow and BBB selective permeability.[25,26] In the case of VOCs, their lipophilicity would allow them to accumulate in the brain, where they might foster oxidative stress.[27] However, experimental evidence supporting a direct action of $PM_{0.1}$ and gaseous molecules on the brain remains limited and controversial. Instead, it has been demonstrated that some inhaled heavy metals (such as uranium and manganese) and nanoplastics can cross the BBB and accrue within cerebral tissue, with neurotoxic effects.[28–30]

Conversely, other gaseous irritants and heavy metals (such as O_3 and aluminum) rather exert their effect via the so-called indirect pathway,[31] which is the only route of action for larger particles (such as $PM_{2.5}$ and PM_{10}). The indirect pathway consists in the release of signaling molecules by the airways or by directly exposed sites; these molecular messengers can enter the circulatory system and reach the BBB, modulating its selective permeability and perturbing brain homeostasis.[24] Signaling molecules do not only include hormones and pro-inflammatory mediators such as cytokines and chemokines, but also more complex entities like extracellular vesicles (EVs), which carry a variegated cargo of regulatory molecules, such as nucleic acids, lipids, and metabolites from the cell of origin. Recent studies suggest that inhaled toxicants can also affect the gut-brain, olfactory-brain, and lung-brain axis, by modulating the composition of the residential microbial flora.[32,33] For instance, increased gut permeability would result in the release of metabolites (including bacterial toxins and oxidized heavy metals) that can trigger inflammatory responses, disrupt the BBB and alter brain functions.[34]

A selection of exemplificative studies regarding the mode of action of the principal air pollutants on the brain is summarized in Table 2. However, it cannot be excluded that such toxicants might affect the brain via other mechanisms or routes. Indeed, experimental evidence unraveling the exact mechanisms underlying the effect of air pollutants on the brain remains scarce. In addition, for pollutants with dual action, it is particularly difficult to discriminate whether neuroinflammation and brain damage occur as a collateral effect of systemic inflammation (jointly with the disruption of the BBB, which would otherwise prevent the passage of pro-inflammatory mediators to the CNS), or due to a direct and specific action of air pollutants; in the latter case, air pollution-induced damage would mostly be confined to the brain.

In this context, disentangling molecular alterations caused by air pollution exposure might be useful for the identification of biomarkers of early drift from homeostasis, which might eventually lead to overt neuropathology.

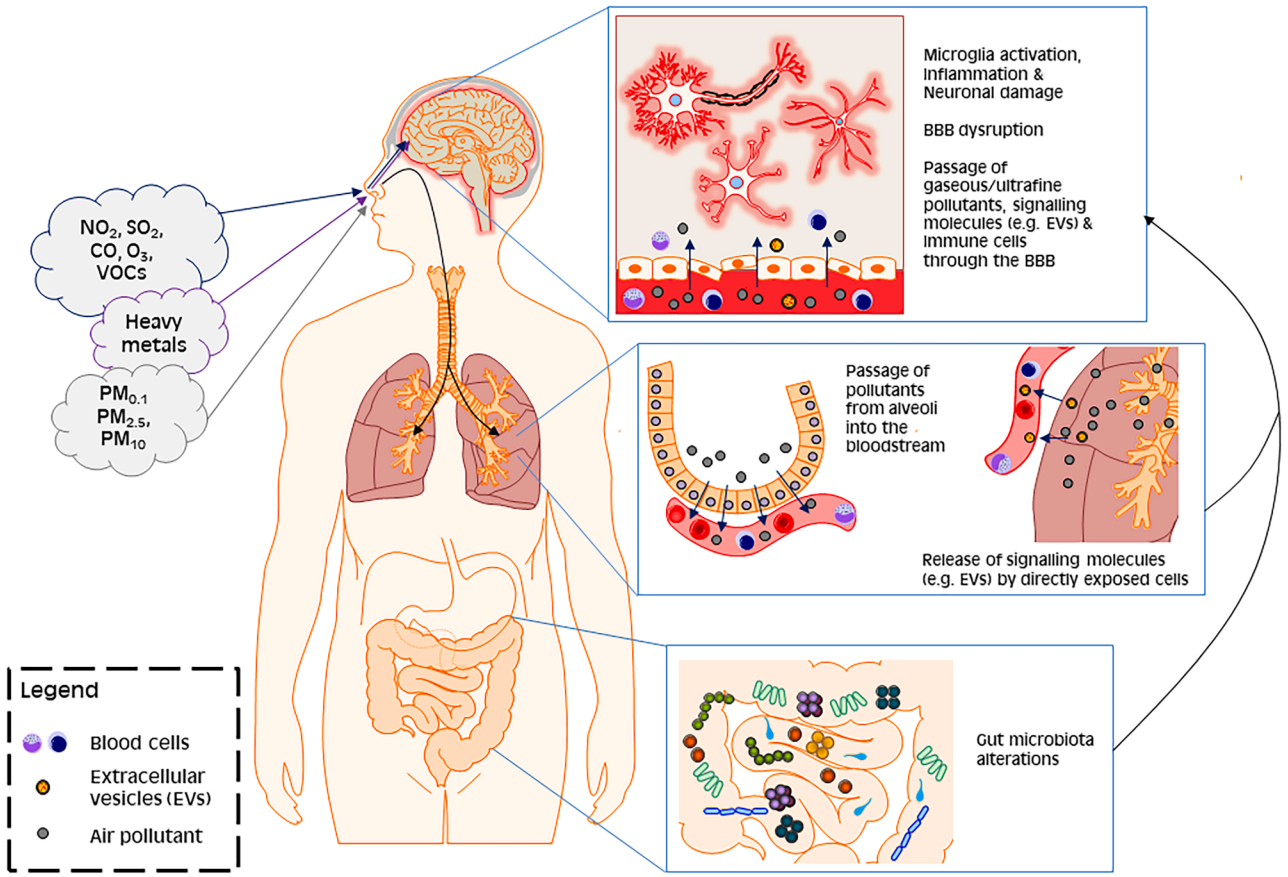

Figure 1. Effect of air pollution on the brain via the direct and indirect pathways

AIR POLLUTION AND NEURODEGENERATION: THE EPIGENETIC CONNECTION

Epigenetic modifications comprise all those mitotically stable, potentially reversible changes in gene expression that occur without altering the DNA sequence. The most common epigenetic modifications include DNA methylation, ncRNAs, and histone post-translational modifications,[46,47] which are briefly described in Box 1.

Epigenetic mechanisms play a pivotal role in a plethora of biological processes in the brain, ranging from neuronal and glial cell differentiation, to the modulation of synaptic plasticity, neurotransmission and neuroinflammation.[48] Of note, the epigenetic landscape of the brain changes throughout the lifetime; indeed, epigenetic marks are highly dynamic and undergo continuous modifications in response to internal signals and to the external environment.[49] While *de novo* DNA methyltransferases, such as DNMT3A and DNMT3B, are primarily expressed during embryonic development to establish DNA methylation patterns, neurons uniquely retain expression of these DNA methyltransferases (DNMTs) beyond developmental stages. In mature neurons, DNMT3A and DNMT3B play critical roles in synaptic plasticity and memory maintenance, enabling epigenetic adaptations in response to environmental stimuli and contributing to the dynamic regulation of neural function throughout adulthood.[50]

To date, multiple lifestyle factors (including diet,[51] physical activity,[52] smoking,[53] and alcohol consumption[54]) and environmental exposures (such as ambient chemicals and air pollution) have been associated with epigenetic changes in the CNS. Considering that the brain is mainly populated by cells that are terminally differentiated and are subjected to little or no self-renewal, the high plasticity of epigenetic modifications is intrinsically beneficial, as it sustains adaptation to the changing environment; however, chronic exposure to stressors and toxins might progressively lead to a shift toward deranged homeostasis and global deregulation of gene expression, fostering neuropathological outcomes.[55]

Indeed, NDs are characterized by a general reshaping of the epigenome, both in the nervous system and in peripheral tissues, which also involves many genes which are well-established to participate in their etiopathology. In patients with AD, the hippocampus has been found to be globally hypomethylated; instead, the cerebral cortex seems to predominantly feature gene-specific alterations. Here, the accumulation of amyloid-β (Aβ) plaques due to aberrant processing of the amyloid precursor protein (APP) might be enhanced by lower methylation levels in the *APP* promoter region, leading to increased gene expression.[56] Besides, epigenetics regulation is also implied in the formation of neurofibrillary tangles (containing hyper-phosphorylated tau protein), as AD brains are characterized by HDAC6

Table 2. Mode of action of the principal air pollutants on the brain

Pollutant (route and dose)	Mode of action	Experimental approach	Mediator(s) (for indirect pathway)	Accrual in the brain	Outcome	References
$PM_{2.5-10}$ (instilled at 5 mg/kg in 50 μL of PBS)	Indirect	Mouse model (*in vivo*) + *in vitro*	Inflammatory molecules (including IL-1β, TNF-α, IL-6)	ND	↑microglial activation, motor impairment and dopaminergic neuron death	Choi et al.[35]
$PM_{2.5}$ (inhaled for 4h/day, for 2days, at 2.51 mg/m^3 conc.)	Indirect	Mouse model (*in vivo*)	Lung-derived exosomes	ND	CCL2 ↑ in the lungs and ↓ in the brain; ↑BBB disruption, GFAP, stress and anxiety	Lopez et al.[36]
$PM_{2.5}$ (inhaled for 2 h/day, 5 days/week, for 3/6/9/12 months, at 17–57 μg/m^3 conc.)	Possibly indirect	Mouse model (*in vivo*)	Pulmonary IL-1β, IL-6 and TNFα (only in the short-term)	ND	↑cognitive impairment, neuroinflammation, and BBB disruption; ↑GFAP; ↑stress and anxiety	Shou et al.[37]
$PM_{0.1}$ (inhaled for 4h/day, 4 days/week, for 2 weeks, at 10x real-world concentrations)	Possibly direct	Mouse model (*in vivo*)	Lack of overt lung inflammation	ND	↑microglia activation, ↑phopho-tau	Herr et al.[38]
Polystyrene nanoplastics (inhaled for 5h/day, 7 days, at 1 mg/mL conc.)	Direct	Mouse model (*in vitro*)	ND	Yes (temporarily)	↓olfactory discrimination, ↓neuronal functionality, ↑microglia activation, ↑olfactory neurogenesis	Prosperi et al.[29]
Carbon quantum dots (instilled at 0.5 or 5 mg/kg conc.)	Mainly indirect	Mouse model (*in vivo*)	Lung microbiota	Yes (little)	↑neuronal death, ↑motor impairment, ↑anxiety	Wu et al.[33]
O_3 (inhaled for 4h, 1 ppm conc.)	Indirect	Rat and mouse models (*in vivo* and *ex vivo*)	Serum circulating factors (not cytokines)	ND	↑microglia activation	Mumaw et al.[39]
NO_2 (inhaled for 5h/day, 7 days, at 20 mg/m^3 conc.)	Unknown	Rat model (*in vivo*)	ND	ND	↑Impaired mitochondrial energy metabolism, ↑ROS	Yan et al.[40]
SO_2 (inhaled for 90 days, at 3.50–7.00 mg/m^3 conc.)	Unknown	Rat model (*in vivo*)	ND	ND	↓spatial memory, ARC and glutamate receptors mRNA, memory kinases; ↑inflammatory cytokines	Yao et al.[41]
Metal-rich nanoparticles (chronically inhaled at real-world conc.)	Direct	Humans (post-mortem) + mouse model (*in vivo*)	ND	Yes	↓brain chromatin silencing and DNA integrity, ↑AD risk	Calderón-Garcidueñas et al.[42]
Iron-soot particles (inhaled for 6h/day, 5 days/week, 5 weeks, at 200 μg/m^3 conc.)	Direct	Mouse model (*in vivo*)	ND	Yes	↑microglia activation and neuroinflammation, ↑IL-1β	Hopkins et al.[43]
Manganese oxide (inhaled for 6 h/day, 5 days/week up to 12 days, at 500 μg/m^3)	Direct	Rat model (*in vivo*)	Lack of overt lung inflammation	Yes	↑TNF-α, Macrophage inflammatory protein-2, GFAP, and neuronal cell adhesion molecule in the brain	Elder et al.[30]
Uranium oxides (inhaled for various times and concentrations)	Direct	Rat model (*in vivo*)	ND	Yes	ND	Tournier et al.[28]
Aluminum salts (instilled for 10 days, at 10μg/30μL conc.)	Possibly indirect	Rat model (*in vivo*)	ND	No	ND	Chalansonnet et al.[44]
Lead oxide (inhaled for 2/5/13 weeks, at 192.5 μg/m^3 conc.)	Direct and possibly indirect	Mouse model (*in vivo*)	Systemic inflammation (potentially)	Yes	DNA and lipid damage, malondialdehyde	Bláhová et al.[45]

Box 1. Types of epigenetic modifications

DNA methylation is the covalent attachment of a methyl group (-CH_3) to the carbon 5 position of nitrogen bases of the DNA. In humans, this process mainly occurs at cytosines (5-methyl-cytosines or 5mCs) followed by guanine nucleosides, i.e., CpG dinucleotides, which are particularly abundant in gene promoters; in general, promoter hypermethylation results in gene silencing, by steric hindrance or recruitment of transcriptional inhibitors. DNA methylation is catalyzed by DNA methyltransferases (DNMTs), whereas demethylation can result from inhibition of DNMTs (passive demethylation) or from the activity of Ten-eleven translocation (TET) enzymes. Besides, TET enzymes can also convert 5mCs into 5-hydroxymethylcytosines (5hmCs), which are specifically enriched in the brain.[17,32]

NcRNAs encompass a broad class of RNAs that are not translated into a protein product. According to their length, they can be classified into small ncRNAs (sncRNAs), ranging from 18-20 to 200 nucleotides, and long ncRNAs (lncRNAs), which are longer than 200 nucleotides. SncRNAs include transport RNAs (tRNAs) and ribosomal RNAs (rRNAs), which are implied in protein translation; and microRNAs (miRNAs), which are key regulators of gene expression (usually resulting in translational inhibition). LncRNAs include linear and circular RNAs (circRNAs), which are implied in chromatin remodeling and can act as "sponges" for miRNAs.[17,32]

Histone modifications are key regulators of chromatin state which result from the covalent attachment of various chemical groups to the amino terminal domain of histones. The most studied histone modifications include acetylation, which is regulated by histone acetyltransferases (HATs) and histone deacetylates (HDACs) and is generally associated with transcriptional activation (due to the introduction of negative charges, which favor the opening of chromatin). Other widely studied modifications include histone methylation, phosphorylation, deamination, ubiquitination, serotonylation, and sumoylation, which promote the recruitment of other proteins that re-shape the chromatin structure.[17,32] Some modifications, such as the phosphorylation of histone H2AX (γH2AX), are also implied in DNA damage response.[33]

increments, which promote histone deacetylation and increased expression of the *MAPT* gene encoding the tau protein.[57] Similarly, *BDNF*, a key gene implied in neuronal survival and growth, has been found to be epigenetically downregulated in many NDs.[58] In addition, a plethora of ncRNAs have been reported to be differentially regulated in NDs, fostering ND-related hallmarks; for instance, miRNA and lncRNA alterations were shown to promote overexpression of the *SNCA* gene and consequently aggregation of α-synuclein in PD.[59] Importantly, epigenetic dysregulation of many ND-related genes might occur years before the insurgence of disease symptoms, and has been observed also in psychiatric conditions, such as depression and autism,[60,61] which have been associated with hypersusceptibility to sporadic NDs.

In the following paragraphs, we will provide a comprehensive summary of the state-of-the-art knowledge regarding the association between exposure to airborne toxicants, epigenetic modifications, and ND-related processes. Among inhalation exposures, we focused on urban PM and traffic-related air pollutants (such as NO_2 and diesel exhaust particles), as well as on volatile compounds highly enriched in the manufacturing and metalworking environments (including VOCs and airborne solvents, graphene, phthalates, nanoplastics, and heavy metals). Exposures related to personal choices, i.e., tobacco smoking and vaping, were excluded. Studies dealing with inhalable toxicants causing neurodevelopmental disorders were also excluded, unless they might have implications in late-life ND risk. Evidence from *in vitro* research was included only if contextualized within population-based or *in vivo* studies dealing with inhalation exposures or intranasal/intratracheal instillation, thus providing mechanistic insights into the biological effect of inhaled pollutants on CNS cell homeostasis.

Airborne toxicants, non-coding RNAs, and neurodegeneration

Multiple *in vivo* studies have shown that urban or "real world" PM exposure can modulate ncRNA networks in the CNS, with potential effects on cognitive performances and ND risk. In this regard, outdoor $PM_{2.5}$ has been associated with impaired learning memory in rats, as well as with differential expression of 100 circRNAs, 67 lncRNAs, and 28 miRNAs in exposed animals (if compared to controls breathing filtered air).[62] Another study reported that exposure to $PM_{2.5}$ for eight weeks aggravated AD-related spatial memory deficits and caused multiple brain alterations, including increased levels of pro-inflammatory cytokines, acetylcholinesterase, and Aβ-42, in mice; of note, these changes were paralleled by altered expression of seven miRNAs which were predicted to target several genes implied in AD pathogenesis.[63] Similarly, repeated administration of $PM_{2.5}$ for four weeks caused neuroinflammation and impairment in synaptic function, as well as altered spatial learning and memory, in treated mice. This effect might be mediated by the hippocampal downregulation of miR-574-5p, which targets *BACE1* (which codes for an enzyme implied in the generation of the Aβ peptide); indeed, overexpression of miR-574-5p attenuated $PM_{2.}$5-induced AD-related symptoms.[64] Notably, ncRNA-mediated neurotoxicity of "real world" PM can have transgenerational effects, as the offspring of exposed female mice had impaired memory functions, paralleled by increased microglia proliferation and cerebellar levels of 8-hydroxyguanosine (a marker of oxidative damage) within miRNAs.[65]

Of note, the noxious effect of $PM_{2.5}$ might be potentiated by other molecules that are associated with engine combustion and in general with traffic-related air pollution (TRAP). Low-dose, combined exposure to $PM_{2.5}$ and sulfur dioxide (SO_2) for four weeks was reported to increase tau and phosphorylated tau protein levels in both mice cerebral cortex and cultured primary cortical neurons; such neurodegenerative outcomes might be mediated by reduced levels of miR-337-5p, which targets the *Mapt* gene encoding the tau protein.[66] In addition, ozone (O_3) can modulate synaptic plasticity by affecting the expression of miR-221-3p in the hippocampus and serum of exposed rats.[67] The effect of TRAP on ncRNAs and ND was also investigated by two population-based studies. Colicino and colleagues showed that SNPs within three miRNA-processing genes modify the association of black carbon exposure (a proxy for TRAP) with cognitive functions in a population of 533 elderly men, possibly due to an effect on miRNA expression.[68] Another study

conducted on 24 non-smoking subjects showed that TRAP is associated with plasma levels of five brain-enriched miRNAs which are known to be implied in AD and/or PD; of these, miR-107, miR-433-3p, and miR-1224-5p were found to be increased in response to TRAP, while miR-885 and miR-34a-5p had the opposite trend.[69]

Long-term occupational exposure to airborne neurotoxic substances might be paralleled by ncRNA changes, which might modulate the risk of NDs. A study conducted on 59 workers in a Korean industrial park showed that chronic exposure to toluene resulted in altered blood expression of 446 lncRNAs and 26 miRNAs; among them, downregulation of *NEAT1*, a lncRNA implied in axonal growth, was also confirmed in the hippocampus of toluene-treated mice and in cultured neuroblasts.[70]

In addition, many studies have pointed out a detrimental effect exerted by inhalable heavy metals on the brain, especially for chronically exposed subjects such as miners and metalworkers; here, the effect of these compounds might be at least partially mediated by ncRNA alterations.[71] In this regard, coke oven emissions (which are rich in coal tar, polycyclic aromatic hydrocarbons, and metals) were found to promote cognitive impairment and synaptic damage in exposed mice, which were accompanied by reduced miR-145a-5p and increased expression of *Sik1*(a gene coding for a serine/threonine kinase implied in CNS physiopathology) in the hippocampus.[72] Another study reported that 27 miRNAs were differentially expressed in cerebrovascular cells obtained from mice exposed for 2 weeks to wind-blown dust nearby a uranium mine, if compared to filtered air controls; of these miRNAs, 8 were also altered with the same directionality in the serum of exposed mice. The authors demonstrated that overexpression of mmu-let-7a, which was found to be the top upregulated miRNA by dust, impaired the integrity of the cerebrovascular endothelium.[73]

Regarding individual heavy metals, manganese is well-known to cause alterations in ncRNAs implied in synaptic transmission, autophagy, and apoptosis, as reported by multiple *in vitro* studies on neural cells.[74–78] Interestingly, the miRNA cargo of Mn-induced EVs was found to participate in ND-related processes[79] and might be exploited for therapeutic purposes. Here, intranasal administration of EVs derived from mesenchymal stem cells differentiating into dopaminergic progenitors were shown to ameliorate neuroinflammation and motor dysfunction in Mn-exposed mice, possibly by shuttling miR-494-3p, which targets the inflammatory genes *Cmpk2* and *Nlrp3*.[80]

Besides Mn, also lead has been found to promote brain alterations by modulating ncRNAs; however, while many *in vivo* studies have shown an ND-related effect of Pb exposure via drinking water or diet,[81–83] evidence regarding Pb inhalation is currently lacking.

The main characteristics of the cited studies are summarized in Table 3.

Airborne toxicants, DNA methylation, and neurodegeneration

Over the last decades, it has strongly emerged that air pollution can modulate DNA methylation, either globally or at specific loci, with possible detrimental consequences on the CNS throughout the lifespan. To date, many population-based studies have reported an association between air pollution exposure, DNA methylation changes in peripheral tissues, and NDs. Here, a study conducted by Gondalia and co-workers on 8397 subjects from twelve multi-racial cohorts showed that monthly mean exposure levels to PM is associated with altered methylation levels at 3 CpG sites in peripheral blood leukocytes; among them, one mapped within the *ARPP21* gene, which encodes an RNA-binding protein implied in AD pathogenesis.[84] Similarly, Huang and colleagues reported an association between long-term exposure to PM, NO_2, and O_3 and the methylation status of the *BDNF* promoter in 101 subjects with AD, suggesting that such effect might be the result of the synergistic interaction of single pollutants.[85,86] Another study conducted on policemen working in different Polish cities suggested that differential methylation of the *NR4A2* gene, which is implied in brain dopaminergic regulation, might be due to different levels of air pollutants.[87] Besides, exposure to multiple VOCs (benzene, toluene, ethylbenzene, and xylene) was found to be associated with differential blood methylation of 201 CpG sites, many of which map within genes implied in GABA receptor- and oxytocin-mediated signaling, in 64 pregnant African-American women.[88]

If on one hand numerous studies have highlighted a link between air pollution exposure and epigenetic changes in peripheral blood, on the other hand DNA methylation alterations in brain tissue remain relatively unexplored. The only population-based, genome-wide research available thus far, conducted by Li and colleagues, identified 24 CpG sites as possible mediators of the adverse effects of long-term $PM_{2.5}$ exposure on neuropathology markers in the prefrontal cortex of 159 individuals with AD; of note, many of these CpG sites mapped within genes implied in neuroinflammation.[89] Despite the lack of additional studies conducted on the human brain, multiple *in vitro* studies seem to support that brain DNA methylation alterations might link air pollution to NDs.[90,91] Besides, research by Xu et al. demonstrated that TRAP impairs memory and triggers microglial activation, neuroinflammation, and oxidative stress in aged mice; of note, such alterations were paralleled by hypermethylation at the *Abca7* gene promoter—known to play a role in AD-related microglial activation and Aβ processing—while the promoter region of *Pyk*, which participates in synaptic plasticity and tau pathology, was hypomethylated.[92] Few studies also suggested that prenatal exposure to air pollution might modulate DNA methylation in neurodevelopmental processes[93,94]; however, it remains unclear whether such dysregulation might also modulate the risk of NDs in late life.

DNA methylation can be also altered in response to different occupational inhalation exposures, with detrimental consequences on the nervous system. In this regard, many studies have focused on the effect of welding fumes (WFs) rich in Mn on ND-related DNA methylation changes. Indeed, exposure to WFs might foster ND-related neuroinflammation by inducing DNA hypomethylation at the *NOS2* gene, which codes for the inducible nitric oxide synthase; accordingly, in a population of workers (or former workers) at welding sites, PD cases (n = 49) had lower *NOS2* blood methylation than controls (n = 103).[95]

Table 3. Studies associating air pollution inhalation exposure, ncRNA changes, and ND

Pollutant (route/concentration)	Experimental approach	Altered ncRNA	ncRNA targets (experimentally validated)	ND outcome (experimentally validated)	References
$PM_{2.5}$ (inhaled for 8h/day, 8 weeks, at a conc. eight-fold higher than real-world one)	Rat model	100 circRNAs, 67 lncRNAs, and 28 miRNAs	ND (predicted)	↓spatial learning and memory	Chen et al.[62]
$PM_{2.5}$ (inhaled for 8 weeks, at 61 μg/m^3 conc.)	Mouse model	7 miRNAs	ND (predicted)	↑brain damage, pro-inflammatory cytokines, Aβ-42 and AChE; ↓ChAT	Fu et al.[63]
$PM_{2.5}$ (inhaled every other day for 4 weeks, at 1–5 mg/kg bw)	Mouse model	20 miRNAs	*BACE1*, targeted by miR-574-5p	↑brain and lung inflammation, ↓synaptic integrity and spatial learning and memory	Ku et al.[64]
$PM_{2.5}$ (inhaled for 8h/day, 15 days, at 73 μg/m^3 conc.)	Mouse model	miRNAs (8-OHG levels)	ND	↓spatial learning and memory, cerebellar microglia; ↑cerebellar inflammation	Zhang et al.[65]
SO_2 (inhaled for 6h/day, 28 days, at 1 μg/mL) and PM2.5 (instilled every other day, 28 days, at 10 μg/mL)	Mouse model	miR-337-5p	ND (predicted)	↑neuronal apoptosis, phospho tau, synaptic abnormalities	Ku et al.[66]
O_3 (inhaled for 4h/day, 7 days, at 2.0 ppm conc.)	Rat model	miR-221–3p	*PIK3R1*	↑depression-like behavior and hippocampal damage; ↓levels of synaptic proteins	Cao et al.[67]
TRAP (real-world exposure)	Population-based study	54 miRNAs	ND (predicted)	↑AD and PD risk (predicted)	Krauskopf et al.[69]
Toluene (mean exposure: 9h/day, 6.1 years; at 24X conc. than controls)	Population-based study (+ mouse model and *in vitro*)	446 lncRNAs and 26 miRNAs	ND (predicted)	ND (↓spatial memory and motor control in the mouse model)	Yu et al.[70]
Coke oven emissions (instilled for 3 times/week, 3 weeks, at 160 μg/50 μL conc.)	Mouse model	20 miRNAs	*SIK1*, targeted by miR-145a-5p	↓spatial learning and memory, ↓synaptic plasticity	Sanchez et al.[73]
Metal-rich PM (inhaled for 4h/day, 2 weeks, at 96.6 μg/m3 conc.)	Mouse model	27 miRNAs	ND (predicted)	↓pulmonary endothelial barrier and BBB integrity,	Lu et al.[78]

The effect of Mn exposure on ND-related DNA methylation is also supported by *in vitro* evidence[96,97]; besides, a study reported that rats chronically exposed to stainless steel WFs had lower global DNA methylation in the brain, if compared to filtered air controls.[98]

Regarding Pb, to date most *in vivo* studies have focused on prenatal or early life exposures, showing that it can promote neurodevelopmental disorders via aberrant DNA methylation; nevertheless, most studies have focused on exposure via diet,[99,100] soil,[101] or water,[102–105] with the effect of inhaled Pb remaining uninvestigated. Besides, it is not clear whether such modifications can persist into adulthood and increase the risk of NDs in older individuals. However, a study conducted on *Macaca fascicularis* showed that Pb exposure during infancy resulted in prominent AD-like alterations in aging animals; of note, such pathological changes were accompanied by a massive epigenetic reprogramming in the brain of exposed primates, including a decrease in Dnmt levels and global demethylation late in life.[106]

The main characteristics of the cited studies are summarized in Table 4.

Airborne toxicants, histone modifications, and neurodegeneration

Unlike DNA methylation and ncRNAs, to date few studies have focused on the role of histone modifications in ND-related processes induced by airborne toxicants. This is likely due to the challenges in studying histone modifications, as they are more complex, time-consuming, and less amenable to high-throughput methodologies. Although evidence is still scarce, some authors reported an effect of air pollution exposure starting from the very early stages of life, and even before birth. In a study conducted on post-mortem brain samples from 23 young adults, lower nuclear levels of H3K9me2 and H3K9me3 (markers of transcriptionally inactive chromatin), as well as increased γ-H2AX (a marker of DNA double-strand-break), were associated to living in highly polluted urban areas; of note, these epigenetic alterations were paralleled by accumulation of hyperphosphorylated tau protein and Aβ plaques, suggesting a link between air pollution-related chromatin silencing/DNA damage and AD pathogenesis. These findings were also confirmed in mice chronically exposed to air pollution[42] Besides, maternal exposure to $PM_{2.5}$

Table 4. Studies associating air pollution inhalation exposure, DNA methylation changes, and ND

Pollutant (route/concentration)	Experimental approach	Differentially methylated sites/targets	Tissue/sample	ND outcome (experimentally validated)	References
$PM_{2.5}$, PM_{10}, $PM_{2.5-10}$ (mean 1-month exposure: 0.9, 13.2 and 7.7 μg/m^3, respectively)	Population-based study	3 CpG sites within *MATN4*, *ARPP21/miR128-2,* and *CFTR*	blood leukocytes	ND	Gondalia et al.[84]
PM_1, $PM_{2.5}$, PM_{10}, and NO_2 (3-year, real life exposures)	Population-based study	7 CpG sites within *BDNF*	Whole blood	ND	Huang et al.[85]
$PM_{2.5}$ and ozone (3-year, real life synergic exposures)	Population-based study	1 CpG site within *BDNF*	Whole blood	ND	Huang et al.[86]
$PM_{2.5}$, benzo(a)pyrene, NO_2 (3-month/1year, real life exposures grouped according to the city)	Population-based study	3/31/13643 CpG sites (depending on city comparisons)	Whole blood	ND	Honkova et al.[87]
Benzene, toluene, ethylbenzene, xylenes (second trimester, real life exposures)	Population-based study	201 CpG sites	Whole blood	ND	Straughen et al.[88]
Traffic-related $PM_{2.5}$ (1/3/5-year, real life exposure prior to death)	Population-based study	22 CpG sites	Prefrontal cortex	↑AD-related neuropathological markers	Li et al.[89]
Traffic-related $PM_{2.5}$ and NO_x (inhaled for 12h/day, 2/4/12 weeks, at 690.40μg/m^3 and 489.00μg/m^3 conc. respectively)	Mouse model	5 CpG sites within *ABCA7* and *PYK2*	Hippocampus and dorsolateral prefrontal cortex	↓memory, ↑neuroinflammation and oxidative stress	Xu et al.[92]
Indoor PM_{10} (3-month, real-life pregnancy exposure, mean 64.5 μg/m^3 conc.)	Population-based study	29 CpG sites	Cord blood	ND	Feil et al.[93]
$PM_{2.5}$, PM_{10}, NO_2 (real-life pregnancy exposure, mean conc. 19.7 μg/m^3 for NO_2, 18.1 μg/m^3 for PM_{10}, and 12.1 μg/m^3 for $PM_{2.5}$)	Population-based study	4 CpG sites (total population)	Placenta	ND	Broséus et al.[94]
Welding fumes (mean exposure 19.8 years)	Population-based study	3 CpG sites within *NOS2*	Whole blood	↑PD risk	Searles Nielsen et al.[95]
Welding fumes (inhaled for 3h/day, 4 days/week, 5 weeks, at 20 mg/m^3 conc.)	Rat model	Overall DNA methylation	Whole brain	↑telomere length, phospho tau, presenilin 1-2, α-synuclein	Shoeb et al.[98]

was found to impair hippocampal synaptic development and cognition in the offspring by decreasing the expression and protein levels of KDM5A, a histone lysine demethylase implied in transcriptional repression; indeed, $PM_{2.5}$-induced decline of KDM5A was paralleled by elevation of H3K4me3 in hippocampal neurons of prenatally exposed mice. Similar trends were also observed in $PM_{2.5}$-treated hippocampal neuronal cultures.[107] However, these effects seem to be sex-specific, with males undergoing memory impairment in the adulthood; this might be due to their incapacity to cope with PM exposure by upregulating histone demethylases KDM5A and KDM6A, as observed in their female littermates.[108]

In addition, there is emerging evidence supporting an effect of inhaled plastic particles on histone-related processes in the context of NDs. Han and co-authors showed that intranasally administered polystyrene nanoparticles (PNs) caused neurotoxic damage in the brain of treated mice. This noxious effect induced by PN accrual in the brain might be promoted by HDAC6, which is implied in retrograde transport and perinuclear accumulation of PNs; indeed, treatment with an HDAC6 inhibitor ameliorated NP-induced cell damage and oxidative stress in cultured primary neurons.[109]

Regarding inhaled heavy metals, a study conducted on Chinese subjects showed that people residing near electronic waste recycling areas (n = 99) had higher blood metal concentrations, increased euchromatic histone lysine methyltransferase 1 (EHMT1) and markers of oxidative stress, and lower BDNF and Aβ42 if compared to the non-exposed group (n = 96).[110] In addition, multiple studies reported that Mn (injected intraperitoneally) can induce histone hypoacetylation in nervous tissues. In the striatum of rats, Mn was found to increase HDAC levels and decrease histone acetylation in the promoter region of genes

Table 5. Studies associating air pollution inhalation exposure, histone modifications, and ND

Pollutant (route/concentration)	Experimental approach	Histone modification (HM) and/or HM enzymes	Tissue/sample	ND outcome (experimentally validated)	References
Metal-rich $PM_{2.5}$ (inhaled at real-word conc., 1 year prior death; for mice: 7months, mean $PM_{2.5}$ > 55 μg/m^3, UFP> 26000 counts/cm^3)	Population-based study (post-mortem) + mouse model	H3K9me2/me3 and γ-H2A.X	Brain (different regions)	↑phospho tau, Aβ plaques	Calderón-Garcidueñas et al.[42]
$PM_{2.5}$ (inhaled every 3 days, for 15 days, at 0.2592, 1.728 and 3.456 mg/kg b.w conc.)	Mouse model (+ *in vitro*)	H3K4me3 (potentially by KDM5A)	Hippocampus	↓synaptic development	Huang et al.[107]
Traffic-related $PM_{2.5}$ (instilled for 6 weeks, 5 μg/mouse/day)	Mouse model	KDM5A and KDM6A	Whole brain	↓spatial and learning memory, mitochondrial function	Oliver et al.[108]
polystyrene nanoplastics (instilled at 200 mg/L conc.)	Mouse model (+ *in vitro*)	HDAC6	Brain (different regions)	↑Gfap and Lcn2, neuroinflammation and neurotoxicity; ↓Tubb3	Han et al.[109]
E-waste toxicants (exposure >10years, possibly by inhalation)	Population-based study	EHMT1	Plasma	↓BDNF and Aβ42; ↑BAZ2B and malondialdehyde	Zhu et al.[110]
$MnCl_2$ (instilled fpr 21 days, at 30 mg/kg conc.)	Mouse model	H3ac and H4ac (potentially HDAC)	Midbrain and striatum	↓Motor activity and coordination; ↓GLT-1 and GLAST	Johnson et al.[116]; Johnson et al.[117]

implied in oxidative stress response, causing oxidative damage, and memory impairment[111–113]; similar findings were also obtained in neuroblastoma cells, where also HATs were found to be downregulated by Mn treatment.[112,114,115] The importance of Mn-induced, ND-related alterations due to histone deacetylation was also supported by Johnson Jr and colleagues, showing that HDAC inhibitors can restore locomotor abilities and the levels of glutamate/aspartate transporters in the brain of mice intranasally instilled with Mn.[116,117] Lastly, Mn treatment of microglial cells previously exposed to a pro-inflammatory cue resulted in enhanced deposition of H3K27ac, H3K4me1, and H3K4me3; this might be relevant in the context of ND-associated neuroinflammation, as the same modifications were also found to be increased in a PD mouse model and in post-mortem human PD brains, if compared to healthy controls.[118]

Similar to Mn, also lead was found to upregulate HDACs and alter histone acetylation patterns, causing neurotoxicity and cognitive deficits[119,120]; besides, these HDAC-mediated effects might be further worsened by concomitant exposure to other heavy metals such as cadmium.[121] Instead, HDAC inhibitors were shown to ameliorate such Pb-induced, ND-related alterations.[119,120] Interestingly, butyrate supplementation was found to alleviate neuroinflammation and memory impairment caused by chronic Pb exposure, by restoring H3K9ac at *Bdnf* promoter region in the hippocampus of mice.[122] Instead, there is substantial lack of evidence regarding the effects of other heavy metals on histone modifications. Nevertheless, it is likely that exposure to As and Hg might indirectly impact on the enzymatic activity of histone methyltransferases, since these enzymes utilize SAM as a methyl donor, and the synthesis of SAM and of methionine (its precursor) is inhibited by both As and Hg.[123]

The main characteristics of the cited studies are summarized in Table 5.

DISCUSSION

Strengths of current evidence

In recent years, considerable progress has been made in understanding the influence of air pollution and occupational inhalation exposures on NDs, specifically in relation to epigenetic modifications. It is now well-established that exposure to PM, VOCs, and heavy metals—commonly present in urban air pollution and enriched in specific occupational settings—correlates with ND risk. Epidemiological studies, together with animal and cellular models, consistently show that such exposure can induce molecular changes linked to ND pathogenesis, particularly in AD and PD. Key findings demonstrate that exposure to fine PM and VOCs can alter the expression of ncRNAs, promote DNA methylation changes in blood and brain tissues, and trigger histone modifications associated with inflammation, oxidative stress, and neuronal damage (Figure 2). Although the study of epigenetic alterations occurring in the brain is intrinsically problematic in living subjects, circulating EVs derived from neurons, astrocytes, and microglia are emerging as promising candidates to overcome such hurdle, providing an avenue for assessing ND risk without resorting to invasive sampling of brain tissue. Indeed, peripheral blood measures may not fully reflect epigenetic states in the brain.

Critical gaps

While substantial findings have emerged, notable gaps and complexities in the field warrant further investigation, especially

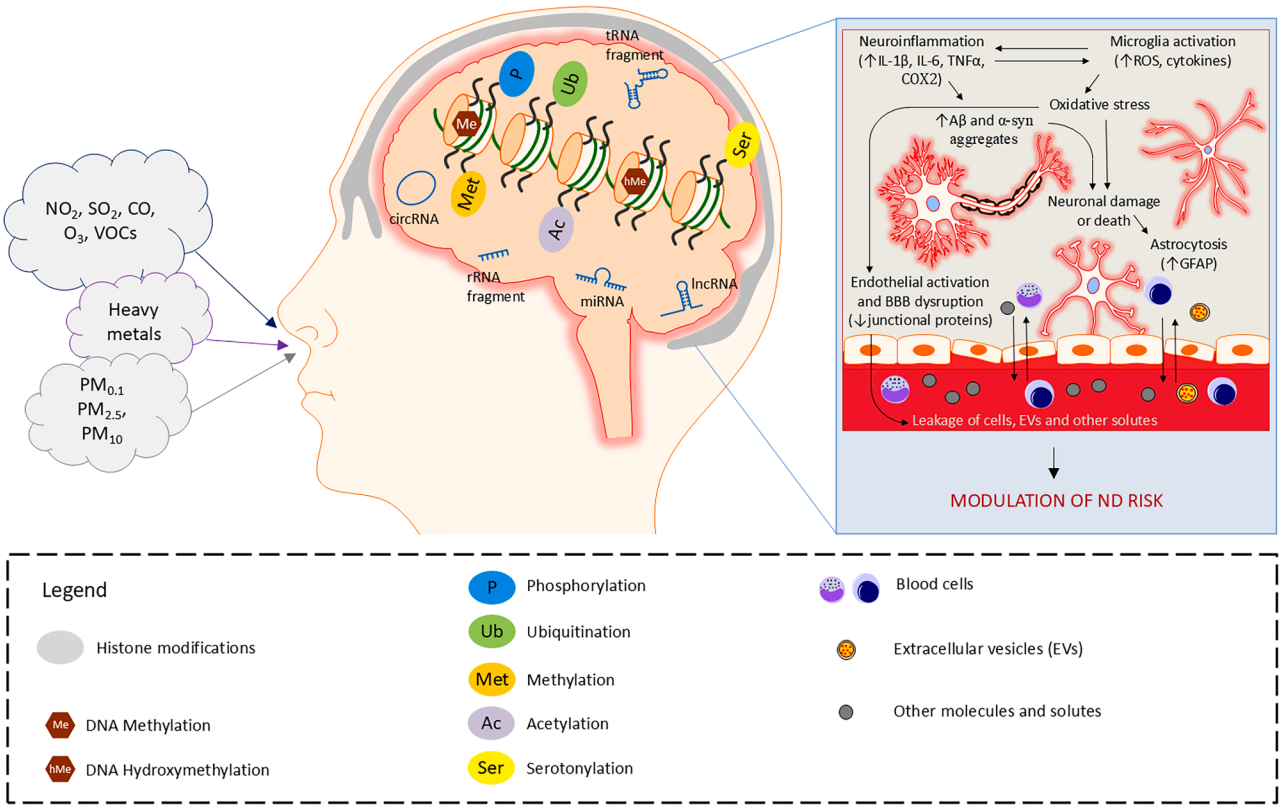

Figure 2. Effect of air pollutants on epigenetic regulation in the brain

as the adoption of preventive strategies to reduce the burden of NDs becomes increasingly imperative.

Firstly, the exact molecular mechanisms linking air pollution exposure to epigenetic modifications are difficult to determine, especially considering "real-world" pollution, which is a mixture of many different molecular components whose effect can vary depending on size and chemical composition. On one hand, nanosized particles can penetrate into exposed tissues and competitively interact with epigenetic regulators[124]; on the other hand larger particles rather exert an indirect action, fostering systemic inflammation. Here, it has been shown that macrophages can internalize $PM_{2.5}$, leading to NLRP3 inflammasome activation and subsequent release of the pro-inflammatory cytokine IL-1β.[125] Interestingly, IL-1β can promote cognitive deficits by upregulating the epigenetic repressor methyl-CpG binding protein 2 (MeCP2), a DNA binding protein which in turn silences synaptic plasticity-related genes by cooperating with histone deacetylate HDAC4.[126] Besides, the dose/concentration of inhaled particles and the health status of the individual also determine the impact on epigenetic modifications, and consequently on the phenotype. For instance, subjects with obesity inhale a larger volume of air if compared to those with normal weight (therefore, they are exposed to higher doses of air pollutants) and are hypersusceptible to air pollution-induced DNA methylation changes due to their basal, low-grade inflammatory status.[127] Similarly, it is likely that all disease states characterized by chronic inflammation (including NDs) provide fertile ground for air pollution-induced epigenetic changes. Accordingly, a recent study has shown that exposure to diesel exhaust triggers a massive epigenetic reshaping in olfactory cells from AD patients, if compared to those from controls.[128]

Due to the complexity of dealing with multiple variables that can modulate the effect of air pollution on ND risk, such as the inflammatory status and the gut microbiota, few population-based studies have been conducted so far, with the majority of them relying on a cross-sectional approach, which limits insights into temporal relationships and causality. Also, most of these studies involve participants in old age. In this scenario, it is difficult to estimate the predictive value of epigenetic biomarkers in the context of implementing preventive strategies, considering that they are assessed in a population most likely characterized by general age-related dysfunctions. In this regard, another notable gap lies in the need to understand how early-life exposure to pollutants might affect ND risk later in life, as epigenetic "priming" could sensitize individuals to neurodegenerative conditions in adulthood.

In addition, most studies have focused on PM and heavy metals, while other air pollutants remain largely neglected. Research into the direct effects of $PM_{0.1}$ on the brain is limited, particularly in human studies, where ethical and technical challenges restrict research. Similarly, although animal studies suggest that PM and VOC exposure can affect ncRNA networks in the brain, longitudinal human studies are required to confirm these findings and establish causality. This is particularly

important since the translation of findings from animal models to humans is complicated by anatomical differences in inhalation routes; for example, the substantial differences in nasal structures between rodents and humans might affect the deposition and effects of inhaled toxicants. Another area of concern is the limited research on nanoplastics and graphene, which, while not classified as recognized airborne pollutants, may still pose significant neurotoxic risks due to their potential to accumulate in brain tissues.

Recommendations for future research

Overall, existing studies have generated invaluable insights into the links between airborne pollutants and ND-associated epigenetic modifications, benefiting from diverse models and multidisciplinary approaches. *In vivo* and *in vitro* models have allowed controlled analyses of mechanistic pathways, while few epidemiological studies have provided essential population-based evidence and highlighted public health implications. However, these studies face limitations related to environmental variability, potential confounding factors, and the challenge of translating animal findings to human populations. Occupational studies tend to group exposures broadly, without accounting for the variability in exposure levels, duration, or combinations of toxicants, which may lead to inconsistent findings. In this perspective, future population-based studies need to rely on an exposome-based, one-health approach, taking into account other potentially confounding exposures. Future studies would also benefit from longitudinal designs to investigate the long-term effects of pollution exposure on ND risk. Besides, evidence is mounting that some air pollutants can enter the organism via non-inhalatory routes, such as diet and water, expanding the scope of exposure risk beyond the respiratory system. Further research on these alternative routes of exposure, as well as on non-traditional exposure pathways such as the gut-brain axis and early developmental exposures, could reveal novel intervention targets.

Notably, although AD and PD have been extensively studied, other high-prevalence NDs—such as multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease—remain comparatively under-researched in the context of air pollution and epigenetic alterations. Since all these NDs are characterized by systemic inflammation and by epigenetic alterations, both in peripheral tissues and CNS, air pollution might be implied in their pathogenesis by modulating these processes. However, this hypothesis has not yet been experimentally tested, highlighting the need for future research in this area.

Finally, there is a pressing need to study the crosstalk among different epigenetic modifications, as current evidence indicates that they interact dynamically rather than being functionally independent, and that pollutants can modulate molecular processes that control the overall epigenetic landscape. For instance, heavy metals, such as lead and manganese, are known to disrupt ion channel function within neurons, thus interfering with calcium homeostasis[129]; such dysregulation can impact the activity of calcium-dependent enzymes, such as HDACs and DNMTs, potentially leading to massive epigenetic changes in the expression of ND-related genes. To date, few studies have tried to draw a more comprehensive picture of overall epigenetic reshaping induced by air pollutants in the context of NDs, by analyzing different types of epigenetic marks. For instance, a study has shown that Pb promotes cognitive impairment by diminishing H3K27me3 levels via modulation of the interplay between EZH2 (an histone methyltransferase) and miR-137.[130] Another study reported that toluene exposure broadly alters miRNA, lncRNA, and DNA methylation targeting genes associated with NDs.[70] In this framework, omics-based techniques could provide a more comprehensive understanding of how these epigenetic marks collectively modulate ND-related processes. Integrating advanced bioinformatics and machine learning approaches could help identify specific epigenetic biomarkers for ND susceptibility and progression, allowing for more precise risk assessments. In terms of epigenetic mechanisms, further studies of histone modification patterns in response to pollutants may uncover potential therapeutic or preventive strategies, such as HDAC inhibitors or dietary interventions, which could mitigate ND risk among high-exposure populations. A targeted, multidisciplinary research approach is essential to fill these gaps, refine our understanding, and develop effective public health strategies that mitigate ND risk among high-exposure populations.

CONCLUSION

Emerging evidence underscores the pivotal role of airborne pollutants, both environmental and occupational, in shaping epigenetic alterations that may contribute to the pathogenesis of NDs. These findings carry important implications at the clinical, regulatory, and research levels.

From a clinical perspective, epigenetic modifications such as DNA methylation shifts, ncRNA dysregulation, and histone remodeling have been shown to occur in response to pollution exposure and may precede the onset of overt neurological symptoms. These molecular changes offer promising avenues for the development of predictive or early diagnostic biomarkers, particularly when measurable in peripheral tissues or through CNS-derived EVs circulating in the bloodstream.

On the regulatory front, the evidence that certain occupational groups are consistently exposed to neurotoxic airborne substances—such as heavy metals, VOCs, and fine PM—points to a need for strengthened environmental and workplace protections. Previously implemented interventions, such as the phase-out of leaded gasoline, have proved successful in reducing levels of blood Pb and its detrimental effects on cognition.[131] Besides, positive urban planning measures—such as increasing green space—could improve air quality and consequently counter ND-related outcomes induced by air pollution.[132] Incorporating epigenetic biomarkers into occupational health surveillance programs may support more tailored preventive strategies, particularly for individuals with heightened susceptibility.

Finally, future research should embrace a longitudinal, interdisciplinary, and multi-omic approach to better elucidate the causal links between pollution exposure, epigenetic dysregulation, and ND onset. Expanding the scope of investigation to underexplored disorders, such as multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease, as well as

accounting for early-life exposures and cumulative risk over the life course, will be essential to advance our understanding and to develop effective, targeted interventions.

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AUTHOR CONTRIBUTIONS

P.M.: conceptualization, investigation, visualization, writing – original draft, writing – review and editing; E.B.:, writing – review and editing, supervision, funding acquisition; V.B.: conceptualization, writing – original draft, writing – review and editing, supervision, funding acquisition.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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