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Review

Neurodegeneration and Environmental Health: Emerging Role of Polluting Metals in Alzheimer's Disease (AD): A Narrative Review

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Abstract

Alzheimer's disease (AD) is a complex neurodegenerative condition characterized by progressive cognitive decline and neuronal dysfunction. In addition to the known, genetic factors, such as the APOE $\epsilon 4$ allele, growing evidence points to the influence of environmental elements, particularly polluting metals and air pollution, in the development and progression of AD. This review explores how metals like iron (Fe), copper (Cu), and manganese (Mn), when present in excess or dysregulated, contribute to oxidative stress, neuroinflammation, mitochondrial damage, and pathological protein aggregation in the brain. Moreover, air pollution, especially exposure to particulate matter, has been associated with higher AD risk. The role of gut dysbiosis and systemic inflammation is also discussed as a potential link between environmental exposure and neurodegeneration. This synthesis of current literature highlights the importance of recognizing environmental metals as modifiable risk factors for AD and the urgent need to incorporate environmental health considerations into dementia prevention strategies.

Keywords: Alzheimer's disease; air pollution; pathways; metals; public health

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cortical atrophy, enlargement of the ventricles, and profound cognitive decline. At the cellular level, AD pathology involves the extracellular aggregation of β -amyloid ($A\beta$) into senile plaques, intracellular accumulation of hyperphosphorylated tau forming neurofibrillary tangles, and the dysregulation of glial cells such as microglia and astrocytes. These alterations disrupt synaptic plasticity and neural networks, ultimately leading to neuronal death and functional impairment [1–3].

Motor dysfunction is increasingly recognized in AD, often preceding cognitive decline. Gait disturbances, balance issues, and reduced strength are early indicators linked to amyloid and tau pathology. Neuroimaging and digital tools enable early detection. While drug options are limited, physical therapy and dual-task training improve mobility and may delay progression, enhancing patient autonomy and quality of life [4].

Recent advancements in immunoassay technologies have enabled more precise quantification of biofluid biomarkers. Brain-derived tau (BD-tau), a tau isoform specific to the central nervous system (CNS), has emerged as a promising biomarker with high specificity for Alzheimer's disease (AD). In addition, elevated levels of neurofilament light chain (NFL), indicative of axonal damage, are observed in AD and are even more pronounced in other neurodegenerative conditions [5].

Using the Nucleic Acid Linked Immuno-Sandwich Assay, plasma p-tau217 and NFL have been identified as key blood-based biomarkers in both AD and GRN mutation carriers [6].

The global burden of AD and related dementias (ADRD) is projected to surpass 140 million cases by 2050, driven largely by increasing life expectancy [7]. Despite extensive research, the precise etiology of AD remains elusive, though numerous contributing factors have been identified.

The APOE ϵ 4 allele remains the most significant genetic risk factor for AD. Carriers demonstrate greater hippocampal atrophy and accelerated cognitive decline, not only in individuals with AD and mild cognitive impairment (MCI) but also in cognitively normal populations [8].

Notably, the effects of APOE ϵ 4 exhibit sex-based dimorphism, with female carriers showing more pronounced hippocampal volume loss than their male counterparts [9]. However, the impact of APOE ϵ 4 varies across populations; among older adults in sub-Saharan Africa, its influence appears attenuated [10].

Environmental and inflammatory factors are increasingly recognized as contributors to AD pathogenesis. Exposure to air pollutants such as nitrogen dioxide and particulate matter (PM) has been linked to a heightened risk of dementia. In sub-Saharan Africa, chronic inflammation and co-infections, including HIV and helminthiasis, are associated with elevated serum iron and hepcidin levels, which may contribute to neuronal injury [11,12]. In individuals with HIV, increased inflammatory markers also correlate with poorer cognitive performance [13].

Iron (Fe) dysregulation represents a key mechanistic link between systemic inflammation and neurodegeneration. Hepcidin, the central regulator of Fe metabolism, orchestrates iron absorption, storage, and recycling. In the absence of a physiological excretory pathway, excess iron accumulates in tissues such as the brain, where it catalyzes the formation of reactive oxygen species and exacerbates neuronal damage [14,15].

Notably, elevated dietary iron intake, particularly common among adult men and older individuals through red meat consumption, supplements, and fortified foods, has been associated with multiple chronic conditions, including AD [16–18].

Expanding on this, the gut–liver–brain axis offers additional insight into how iron excess contributes to neurodegeneration. Elevated dietary iron levels disrupt gut microbial composition, promoting dysbiosis, impairing intestinal barrier function, and triggering hepatic and systemic inflammation [19]. This dysbiotic state has been linked to increased LDL-C levels and plays a role in amplifying neuroinflammatory processes associated with AD pathogenesis [20–22].

The absorption and systemic distribution of essential trace metals such as Fe, zinc (Zn), copper (Cu), and manganese (Mn) are tightly regulated to maintain cellular homeostasis and support enzymatic functions [23]. These divalent cations frequently utilize shared transport mechanisms in the gastrointestinal tract, including DMT1 (divalent metal transporter 1), ZIP family proteins, and ferroportin [24,25].

Notably, these metals also compete for binding to gastrointestinal mucins, which modulate their bioavailability for intestinal absorption. Zinc exhibits the highest mucin-binding affinity, followed by iron, copper, and manganese. Their mutual interactions can influence each other's accessibility to enterocytes, with iron showing a relatively stable binding unless displaced by manganese. Thus, metal competition begins at the mucus barrier, acting as a selective filter that regulates nutrient uptake and may contribute to trace metal imbalances or deficiencies [26].

Consequently, dietary competition among these metals can significantly influence their respective bioavailability and systemic levels [27].

Excessive intake of a single divalent metal can impair the absorption of others due to competitive inhibition at shared transporters. For instance, high oral zinc intake has been shown to reduce copper absorption, potentially resulting in hypocupremia [28]. Similarly, elevated dietary iron may interfere with the uptake of Mn [29] and zinc [30], thereby compromising antioxidant defenses and metabolic processes reliant on these cofactors.

This interaction becomes particularly significant in populations with unbalanced diets, widespread use of supplements, or altered gastrointestinal physiology. In addition, competition among essential metals can influence the absorption and distribution of toxic heavy metals such as lead (Pb) and cadmium (Cd), which exploit the same transport pathways to enter cells [31].

Although competition between divalent metals such as Fe, zinc, Mn, and Cd is well documented in the duodenum, similar mechanisms also occur in the brain. Transporters including DMT1, ZIP8, and ZIP14 are expressed in neurons and glial cells and facilitate the uptake of these metals across the blood–brain barrier (BBB). Due to their overlapping substrate specificity, these transporters mediate competitive interactions that influence cerebral metal homeostasis and may promote neurotoxicity, particularly in the presence of non-essential or toxic metals like cadmium and lead. This phenomenon is especially relevant in neurodegenerative diseases, where altered metal levels and disrupted transport have been implicated in oxidative stress and neuronal injury [32–34].

Inadequate levels of essential metals can increase the brain's vulnerability to toxic metal accumulation and oxidative damage [35]. Specifically, the disruption of metal balance due to Mn dysregulation through competition with essential elements such as Fe, magnesium (Mg), zinc, Cu, and calcium (Ca), as well as with neurotoxic metals like lead (Pb) or vanadium (V) excess can contribute to neurodegenerative processes. This disturbance may impair metal-dependent enzymatic functions and neuronal signaling. Therefore, neurotoxicity may not result solely from excess or deficiency of a single metal, but from systemic imbalances driven by competitive displacement [36–38].

Therefore, maintaining balanced intake and homeostasis of divalent metals is crucial not only for optimizing essential nutrient function but also for mitigating the toxicological risks of environmental metal exposure.

A recent bibliometric review highlights growing global interest in the roles of inflammation, immune dysregulation, and gut-brain interactions in AD, emphasizing the importance of biomarker development and neuroprotective interventions [39].

Accordingly, this narrative review aims to synthesize current evidence on the contribution of polluting metals to the development and progression of AD. It explores their role in triggering inflammation, oxidative stress, gut dysbiosis, and neurodegeneration, and considers implications for biomarker discovery and environmental health policy.

2. Air Pollution as an Environmental Risk Factor in AD

AD and related dementias result from gene-environmental interactions. Air pollution is a key modifiable risk factor. Proposed mechanisms include peripheral inflammation, neuroinflammation, and epigenetic changes, though significant data gaps remain [40].

Fewer than 5% of AD cases are demonstrably directly inherited, indicating that environmental factors may be important in initiating and/or promoting the disease [41].

Global data (1990–2019) show air pollution, especially PM_{2.5} and ozone (O₃), is significantly associated with increased AD and dementia burden. Stronger effects were seen in the Global South. Findings highlight the need for stricter pollution control measures [42]. South Asia hosts 37 of the 40 most polluted cities, with PM_{2.5} levels far exceeding WHO limits, reducing life expectancy by five years, unlike high-income countries with stricter regulations and improved air quality [43].

Latin America, part of the Global South, generally experiences higher levels of air pollution compared to North America. According to the 2023 World Air Quality Report by IQAir, many Latin American cities exceed the World Health Organization's recommended limits for pollutants such as PM_{2.5}, ozone, nitrogen dioxide, and sulfur dioxide, posing greater public health risks than in North American cities [44,45].

Neighborhood factors like housing, green space, and pollution influence AD prevalence. Geographically weighted random forest (GWRf) modeling reveals strong spatial variability, highlighting the need for targeted, county-specific interventions to address key local risk factors [46]. AD is more frequent in the global south, particularly in women [47].

Global South accounts for around 80% of deaths due to air pollution. These findings highlight the importance of considering environmental inequality between the Global North and the Global South, as well as the co-benefits of air pollution-climate change mitigation during policymaking processes [48].

From what has been described, the southern part of the world faces a high risk of increasing its incidence of AD in the future due to the high presence of polluted air and the inequity that still exists.

2.1. Sources of Air Pollution: Fine Particulate Matter, $PM_{2.5}$ ($\leq 2.5 \mu m$) and PM_{10} ($\leq 10 \mu m$), Organic Compounds, Heavy Metals

Airborne magnetite nanoparticles ($<200 \text{ nm}$) from traffic can enter the brain via olfactory pathways, bypassing the blood-brain barrier. Their neurotoxicity and prevalence may pose a global environmental risk factor for AD development [41]. Figure 1 shows how easily the entry of metals in PM into the human brain is through the olfactory pathway.

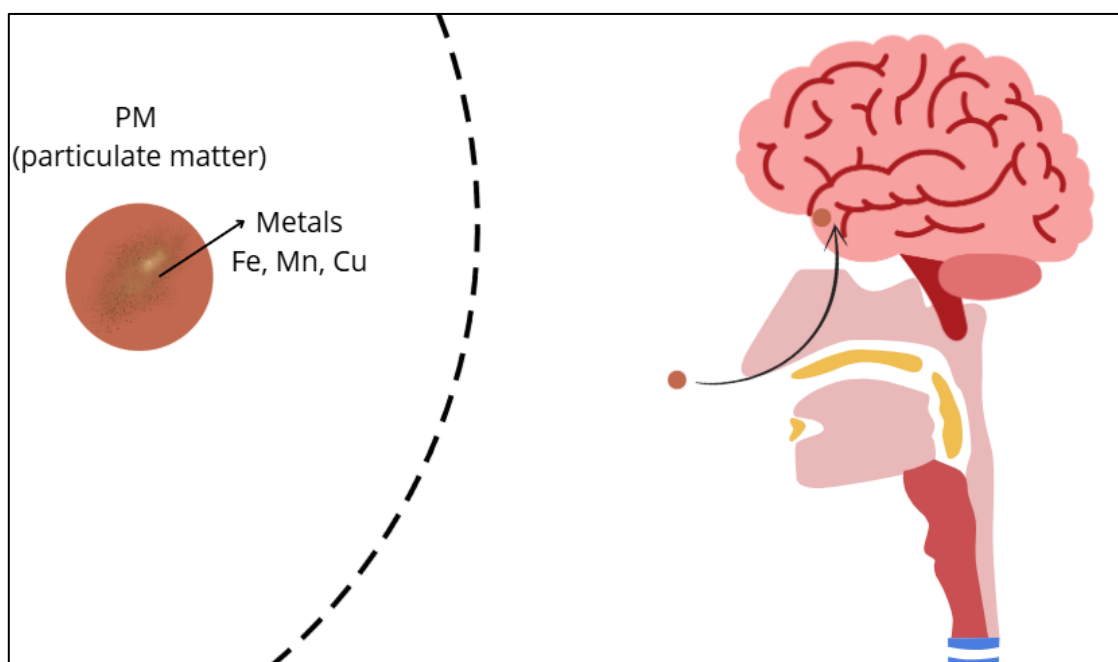


Figure 1. Entry of metals in particulate matter into the human brain directly from olfactory pathway.

Magnetite nanoparticles, capable of catalyzing the formation of reactive oxygen species, occur in AD plaques and tangles; they are thought to form *in situ*, from pathological iron dysfunction [41].

Excess brain iron and air pollution exposure increase neurodegenerative disease risk. Iron, abundant in air pollution, especially in subways, may enter the brain via olfactory pathways, contributing to lifelong accumulation linked to neurological disorders [49].

Higher hippocampal iron uniformity in mild cognitive impairment suggests a pathological continuum from aging to AD, supporting non-heme iron accumulation as an early biomarker of cognitive decline and AD risk [50].

Iron in PM_{10} was linked to higher AD and dementia rates in Lima, Peru, a city with high air contamination [51]. Inhaled iron nanoparticles accumulate in the brain, showing sex-dependent neurodegenerative effects, Alzheimer-like in females and Parkinson-like in males. Prolonged exposure may raise brain Fe and disease risk, highlighting the need for regulation [49].

Although iron has been linked with different neurodegenerative diseases, this may be because it is differentially distributed across brain regions. For example, a study demonstrates a region-specific distribution of brain iron in amyotrophic lateral sclerosis (ALS). Significant susceptibility differences across hippocampal, amygdala, and thalamic regions were observed based on disease progression rate and motor phenotype. These findings suggest localized iron dyshomeostasis and spatial iron changes in neurodegeneration [52].

Moreover, increased thalamic iron levels have also been observed in other neurodegenerative diseases, particularly in younger individuals and in studies using high-resolution imaging, further supporting a regionally differentiated pattern of iron accumulation in the brain [53].

The reasons why iron is differentially distributed in the brain are not yet fully elucidated; however, it may determine the generation of different neurodegenerative diseases in men and women.

The primary neurotransmitter system affected in Parkinson's disease (PD) is the nigrostriatal dopaminergic pathway, whose dysfunction gives rise to the hallmark motor symptoms. Substantial evidence indicates sex-based differences in PD prevalence and progression, with men more commonly affected and exhibiting faster symptom progression than women [54,55]. In contrast, AD is more prevalent in women (35% vs. 17%), whereas vascular dementia is slightly more frequent in men (21% vs. 17%) [56].

Environmental air pollution remains a critical issue in large cities due to anthropogenic activities like fossil fuel combustion, which emit suspended particulate matter (PM) [57].

Trace metals, particularly Fe, Zn, and Cu, are key drivers of PM_{2.5} toxicity, contributing up to 52% of ROS production in Hong Kong [58]. A meta-analysis confirmed that PM_{2.5} constituents such as iron are consistently linked to increased mortality and cardiovascular and respiratory diseases, underscoring the need to regulate specific components to protect health [59].

Long-term exposure to PM_{2.5} notably more so than PM₁₀ is associated not only with increased respiratory disease risk, particularly in low- and middle-income countries [60], but also with adverse neurological outcomes. In Shijiazhuang, seasonal spikes in PM_{2.5} and Mn during heating periods further elevating health risks, despite overall air quality improvements, underscoring the need for stricter seasonal pollution controls [61]. Importantly, PM_{2.5} can cross the blood-brain barrier via inhalation or olfactory pathways, triggering neuroinflammation, oxidative damage, and microglial activation. These effects are strongly linked to neurodegenerative disease risk, cognitive decline, and structural brain changes in older adults [62,63].

Aerosol particles impact health due to their oxidative potential. On Fukue Island, Japan, anthropogenic sources contributed 17% of Fe and 44% of Mn in PM_{2.5}, mainly transported from industrial regions in Asia [64].

In Seoul (urban, traffic), the main sources of Mn, Fe, V, and Zn in PM_{2.5} were road dust and tire wear. In Wonju (rural, industrial), the high levels were attributed to industrial emissions [65]. This shows how different anthropogenic sources (traffic, industry) determine the concentration of Fe and Mn in the air, with negative implications for health.

A ferromanganese (FeMn) smelter located in Meyerton, South Africa, has been in operation since 1959 and produces approximately 540 kilotons of FeMn annually. PM_{2.5} levels in nearby residential areas have been found to contain elevated manganese (Mn) concentrations in both indoor and outdoor environments. Fine particles (<2.5 μm) predominated, which can readily enter the respiratory tract, reach the bloodstream, and translocate to the brain via the olfactory pathway. These findings highlight the impact of metallurgical industries on the bioavailability of environmentally relevant manganese [66].

Air pollution involving trace metals such as Fe and Mn has become a growing public health concern due to their toxic potential, especially in soluble or ultrafine particulate forms that can bypass respiratory defenses. Although both elements are essential micronutrients, chronic inhalation exposure can lead to adverse pulmonary, cardiovascular, and neurological outcomes. In Peru, several regions face heightened risk from combined mining, industrial, and vehicular emissions including La Oroya, Cerro de Pasco, El Callao, and the mining zones of Junín [67].

Complementing environmental data, experimental evidence further supports the biological impact of Mn and Fe co-exposure on the brain.

A study conducted in 2025 showed that Mn exposure alone induces oxidative stress in astrocytes by downregulating the STAT3/SOD2 pathway, whereas co-exposure with iron (Fe) activates the NRF2/NQO1 antioxidant pathway, leading to a reduction in reactive oxygen species (ROS) levels. These findings suggest a complex interaction between Mn and Fe in neural tissue that may involve protective mechanisms [68].

2.2. General Mechanisms by Which Air Pollution Impacts Neurological Health

Air pollution is a critical global concern with far-reaching effects beyond respiratory health, notably impacting neurological and psychiatric disorders. Growing evidence links exposure to PM_{2.5}, sulfur dioxide (SO₂), and nitrogen dioxide (NO₂) with increased risks of dementia, AD, schizophrenia, ADHD, stroke, PD, and multiple sclerosis. In Figure 2, air pollution is observed as a risk factor for the development of AD.

PM_{2.5} can impair cognitive function through direct entry into the brain via the nose-to-brain route. Short-term exposure in mice induced learning and memory deficits, along with neuronal damage and glial activation, without marked systemic inflammation. Transcriptomic analysis revealed that PM_{2.5} primarily disrupts synaptic function rather than triggering classic neuroinflammatory pathways. Moreover, microglial depletion did not reverse cognitive impairment, reinforcing the role of synaptic dysregulation as a central mechanism. These findings highlight a direct neurotoxic effect of PM_{2.5} on brain function, independent of peripheral inflammation [69].

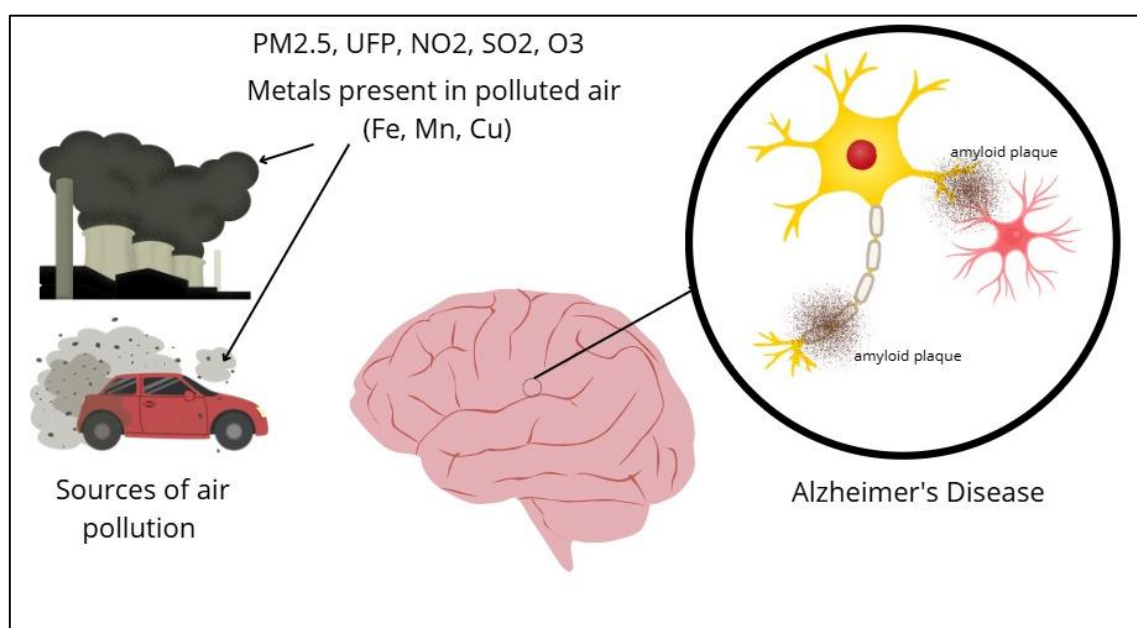


Figure 2. Air pollution as a risk factor for the development of Alzheimer's disease.

Air pollution, particularly ultrafine particles (UFPs), disrupts the PI3K/AKT signaling pathway, which regulates neuronal survival, especially in AD. UFPs increase oxidative stress and DNA damage without causing immediate cell death. In AD olfactory mucosa (OM) cells, altered microRNA and DNA methylation profiles impair gene regulation, making them more susceptible to air pollutant-induced toxicity [70].

Air pollution accelerates cognitive decline and may contribute to AD by targeting glutamatergic synapses. Chronic exposure to diesel exhaust particles reduces postsynaptic markers and the glutamate receptor, N-methyl-D-aspartate (NMDA) receptor subunits in the cortex, while upregulating antioxidant enzymes involved in ferroptosis mitigation. These synaptic changes suggest a molecular link between air pollution and AD pathogenesis [71].

Gamma-secretase modulator (GSM-15606) attenuates the amyloidogenic amyloid beta (A β)₄₂ peptide during exposure to air pollution, which may be a mechanism by which air pollution increases AD risk [72].

Proposed mechanisms underlying neurodegenerative disorders include neuroinflammation, oxidative stress, microglial activation, cerebrovascular dysfunction, and disruption of the blood–brain barrier [73]. Although the precise pathways by which air pollutants contribute to neurological disorders are not fully elucidated, current evidence highlights the roles of BBB compromise, glial activation, and sustained oxidative and inflammatory responses [74].

Microglia, the brain's resident immune cells, act as key environmental sensors and play a central role in air pollution-induced neuroinflammation. In response to various stimuli, microglia can polarize into either a pro-inflammatory (M1) or an anti-inflammatory (M2) phenotype. A shift toward the M1 state promotes the release of inflammatory cytokines, oxidative stress, and synaptic dysfunction, all of which contribute to neuronal damage and cognitive decline in AD [75].

Chronic PM_{2.5} exposure promotes Alzheimer's-like pathology by shifting microglia to a pro-inflammatory state that releases extracellular vesicles (EVs) rich in miR-34a-5p. This suppresses neuronal DUSP10, activates p38 MAPK, and triggers tau phosphorylation, β -amyloid buildup, and neuronal death. Silencing miR-34a-5p mitigates these effects, linking PM_{2.5} to neurodegeneration [1].

Ultrasound stimulation has been shown to modulate microglial polarization in AD models by reducing M1 and enhancing M2 populations, thereby lowering amyloid plaque burden and increasing hippocampal IL-10 levels. Proteomic analyses link these changes to enhanced mitochondrial oxidative phosphorylation, suggesting a novel mechanism for therapeutic intervention [76].

Circular RNA circAPP, encoded by the amyloid precursor protein gene, is upregulated in AD and promotes M1 polarization by acting as a molecular sponge for miR-1906, which in turn increases Chloride Intracellular Channel 1 (CLIC1) expression and activity. CLIC1 is a redox-sensitive chloride channel activated in microglia during inflammation. Its upregulation contributes to oxidative stress and neuroinflammation in AD, promoting a pro-inflammatory microglial phenotype. The circAPP/miR-1906/CLIC1 axis exacerbates neuroinflammation and cognitive impairment, identifying circAPP as a promising therapeutic target [77].

Similarly, the microglia-enriched circRNA circDlg1 contributes to neuroinflammation in APP/PS1 mice by regulating the degradation of PDE4B. Loss of circDlg1 enhances microglial responses to A β deposition and reduces neuroinflammation, underscoring its potential as a microglia-specific therapeutic target in AD [78].

Finally, the Methyltransferase-like 3/ Insulin-like Growth Factor 2 mRNA-binding Protein 2/ Inhibitor of kappa B alpha (METTL3/IGF2BP2/I κ B α) signaling pathway also modulates microglial polarization, offering further insight into molecular targets for regulating neuroinflammation in AD [79]. This epigenetic signaling pathway regulates microglial polarization by enhancing inflammatory gene expression through m6A RNA methylation. It contributes to sustained neuroinflammation in AD by activating the NF- κ B pathway.

Disruption of microglial metabolism, particularly glycolysis impairs their neuroprotective functions and promotes pro-inflammatory phenotypes, contributing to synaptic damage and cognitive decline characteristic of AD. Understanding how environmental pollutants influence microglial phenotypes is essential for developing targeted prevention and treatment strategies. Modulating microglial glycolytic pathways may represent a promising therapeutic approach for pollution-related neurodegenerative disorders [80,81].

Particulate matter (PM) represents a major environmental health risk due to its complex mixture of organic and inorganic compounds of varying sizes, compositions, and sources. Its ability to penetrate deep into tissues and cross the BBB contributes to neurotoxicity and the pathogenesis of neurodegenerative diseases. Beyond initiating oxidative stress, inflammation, and excitotoxicity, air pollution also induces epigenetic alterations that can affect the expression of genes involved in stress responses, neuroprotection, and synaptic plasticity [82].

PM_{2.5} exposure has been linked to epigenetic modifications, such as changes in DNA methylation, histone structure, and non-coding RNAs which are associated with cognitive impairment through mechanisms involving inflammation, synaptic dysfunction, cardiovascular factors, and neuronal structural changes [83].

AD is characterized by the progressive misfolding of proteins and the formation of plaques, which initially develop in specific brain regions before spreading to the entire cortex [84]. The inhalation of diesel engine exhaust (DEE), a major source of particulate air pollution, has been shown to accelerate A β plaque formation in the cortex and hippocampus [85].

Noise exposure may also contribute to ADRD. A systematic review highlighted the need for standardized methodologies and adjustment for confounders [86]. In the UK Biobank study, night-time road traffic noise above 45 dB was linked to higher AD risk, while railway noise was associated with PD-related dementia. Cardiovascular health may mediate these effects [87]. Simultaneous exposure to noise and carbon monoxide increases the risk of AD [88].

Soluble PM, such as metals and nano-sized particles, may translocate across the olfactory, trigeminal, or vagal nerves through retrograde axonal transport, or systemic circulation, which may disrupt the BBB and deposit in neural tissue. Systemic hormonal and immune changes may further affect the brain through adrenal hormone-dependent pathways [89].

In mice, postnatal exposure to ultrafine particulate matter (UFPs) leads to neurotoxicity marked by brain iron accumulation. Given iron's redox activity and neurotoxicity, the study suggests that inhaled iron contributes significantly to UFP-induced brain damage. The neurotoxic effects may vary depending on the chemical composition of the particulate mixture, underscoring iron's role in air pollution toxicity. [90].

Exposure to ultrafine particles (UFPs) during adolescence disrupts neurotransmitter systems and reduces myelination and astrocytes in the corpus callosum, particularly in male mice, indicating high vulnerability. Altered glutamate and corticosterone levels correlated with structural brain damage. These findings support the biological plausibility of links between UFPs and neurodegenerative or psychiatric disorders, highlighting the need for stricter environmental regulation of UFPs [91].

The health risk associated with magnetic iron oxide nanoparticles (Fe_xO_y NPs, mainly Fe_3O_4 and $\gamma\text{-Fe}_2\text{O}_3$) have garnered escalating attention due to their presence in human blood and brain tissues, especially for their potential association with neurodegenerative diseases like AD [92]. An ecological relationship between Fe in PM_{10} and AD has been suggested in human beings [51].

Inhaled iron oxide nanoparticles accumulate in the olfactory bulb and induce sex-specific neurodegenerative features, Alzheimer-like in females and Parkinson-like in males. These findings suggest that chronic airborne iron exposure may elevate brain iron by aging and increase the risk of neurodegenerative diseases, warranting further investigation into its long-term effects [49]. These data suggest a need for regulation of Fe in the air for public health protection.

3. Epidemiological Studies for Alzheimer's Diseases (AD) and Alzheimer's Diseases-Related Dementia (ADRD)

AD is the most common form of dementia worldwide. AD and ADRD disproportionately affect Black Americans compared to non-Hispanic White individuals. Economic hardships, especially low income and unemployment, reduce access to physical and mental healthcare, drive dementia risk. Those from more deprived areas highlighted the need for improved health education, public transportation, healthcare access, and job opportunities [93].

Women suffer more frequently from AD, whereas men suffer more frequently from PD and ALS. Research suggests neuroprotective effects of estrogens and confirms that factors reducing their level may contribute to a higher morbidity rate of neurodegenerative diseases (NDs). Adverse effects of androgens on NDs have been noticed; however, some data suggest their beneficial actions [94].

The cumulative evidence hitherto collected suggests that sex and gender are factors to be considered in explaining the heterogeneity of these NDs. Clarifying the role of sex and gender in AD, PD, and ALS is a key topic in precision medicine, which will facilitate sex-specific prevention and treatment strategies to be implemented soon [95].

A Mendelian randomization study demonstrates a causal protective role of bioavailable testosterone (BT) against neurodegeneration. Genetic analysis revealed that higher BT levels significantly reduce the risk of developing ALS (OR = 0.794, $p = 0.006$), while no associations were found for estradiol or sex hormone-binding globulin (SHBG) with ALS, PD, or AD. These findings support a sex hormone-dependent mechanism in ALS susceptibility and suggest that testosterone may be a modifiable factor for neuroprotection [96].

A Mendelian randomization study identifies a potential causal role of sex hormone-binding globulin (SHBG) in multiple sclerosis (MS). Genetically predicted higher SHBG levels were significantly associated with increased MS risk (OR = 1.634, $p = 0.038$), and bidirectional analysis confirmed that MS may, in turn, influence SHBG levels (OR = 1.005, $p = 0.003$). No causal links were found for estradiol, total testosterone, or bioavailable testosterone. These findings suggest SHBG as a potential biomarker or modifiable factor in MS pathophysiology [97].

AD is increasingly recognized as a systemic disorder with significant contributions from both hepatic and cardiovascular dysfunction [98,99]. Through the liver-brain axis, the liver influences AD progression by clearing peripheral β -amyloid ($A\beta$), modulating systemic metabolism, and secreting hepatokines such as SHBG, FGF-21, SELENOP, and ApoJ. These proteins regulate insulin sensitivity, lipid metabolism, oxidative stress, and immune responses, which in turn contribute to $A\beta$ accumulation, tau hyperphosphorylation, and neuronal damage [98].

Cardiovascular disease contributes to AD through shared genetic risks (e.g., APOE, presenilin), impaired cerebral perfusion, and oxidative stress, which promote $A\beta$ and tau pathology. Systemic protein aggregation, microvascular damage, and blood-brain barrier disruption link neurodegeneration and cardiac dysfunction, highlighting the liver-brain and brain-heart axes as therapeutic targets in AD [99].

Body iron content increases progressively in women after menopause due to the cessation of menstrual blood loss, leading to iron accumulation with advancing age. Iron stores in women remain low during the reproductive years but increase progressively from the fifth decade, reaching levels like those observed in men by the seventh decade. This age-related accumulation of iron has been associated with oxidative stress and neurodegenerative processes. The higher lifetime risk of AD observed in women may, in part, be influenced by postmenopausal iron buildup, which could contribute to greater vulnerability through mechanisms such as amyloid-beta aggregation, tau hyperphosphorylation, and neuroinflammation [100].

3.1. Epidemiological Studies That Link Exposure to Polluted Air with Cognitive Impairment and AD

Alzheimer's disease (AD), a neurodegenerative disorder, accounts for 50–75% of all dementia cases. Numerous studies have identified a significant association between air pollution and increased AD and dementia risk [42,101]. The 2018 Lancet Commission on Pollution described the evidence linking particulate matter (PM) exposure to dementia as compelling [102].

In a cohort of 30,247 adults, air pollution exposure was associated with elevated AD risk [103]. Epidemiological studies further confirm that exposure to fine particulate matter ($PM_{2.5}$) not only increases the likelihood of developing AD but also accelerates its progression, particularly in highly polluted regions [104,105]. In Figure 3, epidemiological evidence linking air pollution to cognitive impairment and AD.

As life expectancy continues to rise, the global elderly population is expected to increase, leading to a higher prevalence of age-related diseases, including AD. Ambient air pollution has substantially contributed to the global burden of disease over the past 25 years, largely due to population aging, increased rates of non-communicable diseases, and rising pollution levels in low- and middle-income countries [106]. The burden of dementia is expected to increase globally, given the continuous expansion of the ageing population.

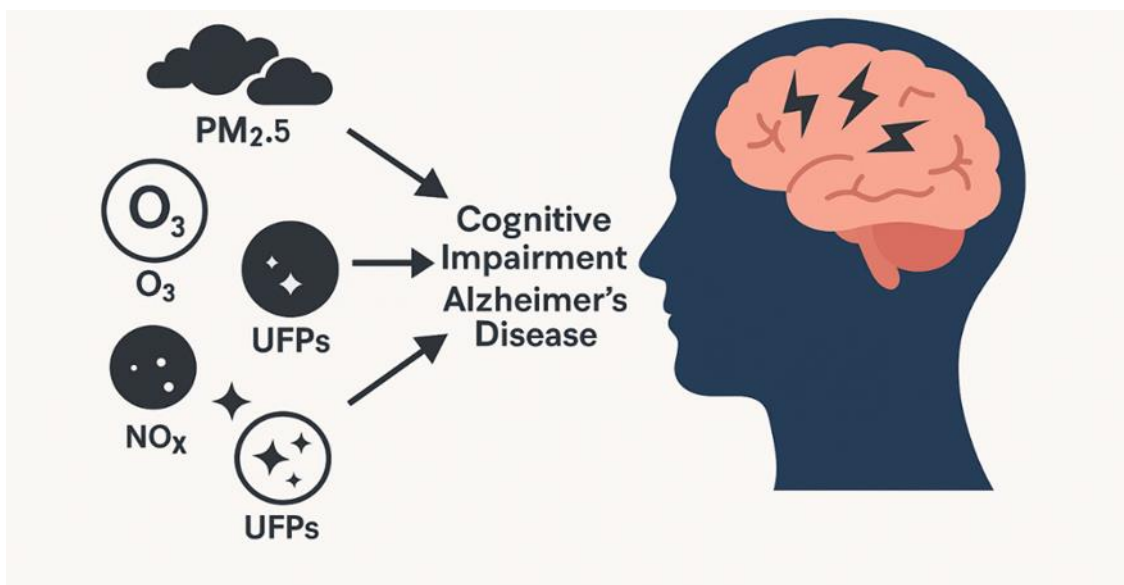


Figure 3. Epidemiological evidence linking air pollution to cognitive impairment and Alzheimer's Disease.

A life-course study found that in-utero and early-life exposure to $PM_{2.5}$ and NO_2 was associated with increased risk of AD and all-cause dementia. Cumulative $PM_{2.5}$ exposure across the lifespan also elevated dementia risk, highlighting sensitive periods of vulnerability [107]. Differences in brain volume may also mediate the relationships between air pollution and AD [108].

Iron-rich UFPM and industrial nanoparticles from air pollution present in the brains of children and young adults, were early signs of AD, PD, and TDP-43 proteinopathy observed. These particles cross biological barriers, accumulate in sleep–arousal centers, and localize in neurovascular units. Their magnetic reactivity and oxidative potential may trigger early, irreversible neurodegeneration, sleep disruption, and cognitive decline. Neurodegenerative changes begin in pediatric ages, underscoring the need for preventive strategies [109,110].

Sporadic Alzheimer's disease (AD) occurs in 99% of all cases and can be influenced by air pollution such as diesel emissions and more recently, an iron oxide particle, magnetite, detected in the brains of AD patients. There are mechanistic links between inflammation and oxidative stress to pollutant particle-induced AD pathologies, with magnetite apparently inducing the most pathological effects [111].

Long-term exposure to air pollutants, especially $PM_{2.5}$ and O_3 , has been associated with increased risk of AD and PD in several countries [112,113]. More than 50 studies over the past two decades have examined the link between air pollution and AD and related dementias (ADRD) [114].

A recent systematic review and meta-analysis of 28 longitudinal cohort studies assessed the association between long-term $PM_{2.5}$ exposure and dementia risk using the Burden of Proof framework. A nonlinear relationship was found, with at least a 14% increased risk of dementia across $PM_{2.5}$ levels ranging from 4.5 to 26.9 $\mu g/m^3$. The association was stronger for AD than for vascular dementia, emphasizing the role of air pollution in brain aging and dementia development [115].

Global ecological data from 162 countries revealed that each 10-unit increase in $PM_{2.5}$ or ozone levels was associated with increased incidence, mortality, and disability-adjusted life years (DALYs) from AD and other dementias, with greater impact observed in countries with lower gross national income and socio-demographic indices [116]. Recent findings show that among individuals previously hospitalized for AD/ADRD, post-discharge exposure to air pollution is significantly associated with higher risk of readmission and mortality [117].

In the U.S., a geographically weighted model showed AD prevalence is influenced by mobile home residency (19.9%), low greenness (17.4%), physical inactivity (12.9%), lack of vehicle access

(11.3%), and PM_{2.5} exposure (10.4%), highlighting the need for region-specific environmental and lifestyle interventions [46].

Vegetation may have a protective role. Higher levels of greenness attenuate the harmful effects of PM_{2.5} and O₃ on dementia outcomes, underscoring the importance of natural environments in mitigating cognitive decline [116].

Moreover, interactions between ambient air pollution and social vulnerability may also influence ADRD mortality [118].

In Latin America and the Caribbean (LAC), more than 172 million people are exposed to unhealthy air. Air pollution contributes to five established dementia risk factors (obesity, hypertension, stroke, diabetes, and cardiovascular disease) and is linked to three additional factors (physical inactivity, cognitive inactivity, and depression), some of which may mediate the pollution-dementia relationship [119].

While PM_{2.5} is a known contributor to cognitive decline, ultrafine particles (UFPs <100 nm) are even more toxic due to their small size and high reactivity [120]. In addition, O₃ exposure has been implicated in neurodegeneration. In China, during 2023, elevated O₃ levels were estimated to have caused approximately 110,000 new AD cases. Reducing O₃ concentrations to 70 µg/m³ could prevent over 210,000 cases, highlighting the need for urgent interventions [121].

Nitrogen oxides (NO_x) are also emerging as key contributors. In dual-pollutant models, only NO_x remained significantly associated with AD risk, particularly with exposures during the previous five years. No association was observed for vascular dementia, indicating the need to differentiate dementia subtypes and use multi-pollutant models [103].

A recent U.S.-based cohort study (2000–2018) identified sulfate (SO₄²⁻), organic carbon (OC), copper (Cu), and iron (Fe), mainly from fossil fuel combustion and traffic, as key PM_{2.5} components linked to higher AD risk [122]. In Lima, Peru an ecological study showed link between SO₄²⁻, iron, manganese and Cu with AD and ADRD risks [51], public health strategies targeting these sources may reduce the neurodegenerative burden.

Furthermore, combined exposure to air pollution and artificial light at night has been associated with memory disorders, suggesting potential synergistic effects mediated by biomarkers [123].

A nationwide U.S. cohort study found that extreme heat increases the risk of ADRD-related hospitalizations. Risk was significantly higher among Asian, Black, and Hispanic populations, indicating disproportionate climate vulnerability [124].

Prevalence of AD is higher in women than in men. Menopause before age 45 years was associated with a 33% greater hazard of AD dementia compared with menopause after age 50 years (hazard ratio [HR] = 1.33, 95% confidence interval [CI]: 1.10-1.59). Hysterectomy was not associated with hazard of AD dementia (HR = 1.08, CI: 0.94-1.26). The association between age at menopause and hysterectomy status and AD dementia was not different for White and Black women [125]. Therefore, the high longevity of women does not explain the mechanisms underlying the biological differences between the sexes causing a female predominance in the development of AD.

In experimental studies, female APP/PS1 mice had greater amyloid deposition, hyperactivity, lower body weight, and reduced cerebral blood flow, as well as less neuroinflammation, which the authors suggest may have potential neuroprotection [126].

Interleukin (IL)-6 was identified as a key pro-inflammatory marker, consistently linked to AD, PD, and dementia, underscoring its significant role in neurodegenerative disease progression. Brain-derived neurotrophic factor levels were associated with improved cognitive performance, particularly in African American participants. Observational studies identified sex-based differences in IL-10 levels, particularly among older African American women [127].

Systemic comorbidities are common in AD and may influence disease progression, severity, and management. Men had a higher prevalence of heart disease, diabetes, chronic obstructive pulmonary disease and smoking, whereas thyroid disease, hypertension and depression were more common in women (all p<0.05) [128].

Astrocytic TNFR2 signaling is essential for maintaining hippocampal synaptic function and plasticity. Selective deletion of TNFR2 in astrocytes disrupted synaptic protein expression and glial-neuronal communication, leading to cognitive deficits. These effects were more pronounced in male mice, who showed increased astrocyte and microglial reactivity, impaired memory, and reduced LTP, highlighting a sex-dependent regulation of astrocyte-mediated synaptic function [129].

In Long-Evans rats, O₃ altered glucocorticoid signaling, microglial activity, and oxidative stress markers differently in males and females. Notably, female rats exhibited greater oxidative damage, with higher levels of protein carbonyls and increased expression of microglia-related genes such as *Aif1*, compared to males. Additionally, antioxidant and glucocorticoid-related genes (*Cat*, *Gpx1*, *Nfe2l2*, *Sod1*) were more strongly modulated in females. These findings suggest that females are more vulnerable to the neurotoxic effects of ozone exposure [130]. Main findings of research on airborne metals and neurodegenerative diseases are shown in Table 1.

Table 1. Research on airborne metals and neurodegenerative diseases.

MATRIX	METALS FOUND / RESULTS	AGE	LOCATION	METHOD	REFERENCE
PM _{2.5} (EXPERIMENTAL EXPOSURE)	Fe, Mn	Mice (juvenile and adult)	Controlled experimental settings	Experimental	[68]
AIRBORNE PM ₁₀	Fe, Cu, Mn, Zn, SO ₂	≥ 60 years	Lima, Peru	Ecology	[51]
AIRBORNE ULTRAFINE PM	Fe, Ti, Hg, Ni, Co, Cu, Zn, Cd, Al, Mg, Ag, Ce, La, Pr, W, Ca, Cl, K, Si, S, Na y C	Pediatric to older adults	Mexico City	Pathology, Imaging	[109]
UFPS		Adolescent mice	Laboratory setting	Experimental Animal Study	[91]
PM _{2.5}	SO ₄ ²⁻ , OC, Cu	≥ 60 years	USA	Cohort study, modeling	[122]
PM ₁₀	Fe, Mn	All ages	La Oroya, Cerro de Pasco, Callao, Junín, Lima (Peru)	Narrative synthesis	[67]
FE EXPOSURE	Magnetite (Fe ₃ O ₄)	Mice: juvenile	University of Rochester Medical Center, USA	Pathology & Imaging	[49]
DIESEL EXHAUST PARTICLES	altered myelin composition in multiple regions	Mice: adult	Zilkha Neurogenetic Institute, Keck School of Medicine, University of	Pathology & Imaging	[198]

				Southern California, USA		
IN BLOOD (FER-1, MNCL ₂ , FER-1 + MNCL ₂)	Mn-exposed mice exhibited movement impairment and encephalic pathological changes, with decreased HIF-1 α , SLC7A11, and GPX4 proteins and increased p53 protein levels. Fer-1 exhibited protective effects against Mn-induced both behavioral and biochemical changes	Mice: juvenile	Department of Preventive Medicine and Public Health Laboratory Sciences, School of Medicine, Jiangsu University, Zhenjiang, Jiangsu 212013, China	Experimental Animal Study	[163]	
POLLUTANT IRON-BASED PARTICLE, HYDROCARBON-BASED DIESEL COMBUSTION PARTICLE AND MAGNETITE PARTICLES	Neuronal cell loss was shown in the hippocampal and somatosensory cortex, with increased detection of A β plaque,	Mice: juvenile	Australian Institute for Microbiology and Infection, University of Technology Sydney, Sydney, Australia	Experimental Animal Study	[111]	

4. Metal Homeostasis in the Brain

Metal ions are widely distributed throughout the brain and are essential for numerous central nervous system (CNS) functions, including neuronal activity and synaptic transmission [131]. Trace elements such as Fe, Cu, Zn, Mn, and selenium (Se) play critical roles in neurotransmitter synthesis, myelination, and antioxidant defense mechanisms. Under normal physiological conditions, the homeostasis of these metals is tightly regulated, as both deficiency and excess can impair neuronal function [132].

The brain regions most consistently affected by metal exposure include the globus pallidus, caudate nucleus, frontal cortex, and cerebellum. Some studies exhibit structural or functional reductions in these areas that correlate with increased levels of metal exposure, suggesting a dose-dependent neurotoxic effect [133].

In AD, pathological alterations are closely linked to disruptions in trace element balance. These elements are also fundamental to key physiological processes such as DNA and protein synthesis, energy metabolism, and enzymatic activity, processes essential for cognition and brain development. Dysregulation in the homeostasis of elements including copper, iron, zinc, selenium, rubidium,

silicon, chromium, and vanadium has been implicated in the pathogenesis of neurodegenerative diseases such as AD [134].

Human exposure to heavy metals occurs through inhalation, ingestion, or the food chain. These metals impair antioxidant defenses by interacting with intracellular glutathione (GSH) or sulfhydryl groups of key enzymes like SOD, catalase, glutathione peroxidase (GPx), glutathione reductase (GR), and related systems [135].

Environmental toxins promote oxidative stress, neuroinflammation, mitochondrial dysfunction, and altered APP/tau processing. Exposure increases GSK-3 β , BACE-1, TNF- α , and caspases, while reducing BDNF and GAP-43 expression. Dysregulated PARP-1, PGC-1 α , and MAPK/ERK signaling contribute to AD [136].

An in vitro study showed that PM_{2.5} promotes neuronal necroptosis via LncRNA Gm16410 downregulation through p38 MAPK, contributing to AD. The SVHRSP peptide mitigated this effect, revealing a novel LncRNA-mediated mechanism and potential therapeutic target for AD [137].

Copper, iron and zinc are accumulated in post-mortem amyloid plaques of Alzheimer's patients (5.7, 2.8 and 3.1 times more than in normal brains, respectively). The use of chelators is proposed to restore metal homeostasis and reduce oxidative damage [138].

The pathophysiology of neurodegenerative diseases is significantly influenced by metal-induced oxidative stress and toxic buildup. For such reasons, therapeutic approaches point to reduce oxidative damage and chelating excess metals. The regulation of these pathways reduces neuronal damage and improves neurons' survival and functionality [139].

Iron participates in a wide array of cellular functions and is essential for normal neural development and physiology. However, if inappropriately managed, the transition metal can generate neurotoxic reactive oxygen species [140].

Mutations in genes such as *C19orf12*, which regulate iron and lipid metabolism, are implicated in neurodegeneration with brain iron accumulation (NBIA), a group of rare, inherited disorders characterized by excessive iron deposition in the brain. Although NBIA is genetically driven, it provides mechanistic insights into how iron dyshomeostasis leads to mitochondrial dysfunction and neurodegeneration. Similar pathways may be environmentally triggered by chronic exposure to air pollutants, suggesting a shared vulnerability in iron-regulating systems between genetic and environmental etiologies [141,142].

Exposure to heavy metals is linked to increased AD risk, triggering oxidative stress, mitochondrial dysfunction, protein aggregation, neuroinflammation, and tau pathology. Metals like Pb, Cd, As, and Mn affect specific AD pathways [143].

Dysregulation of redox-active metals, especially Fe, Cu, and Mn contribute significantly to AD and PD pathogenesis by promoting oxidative stress, mitochondrial dysfunction, and apoptosis [144]. In the hippocampus, Fe, Zn, and Ca are most abundant, with Cu and Mn present in lower concentrations but exhibiting distinct subcellular localization, particularly in CA1 neurons [145].

In Alzheimer's disease, Fe, Cu, and Zn accumulate in amyloid plaques and neurofibrillary tangles. Mn impairs dopaminergic neurogenesis, Fe induces ferroptosis, and Cu disrupts antioxidant defenses. Combined exposure enhances β -amyloid aggregation and neuroinflammation [146].

Fe homeostasis in the brain is essential for maintaining neuronal viability. However, excessive iron accumulation induces oxidative stress and ferroptosis, contributing to poor outcomes not only in AD but also in stroke and other neurological disorders [147]. As a divalent metal, Fe may compete with other divalent metals, such as Zn and Mn, for shared transporters, highlighting the importance of maintaining a balanced trace element profile.

After Fe(II) exposure, labile Fe (II) is stored in lysosomes and transported through neurites. This may aid detoxification and supply iron to neuronal compartments. Iron dyshomeostasis, particularly labile iron contributes to neurodegeneration [148].

Type 2 diabetes patients show increased iron accumulation in the caudate and putamen, correlating with poorer cognitive performance, including slower processing speed, memory decline, and executive dysfunction. HbA1c levels were the strongest predictors of iron deposition, especially

in the anterior putamen and posterior caudate, highlighting brain iron's role in T2DM-related cognitive impairment [149].

While Cu is essential for CNS function, its dysregulation contributes to neurodegeneration. Emerging evidence identifies cuproptosis, a Cu-induced form of cell death, as a potential mechanism in neurological disorders [150]. Trace element imbalances, particularly elevated Fe and Cu have been linked to cognitive decline in older adults. Increased Fe and Cu levels, along with reduced glutamic acid decarboxylase activity, correlate with moderate to severe cognitive impairment [151].

Disruptions in intracellular calcium (Ca^{2+}) balance are another hallmark of AD pathology. Accumulation of amyloid- β_{1-42} ($\text{A}\beta_{1-42}$) disrupts Ca^{2+} homeostasis, promoting neuronal death. *In vitro* studies have shown that dantrolene, a Ca^{2+} antagonist, significantly enhances neuronal survival and reduces apoptosis and necrosis when co-applied with $\text{A}\beta_{1-42}$ [152].

Fe overload in the AD brain extends beyond plaque formation, contributing to glial activation, oxidative stress, and ferroptosis. Targeting iron homeostasis is a promising therapeutic approach, and novel iron chelators are showing encouraging cognitive outcomes in preclinical studies [153].

At the molecular level, transporters such as ZIP14, part of the SLC39A family, play a critical role in the uptake of divalent metals like Mn, Zn, and Fe. ZIP14 knockout models exhibit elevated Mn accumulation in blood and brain, altered Zn/Fe ratios in cerebrospinal fluid (CSF), and decreased CSF Ca^{2+} , indicating compensatory transport mechanisms that disrupt CNS metal and calcium homeostasis [154].

The SLC39A family (also known as ZIP transporters, for *Zrt-, Irt-like Protein*) is a group of membrane proteins that facilitate the influx of metal ions, primarily Zn, but also iron, Mn, and cadmium (Cd^{2+}), from the extracellular space or intracellular organelles into the cytoplasm. These transporters play a critical role in maintaining cellular metal homeostasis, especially in tissues with high metal demand like the brain [154,155].

Lastly, potassium (K^+) homeostasis is also compromised in AD. In 5xFAD mouse models, impaired K^+ clearance and reduced expression of astrocytic Kir4.1 channels have been linked to neuronal dysfunction and disease progression [156], reinforcing the broader role of glial cells in maintaining ionic balance and neuroprotection.

Manganese (Mn), the third most abundant transition metal in Earth's crust, is essential for antioxidant defense, energy metabolism, and immune function. While deficiency impairs growth, excessive Mn common in acidic soils and occupational exposure can cause neurotoxicity, including manganism [157,158].

Brain Mn homeostasis relies on a network of transporters (e.g., DMT1, ZIP8/14, SLC30A10, SPCA1, GPP130) [159]. Disruption leads to Mn accumulation, oxidative stress, mitochondrial dysfunction, Endoplasmic reticulum (ER) stress, and neuroinflammation. Overexposure is linked to neurodegenerative diseases such as AD, PD, Huntington's, and ALS. Therapeutics like metformin, curcumin, and resveratrol show protective potential [36,160].

Environmental Mn exposure is a recognized risk factor for PD, with neurotoxic effects linked to dopaminergic neuron injury and neuroinflammation [161]. Recent studies highlight the HIF-1 α /p53/SLC7A11 axis as a mediator of Mn-induced ferroptosis, contributing to Parkinsonian pathology. HIF-1 α 's role varies depending on hypoxic context, and its pharmacological modulation is being explored as a therapeutic strategy [162,163].

Mn also interacts with insulin and IGF receptors, activating neuroprotective signaling pathways such as Akt, MAPK, and mTOR, which counteract apoptosis and promote neuronal survival. Conversely, Mn triggers neuroinflammatory pathways including cGAS-STING, NLRP3-CASP1, NF- κ B, SIRT, and JAK-STAT, with downstream effects on autophagy, either protective or harmful depending on context [164].

A U-shaped relationship has been observed between Mn levels and health outcomes, where both deficiency and excess are detrimental [36]. Similar patterns are reported for iron (Fe) and cognitive decline (Figure 4). Inorganic Fe above 45% of total iron is linked to increased dementia risk, while levels between 25–40% show the lowest risk [165–167].

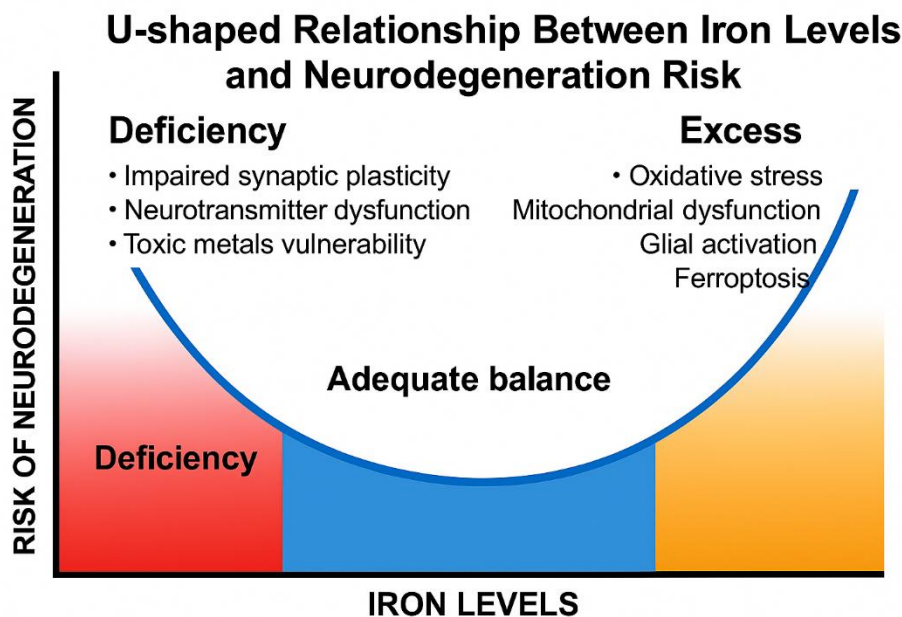


Figure 4. U-shaped relationship between iron levels and risk of neurodegeneration. Iron deficiency is associated with impaired synaptic plasticity, neurotransmitter dysfunction, and vulnerability to toxic metals. Excess iron contributes to oxidative stress, mitochondrial dysfunction, glial activation, and ferroptosis. An adequate iron balance is essential for maintaining cognitive function and minimizing neurodegeneration risk.

4.1. Oxidative Stress and Mitochondrial Damage

Mitochondria fundamental in eukaryotic have cell-type specific phenotypes in response to their environment to perform dozens of interconnected functions and undergo dynamic and often reversible physiological recalibrations [168]. Changes in mitochondrial function and morphology contribute to the development of many neurological diseases. PD is one of the neurodegenerative diseases suspected to be associated with defects in mitochondrial function and quality control [169].

Environmental stressors, particularly air pollutants, have been shown to increase mitochondrial DNA (mtDNA) heteroplasmy, promote reactive oxygen species (ROS) accumulation, and disrupt mitochondrial structure and contact sites [170].

Air pollution, particularly ultrafine particles (UFPs $\leq 0.1 \mu\text{m}$) from traffic emissions, has been increasingly linked to AD. Mitochondria are identified as primary targets of environmental toxicants. Exposure of primary human olfactory mucosa (OM) cells to traffic-related UFPs has been shown to impair mitochondrial function by disrupting oxidative phosphorylation, reducing ATP production, and altering redox balance, resulting in increased oxidative stress. These effects differ between cognitively healthy and AD-derived cells. The findings suggest that mitochondrial dysfunction induced by air pollution may contribute to AD pathogenesis via the olfactory-brain axis [171].

ROS are double-edged swords in biological systems, whereas they are essential for normal cellular functions but can cause damage when accumulated due to oxidative stress. Manganese superoxide dismutase (MnSOD), located in the mitochondrial matrix, is a key enzyme that neutralizes superoxide radicals ($\text{O}_2^{\bullet-}$), maintaining cellular redox balance and integrity [172]. Overproduction of ROS disrupts the body's antioxidant defense, compromising redox homeostasis and increasing oxidative stress, leading to several diseases [173].

Current evidence indicates that epigenetic mechanisms are key mediators of Mn-induced neurotoxicity in both *in vivo* and *in vitro* models. The specific target genes and downstream signaling pathways involved in Mn-associated epigenetic regulation have not fully characterized [174]. However, presenilin-1 (PSEN1) mutations and elevated F2-isoprostanes contribute to brain inflammation, mitochondrial dysfunction, and cognitive decline in AD progression [3].

Environmental exposure to UFPM and industrial nanoparticles (NPs) has been linked to early hallmarks of Alzheimer's, Parkinson's, frontotemporal lobar degeneration (FTLD), and ALS, even in youth. These particles reach the brain via nasal, pulmonary, and placental routes, accumulating in regions like the frontal cortex, olfactory bulb, and substantia nigra. Mitochondria are primary targets. NPs also affect the ER, Golgi, and lysosomes, damaging neurons, glia, and endothelium. These findings suggest mitochondrial disruption from pollution contributes to early neurodegeneration [175].

Short, repeated exposure to PM_{2.5} and heat stress, two key climate change-related stressors, disrupt brain energy metabolism, mitochondrial function, and hippocampal synaptic activity in a mouse model of early-onset AD. It also alters gut permeability and immune signaling, suggesting that climate stress may impair the gut-brain axis and promote neuroinflammation, without immediate cognitive decline [176].

4.2. Activated Microglia and Alzheimer Disease

Glial cells, once considered mere support for neurons, have emerged as key players in brain function across vertebrates. Glial cells include ependymal cells, astrocytes, oligodendrocytes, and microglia [177].

Astrocytes

Astrocytes, the most abundant glial cells in the brain, are essential for synapse formation, neurotransmitter regulation, energy metabolism, and trophic support. They facilitate amyloid- β (A β) degradation and clearance through protease production and the expression of receptors, transporters, and gliotransmitters that mediate intercellular signaling. In AD, the A β accumulation induces astrocyte polarization toward the neurotoxic A1 phenotype, leading to elevated cytokine release and mitochondrial ROS production. These changes impair gliotransmission, glutamate homeostasis, AMPA receptor trafficking, and synaptic plasticity, processes critical for learning and memory [178].

Astrocytes also preserve neuronal homeostasis and BBB integrity. However, exposure to neurotoxicants such as pesticides and heavy metals promotes astrocyte senescence via oxidative stress, DNA damage, and NF- κ B activation, driving inflammation, synaptic dysfunction, and neurodegeneration [179].

Moreover, dopamine significantly modulates astrocyte physiology beyond its classical neuronal functions. Disrupted dopaminergic signaling contributes to neurodegenerative conditions like PD by promoting reactive astrogliosis, glutamate imbalance, and neuroinflammation following dopamine depletion [180].

The brain's high metabolic demand requires tight iron regulation. Both iron deficiency and excess impair function and are linked to neurological disorders. Astrocytes sense iron levels and signal brain microvascular endothelial cells to regulate iron import. Ceruloplasmin (Cp) upregulation and ferritin light chain 1 (Ftl1) downregulation suggest astrocytes promote iron uptake during deficiency, possibly via paracrine signaling involving CD9 and RACK1 [181].

Elevated iron levels, as seen in neuroferritinopathy, drive astrocyte reactivity, inflammation (\uparrow IL-6, IL-1 β , glutamate), and ferroptosis. iPSC-derived astrocytes showed iron dysregulation, altered morphology, and gene expression. While inflammation decreased over time, senescence and ferroptosis increased, underscoring iron's role in astrocytic dysfunction and neurodegenerative disease progression [182].

Astrocytes, which regulate brain Cu homeostasis, are central to this process. Their dysfunction impairs synaptic signaling and promotes AD progression [156,183,184]. Notably, decreased Cu in postmortem AD brains, but increased Cu and non-ceruloplasmin-bound Cu (non-Cp Cu) is associated with a 3–4-fold greater risk of AD despite unchanged total ceruloplasmin levels [185].

Microglia

Microglia, the immune cells of the CNS, play a dual role in AD, contributing to both neuroprotection and pathology. Their activation states (M1/M2), A β and tau interactions, and genetic factors like Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) influence disease progression [186]. Recent studies have indicated that microglial efferocytosis is an important mechanism for clearing apoptotic cells and cellular debris, facilitating the resolution of neuroinflammation [187].

Activated microglia exhibits a spectrum of phenotypes broadly categorized as pro-inflammatory (M1) or anti-inflammatory (M2), though significant overlap exists between these states [188].

In AD, microglia play a central role by responding to amyloid-beta and hyperphosphorylated tau accumulation through inflammatory activation. M1 microglia secrete cytokines such as IL-1 β , IL-6, and TNF- α , promoting neurodegeneration. Dysregulated pathways in AD such as MyD88, CSF1R, and DOCK2 further impair microglial function. Although their precise causal role remains unresolved, microglia-driven neuroinflammation is strongly associated with AD pathology [189].

A β oligomers trigger microglial activation, leading to the release of pro-inflammatory cytokines, which further exacerbate neuroinflammation and neuronal damage. Importantly, the presence of activated microglia surrounding amyloid plaques is correlated with heightened production of cytokines such as interleukin (IL)-1 β and tumor necrosis factor-alpha (TNF- α), creating a vicious cycle of inflammation. While microglia play a protective role by clearing A β plaques during the early stages of AD, their chronic activation can lead to detrimental outcomes, including enhanced tau pathology and neuronal apoptosis [190].

LR4-Lyn interaction drives neuroinflammation in AD; inhibiting Lyn enhances A β clearance, reduces neuronal damage, and boosts protective microglial responses [191].

Exposure to Mn and α -synuclein fibrils upregulates the m6A methyltransferase METTL3 in microglia and astrocytes, enhancing m6A RNA methylation and a proinflammatory secretome. This mechanism may link environmental neurotoxins to chronic neuroinflammation and epitranscriptomic dysregulation in PD and AD. [192].

The pathogenesis of PD is thought to involve microglia-mediated neuroinflammatory injury, with mitochondrial dysfunction playing a role in aberrant microglial activation [157]. *In vivo* and *in vitro* experiments showed that excessive Mn exposure resulted in microglial mitochondrial dysfunction, manifested by increased mitochondrial ROS, decreased mitochondrial mass, and membrane potential. Additionally, with the escalating Mn dose, PINK1/Parkin-mediated mitophagy changed from activation to suppression [157].

Chronic Mn exposure causes Parkinson-like manganism. Estradiol (E₂) protects microglia by downregulating specific protein 1 (Sp1), reducing leucine-rich repeat kinase 2 (LRRK2) expression. Sp1 mediates Mn-induced toxicity, while E₂ promotes Sp1 degradation via ubiquitin and SUMOylation pathways [193].

Oligodendrocytes

Oligodendrocytes and their precursors are involved in A β generation and myelin homeostasis, and their disturbance is responsible for white matter lesions and cognitive impairment [194].

Air pollution affects human health and may disrupt brain maturation, including axon myelination, critical for efficient neural signaling.

The impact of prenatal and long-term exposure to air pollutants (PM and NO₂) on cortical myelination was evaluated in children from the ABCD (USA) and NeuroSmog (Poland) studies. No consistent associations were identified between pollution and T1w/T2w ratios. Subtle regional effects and methodological limitations indicate the need for further investigation across developmental stages [195].

Ambient exposure to PM_{2.5} and NO₂ at ages 9–10 was significantly associated with alterations in white matter microstructure, including key tracts related to the prefrontal cortex, suggesting disrupted neural conduction. Although no consistent links with emotional problems were found,

these findings underscore the potential neurotoxic effects of low-level air pollution on brain connectivity during early adolescence [196].

Nanoscale particulate matter (nPM ≤ 200 nm), a key air pollutant, induces white matter toxicity. In mice, nPM reduced mature oligodendrocytes and increased precursors, impairing myelination. Combined with cerebral hypoperfusion, nPM triggered a 700% rise in apoptosis, highlighting oligodendrocytes' selective vulnerability to airborne particles [197].

Myelin basic protein (MBP) was decreased (corpus callosum: 28%, external capsule: 29%), and degraded MBP increased (corpus callosum: 32%, external capsule: 53%) in the diesel exhaust particulate (DEP) group. White matter is highly susceptible to chronic DEP exposure [198]. In Figure 5 are shown three kind of glial Cells and their association with AD.

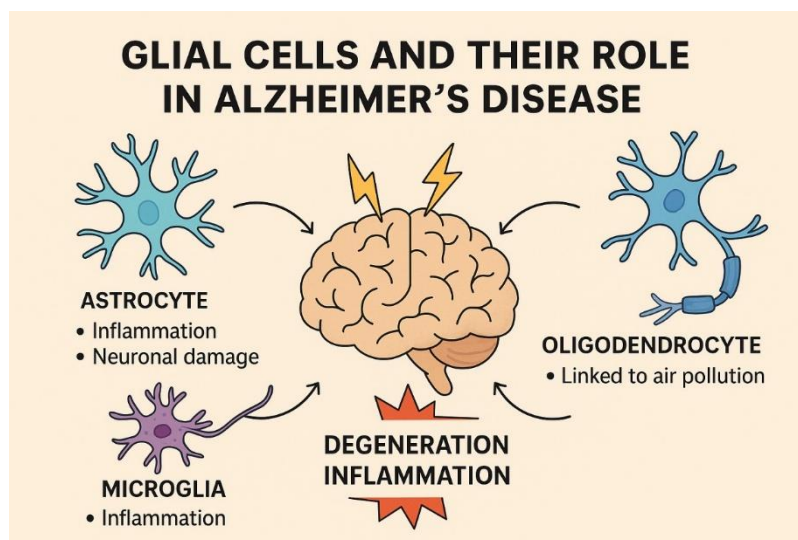


Figure 5. Glial Cells and Their Role in Alzheimer's Disease.

Synapsis and AD

Lipids are essential for synapse formation, neurotransmitter release, and signal transmission in the central nervous system. They regulate membrane structure, vesicle trafficking, and glial-neuronal interactions. Dysregulated lipid metabolism contributes to synaptic dysfunction in neurodegenerative diseases like Alzheimer's and Parkinson's. Targeting lipid pathways offer promising therapeutic strategies, but mechanisms remain under investigation [199,200].

Synaptic dysfunction is a common feature across a broad spectrum of brain diseases, spanning from psychopathologies such as posttraumatic stress disorder and substance use disorders to neurodegenerative diseases such as AD and PD. Changes in the structural interaction between astrocytes and synapses not only play a pivotal role in modulating synaptic function and behavioral states but also are implicated in the initiation and progression of various brain diseases [201].

Emerging evidence highlights synaptic dysfunction as a central feature of AD. The pathological effects of amyloid β oligomers ($A\beta_o$) may be mediated through the metabotropic glutamate receptor subtype 5 (mGluR5), leading to synaptic loss in AD. mGluR5 reduction in AD is closely linked to synaptic loss [202].

This study identifies the Wnt pathway antagonist Dickkopf-3 (DKK3) as a key contributor to synapse loss in AD. Elevated DKK3 levels were found in human AD brains and mouse models, where it disrupted excitatory synapses via Wnt/GSK3 β inhibition and enhanced inhibitory synapses through Wnt/JNK activation. Notably, reducing DKK3 restored synapse number and memory, underscoring its role in synaptic degeneration and cognitive decline in AD [203].

AD is pathologically featured by the aberrant accumulation of amyloid- β plaques, neurofibrillary tangles formed by hyperphosphorylated tau, synaptic loss, and dysfunction of neurotransmitter systems. Evidence from *in vivo* and autopsy studies has consistently shown that synaptic dysfunction and loss are strongly correlated with cognitive decline in AD, particularly in

brain regions such as the hippocampus and cortex, which are critical for memory formation and processing [204].

This study revealed a 49% reduction in the levels of SV2A in the middle frontal gyrus in early-onset AD, a decrease that is more pronounced than that in late-onset AD [205]. Cholinergic and glutamatergic systems are critical for learning and memory and are impaired early in AD and are targets for current symptomatic treatments. The cholinergic system is characterized by a reduction in acetylcholinesterase activity, nicotinic receptors, and degeneration of basal forebrain cholinergic neurons. Glutamate excitotoxicity, particularly through the activation of N-methyl-D-aspartate receptors, contributes to synaptic damage and neuronal loss [206].

Positron emission tomography (PET) imaging with ligands for synaptic vesicle glycoprotein 2A (SV2A) has emerged as a promising methodology for measuring synaptic density in AD. Synaptic vesicle glycoprotein 2A (SV2A) measured by a novel cerebrospinal fluid (CSF) enzyme-linked immunosorbent assay (ELISA) was lower in participants with symptomatic Alzheimer's disease (AD). CSF SV2A was highly correlated with SV2A measured by positron emission tomography (PET) in participants with AD [207].

5. Public Health Implications

Growing evidence shows that PM_{2.5} exposure plays a key role in neurological disorders, especially dementia and AD. It activates glial cells, induces neuroinflammation, increases ROS production, and leads to neuronal apoptosis, synaptic changes, and elevated AD biomarkers such as amyloid-beta and phosphorylated tau. PM_{2.5} also raises enzymes linked to the amyloidogenic pathway. Clinical and animal studies confirm their association with dementia and AD, with increased biomarkers in cerebrospinal fluid, vascular injury indicators, and BBB disruption in at-risk individuals [208].

Air pollution has serious consequences for human health and the environment. However, it can be controlled and reduced through public action and policies. Industry, transportation, and the burning of solid waste are major sources of air pollution that can be managed and reduced. Solutions are required at both the individual and collective levels.

The regulation of metals in the air and epidemiological surveillance are crucial to protecting public health, as exposure to these pollutants can cause serious health problems. Epidemiological surveillance identifies exposure patterns and their health effects, while regulation sets pollution limits and promotes preventive measures.

Achieving stronger air quality targets has the potential to reduce population-level dementia risk. Neighborhood (i.e., greenness and chronic noise) and occupational (i.e., shift work) characteristics are associated with dementia and are viable public health intervention points [209].

The accumulating evidence linking air pollution, particularly fine and ultrafine metal-rich particles to AD, underscores an urgent need for public health action. First, air pollution must be formally recognized as a modifiable environmental risk factor for dementia, warranting inclusion in national and global dementia prevention frameworks such as the WHO's public health approach to dementia.

Primary prevention strategies should focus on enforcing stricter air quality standards, particularly targeting emissions of neurotoxic metals like iron, copper, and manganese. Regulatory interventions are especially critical in low- and middle-income countries (LMICs), where weak environmental protections and high urban pollution levels contribute disproportionately to AD risk and health inequities. Urban planning policies that promote green infrastructure, reduce traffic emissions, and mitigate heat and noise exposure are also essential to reduce cumulative environmental insults to brain health.

From a clinical and surveillance perspective, there is an emerging need to integrate environmental exposure assessments into AD risk screening. This includes the development and deployment of non-invasive biomarkers of exposure and early neurodegenerative change, especially in high-risk populations such as older adults, women, and socioeconomically disadvantaged groups.

Public health systems should also support longitudinal monitoring of pollution exposure across the life course, including prenatal and developmental windows, to inform precision prevention efforts.

Public health programs must further address sex-specific vulnerabilities by promoting research into hormonal and immune differences that affect neuroinflammatory responses and metal homeostasis. Tailored prevention and treatment strategies, considering sex, age, and cumulative exposure profiles, are key to effective intervention.

Lastly, health equity must be at the center of AD prevention. Environmental justice frameworks should guide resource allocation, policy enforcement, and community-level interventions in underserved areas most burdened by pollution. This includes investments in public education, pollution monitoring infrastructure, and accessible healthcare services for early detection and management of dementia-related conditions.

In summary, the intersection between environmental exposure and neurodegenerative disease demands a transdisciplinary public health response integrating environmental science, neuroscience, urban policy, and equity-focused health planning to mitigate the growing burden of AD worldwide.

6. Conclusions and Future Perspectives

Conclusions

This article reviews the progress of research into the association between air pollution and AD. AD, the most common form of dementia, arises from a multifactorial interplay of genetic, hormonal, environmental, and socioeconomic factors. Among these, air pollution particularly fine (PM_{2.5}) and ultrafine particles enriched with metals like iron, copper, and manganese have emerged as a critical and modifiable risk factor. These airborne pollutants contribute to neurodegeneration through converging mechanisms, including oxidative stress, neuroinflammation, mitochondrial dysfunction, BBB disruption, protein aggregation, and epigenetic alterations.

Disruption of brain metal homeostasis, especially involving Fe, Cu, Mn, and Zn, plays a pivotal role in AD pathogenesis by promoting ferroptosis, cuproptosis, and synaptic dysfunction. These metals often accumulate in key brain regions (hippocampus, corpus callosum, frontal cortex), where they impair glial function, particularly in astrocytes, microglia, and oligodendrocytes, affecting synaptic plasticity and myelination.

Furthermore, sex-specific biological differences, including hormonal changes and differential glial responses, contribute to the higher susceptibility observed in women. Disparities in disease burden are also evident among socioeconomically disadvantaged and racially marginalized populations, particularly in regions with high environmental pollution and weak regulatory controls.

Overall, current evidence underscores the urgent need for precision public health strategies that integrate environmental protection, metal homeostasis monitoring, and targeted interventions to mitigate the growing global impact of AD.

Future Perspectives

Advancing our understanding of how air pollution contributes to AD requires deeper exploration of the cellular and molecular mechanisms underlying neurotoxicity. Particular attention should be given to the roles of metal-rich particulate matter, especially iron and manganese, which contribute to oxidative stress, ferroptosis, neuroinflammation, and glial dysfunction. Key areas of mechanistic research include iron homeostasis, microglial polarization, astrocytic TNFR2 signaling, and transporters such as the SLC39A/ZIP family, which regulate metal uptake and detoxification in neural tissue.

Emerging evidence suggests that biological sex and developmental stage strongly modulate brain vulnerability to air pollution. Future studies should investigate sex-specific immune responses, hormonal regulation, and their impact on metal metabolism and synaptic plasticity, particularly during critical windows of brain development and aging. Understanding these interactions will enable the design of personalized prevention and treatment strategies based on sex and life course exposure.

To detect early pollution-related neurodegenerative changes, there is a pressing need for the development of sensitive and accessible biomarkers, including epigenetic signatures, extracellular vesicle content, iron-sensitive imaging modalities, and inflammatory markers such as IL-6 and IL-10. Coupling these tools with advanced neuroimaging and CSF biomarker platforms may improve early diagnosis and disease monitoring, especially in high-risk and underserved populations.

Epidemiological research should move toward multi-exposure and longitudinal models that account for combined effects of airborne pollutants, noise, heat, artificial light, and socioeconomic stressors. Integrating environmental, genetic, and epigenetic data will improve risk stratification and guide targeted interventions. A life-course approach, beginning from prenatal stages and continuing through old age, is critical to identify windows of heightened vulnerability.

At the population level, environmental policy and urban planning must play a central role. Stricter regulation of airborne metal emissions and enforcement of air quality standards, especially in low- and middle-income countries, are necessary to curb rising pollution-related AD cases. Expanding green spaces and promoting climate-resilient infrastructure can also reduce cumulative environmental exposure.

Finally, therapeutic innovation should focus on chelation strategies that restore metal balance without disrupting physiological functions, as well as lifestyle, dietary, and pharmacological interventions that modulate inflammation and oxidative stress. Integrating these with broader environmental justice frameworks will ensure equitable prevention and care for marginalized populations disproportionately affected by neurotoxic exposures.

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