



THE AIR WE BREATHE AND THE BRAIN WE KEEP: AIR POLLUTION AS AN EMERGING DRIVER OF ALZHEIMER'S DISEASE

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Abstract : Alzheimer's disease affects millions worldwide, with the number of cases expected to roughly treble by mid-century. While age and the APOE $\epsilon 4$ gene remain the primary acknowledged risk factors, current evidence points to a subtler contributor: the air we breathe daily. This review examines epidemiological, mechanistic, and autopsy data linking ambient air pollution, namely fine particulate matter (PM_{2.5}) and diesel exhaust, to Alzheimer's development and progression. These pollutants enter the brain through two main routes: direct olfactory nerve translocation, bypassing the blood-brain barrier, and disruption of the barrier itself after systemic absorption. Once within the CNS, they cause oxidative stress, persistent neuroinflammation, and glial activation, speeding amyloid-beta buildup, tau hyperphosphorylation, and reduced glymphatic clearance of toxic proteins. Large cohort studies from Canada, Sweden, the UK, and Taiwan consistently correlate traffic proximity and pollution exposure with greater dementia risk. This risk is significantly magnified in APOE $\epsilon 4$ carriers, demonstrating gene-environment interaction rather than two separate risks. Key limitations include dependence on observational and animal data, geographic emphasis on high-income countries, and near-exclusive focus on a single genetic variant. Addressing air pollution as a modifiable, population-level risk factor, alongside more geographically diverse and biomarker-driven research, could significantly improve future dementia prevention initiatives.

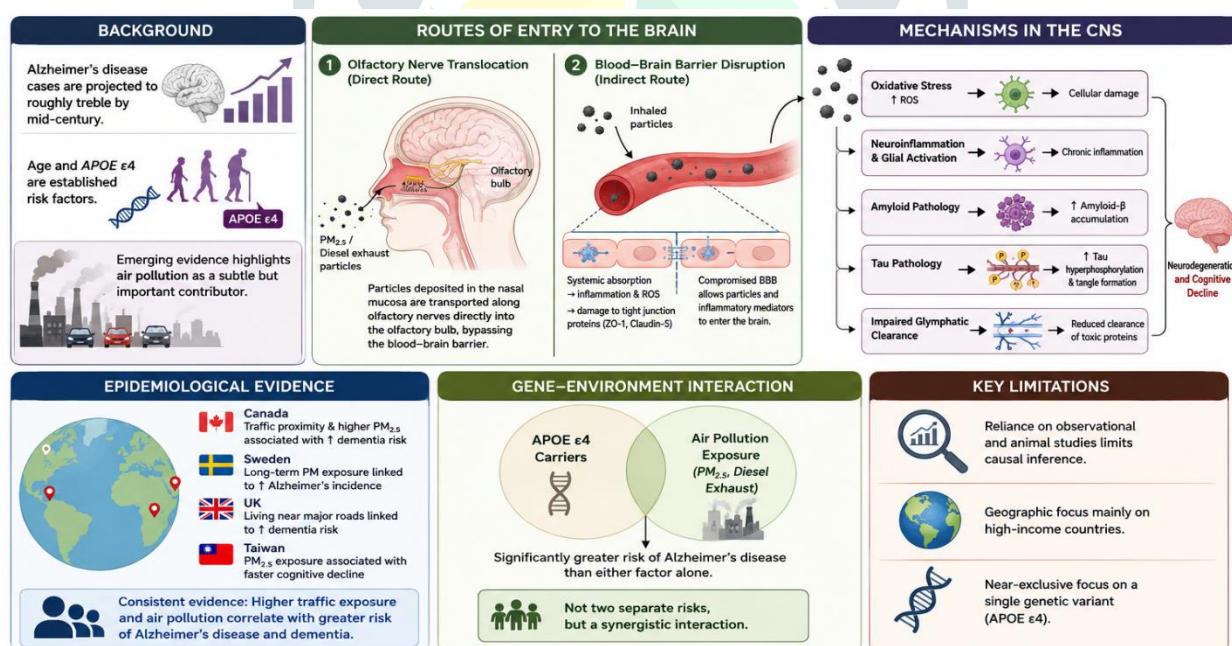


Figure 1: Route of Entry of Inhaled Particles into the CNS

IndexTerms - Alzheimer's disease; Air pollution; PM_{2.5}; Neuroinflammation; Amyloid-beta

Highlights

- Air pollution is an emerging modifiable risk factor for Alzheimer's disease.
- PM_{2.5} exposure is linked to amyloid, tau, and neuroinflammatory changes.
- Air pollutants may reach the brain through systemic and olfactory pathways.
- Pollution-related oxidative stress may accelerate neurodegeneration.

- Air quality interventions may reduce the environmental burden of Alzheimer's disease.

I. INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia worldwide, marked by amyloid-beta plaques, tau tangles, and chronic neuroinflammation, which drive progressive cognitive decline [13,21]. Global prevalence is rapidly increasing; currently, 55–57 million cases are estimated, and it is expected to reach 150–191 million by mid-century [7,10,24], with aging populations only partially explaining this rise. Traditional risk factors fall into two groups: non-modifiable (age, APOE ϵ 4 genotype) and modifiable (hypertension, diabetes, smoking) [8,19,20]. Recently, air pollution has been recognized as a significant danger component. Large cohort studies from Canada, Sweden, and the UK associate traffic emissions and particulate matter exposure with increased dementia risk [1,2]. Experimental data show that fine particulate matter (PM_{2.5}) can penetrate the blood-brain barrier and promote amyloid and tau pathology, especially in APOE ϵ 4 carriers [5,6,23]. Nearly 99% on the planet breathe air that is higher than WHO recommendations [12], making this a near-universal rather than localized risk factor. Although findings converge, evidence remains fragmented across epidemiological, mechanistic, and review studies [15,16]. This review integrates these findings to elucidate air pollution's role in AD risk.

II. NOT ALL POLLUTANTS ARE CREATED EQUAL

"Air pollution" is really shorthand for a mixture of quite different substances, gaseous and particulate alike, and each has its own, distinct relationship to brain health [17,26]. Two components — PM_{2.5} and diesel exhaust particles (DEP) — carry by far the heaviest weight of evidence. Sulphur dioxide and ozone occupy a narrower niche, showing associations that are more specific to how quickly AD progresses once it has already taken hold. PM₁₀, nitrogen dioxide, and carbon monoxide sit in yet another category: they are reasonably well tied to the general risk of developing dementia in the first place, but the evidence linking them to faster decline in patients who already have confirmed AD is much thinner [29,31]. That distinction — pollutants that seem to influence whether AD starts versus pollutants that seem to influence how fast it moves once it has started — turns out to be a useful organising idea that resurfaces throughout the rest of this review.

The table below summarises what each major pollutant is, where it typically comes from, and what the evidence currently says about its link to AD.

Table 1: Major air pollutants, key sources, and Alzheimer's disease-relevant associations

Pollutant	Key Source(s)	AD-Relevant Association
PM _{2.5} ($\leq 2.5 \mu\text{m}$)	Traffic, industry, biomass burning	These agents may penetrate the blood–brain barrier (BBB) or access the central nervous system through the olfactory pathway, thereby contributing to neurodegenerative processes, rising the risk of dementia, and accelerating the deterioration of visuospatial cognition in Alzheimer's who carry the APOE ϵ 4 allele. [28,29].
PM ₁₀ ($\leq 10 \mu\text{m}$)	Dust, construction, traffic	Limited direct access to brain tissue restricts the precise evaluation of neuropathological changes; therefore, these findings are more strongly linked to generalized cognitive decline than with Alzheimer's disease (AD)-specific disease progression. [26,27]
NO ₂	Vehicle exhaust	Exposure to NO ₂ is associated with a dose-dependent increase in the risk of developing dementia; however, it demonstrates limited measurable influence on the rate of cognitive deterioration after Alzheimer's disease (AD) has been clinically established. [29,31]
SO ₂	Industrial combustion	Exposure to SO ₂ is associated with an accelerated rate of memory decline in patients with amyloid-confirmed Alzheimer's disease (AD), independent of the effects of co-exposure to other air pollutants.[29]
Ozone (O ₃)	Photochemical formation from nitrogen oxides (NO _x) and volatile organic compounds (VOCs)	O ₃ is one of the few air pollutants, along with particulate matter (PM), for which a well-established mechanistic link to Alzheimer's disease (AD) has been proposed through the induction of oxidative stress and neuroinflammatory responses. [17,33]
CO	Combustion, vehicle exhaust	Exposure to CO is connected to a dose-dependent increase in the population-level dementia risk; however, no discernible correlation has been established with the pace of disease progression after Alzheimer's disease (AD) is clinically diagnosed. [31]
Diesel exhaust particles	Diesel engines (a marker of traffic pollution)	DEPs may promote Alzheimer's disease (AD)-related neuropathology by inducing microglial activation, increasing soluble amyloid- β (A β) levels, causing white-matter damage, accelerating amyloid plaque formation, and impairing glymphatic-mediated clearance of A β from the brain. [34,37]

III. PATHWAYS OF POLLUTANT TRANSLOCATION INTO THE BRAIN

It's worth pausing on a question that's easy to skip past: how does something inhaled through the nose or lungs end up affecting brain tissue at all? Two distinct, and largely complementary, routes have been identified.

The first is the olfactory pathway. Ultrafine particles that land on the olfactory mucosa — the tissue lining the upper nasal cavity — are picked up by olfactory nerve endings and ferried directly into the olfactory bulb, effectively sidestepping the blood–brain barrier altogether. This route has been demonstrated experimentally in both primates and rodents [39,40], but the most striking confirmation comes from human tissue. An autopsy series conducted on residents of Mexico City, most of them under 40 years old and including toddlers and infants, found hyperphosphorylated tau and amyloid-beta plaques already present within the olfactory bulb — with the pathology noticeably worse in those carrying the APOE ϵ 4 allele [41,42,44]. It's a genuinely unsettling finding: markers of Alzheimer's-type pathology showing up in the brains of children, apparently as a consequence of the air they were breathing.

The second route involves outright breach of the blood–brain barrier itself. Particulate matter absorbed into the bloodstream generates reactive oxygen species, which in turn damage the tight-junction proteins ZO-1 and claudin-5, among them — that hold

brain endothelial cells together. Once that seal is compromised, particles and inflammatory signalling molecules can pass more freely into brain tissue [45,46].

A third, less well-characterised route, running via the vagus nerve and the gut–brain axis, has also been proposed for certain nanoparticles, though the evidence here is thinner [40]. What's notable is that both of the well-established routes ultimately converge on the same endpoint: the build-up of amyloid and tau. That convergence forms a useful bridge between the epidemiological patterns described in Section 2 and the cellular mechanisms explored next.

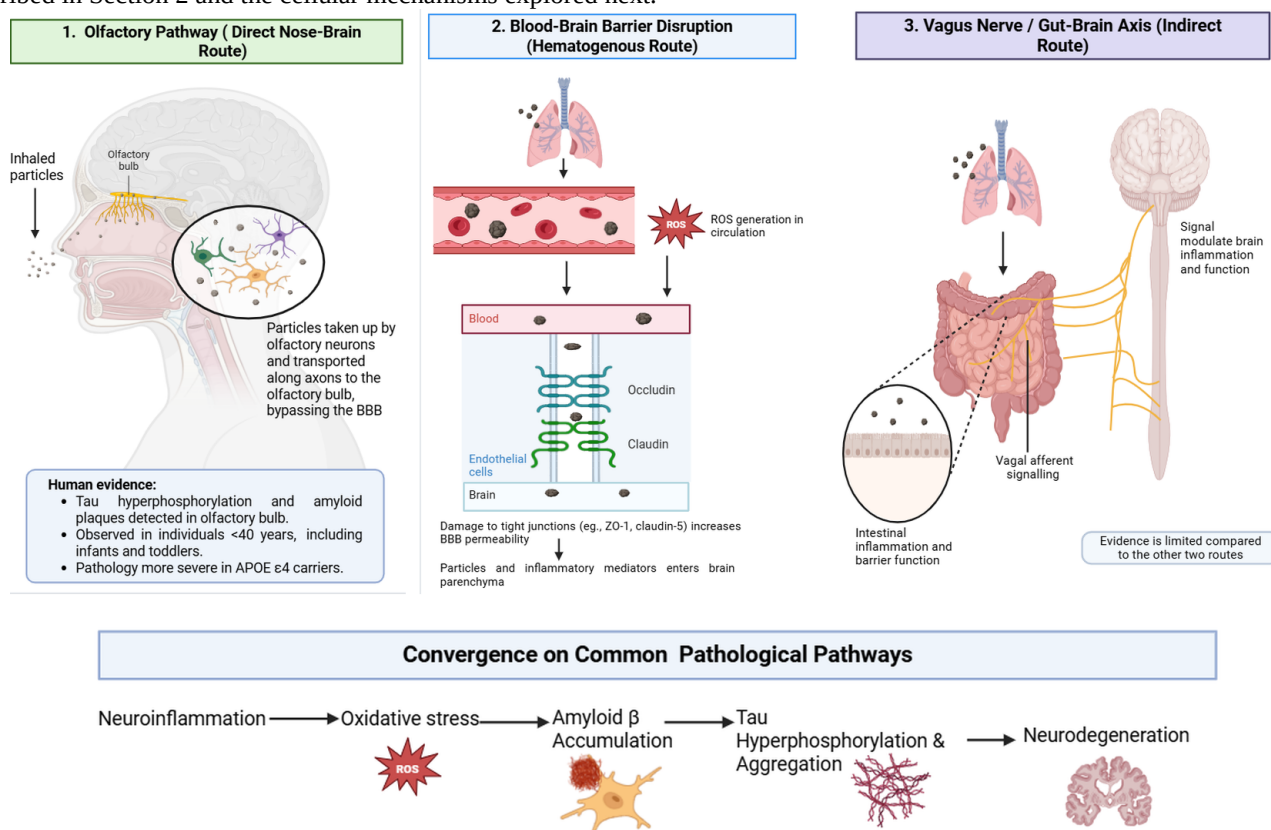


Figure 2: Routes of entry of inhaled particles into the CNS

IV. MOLECULAR AND CELLULAR MECHANISM

Environmental pollutants that reach the central nervous system (CNS) can trigger a complex and interconnected cascade of molecular and cellular events involved in the pathogenesis and progression of Alzheimer's disease (AD). The main mechanisms involved are oxidative stress, neuroinflammation, amyloidogenic processing, tau hyperphosphorylation, blood–brain barrier (BBB) dysfunction, mitochondrial impairment, epigenetic changes, and glymphatic disruption of amyloid-β (Aβ) clearance. Figure :3 shows these overall mechanisms

4.1 Oxidative Stress

Oxidative stress is thought to be one of the earliest and most critical events in pollution-induced neurodegeneration. Exposure to air pollutants, particularly particulate matter (PM), induces excessive generation of reactive oxygen species (ROS), leading to oxidative damage to cellular macromolecules, including DNA, proteins, and lipid bilayers. Studies on subjects living in highly polluted environments have shown increased markers of oxidative DNA damage associated with increased cerebral Aβ accumulation [22,42,45]. Furthermore, PM may engage directly with cerebrovascular endothelial cells and prompt rapid ROS generation, thereby contributing to endothelial dysfunction and oxidative injury within the neurovascular unit [22,42,45].

4.2 Neuroinflammation and Glial Activation

One of the contributing factors to chronic neuroinflammation is oxidative stress caused by pollutants, which activates inflammatory signaling pathways. Experiments on human brain tissue models show that exposure to PM_{2.5} induces astrogliosis and drives microglia polarization toward a pro-inflammatory M1-like phenotype [6]. Next, activated microglia and astrocytes release pro-inflammatory cytokines, chemokines, reactive nitrogen species, and other neurotoxic mediators that worsen neuronal damage. In experimental animal models, exposure to diesel exhaust particles has been associated with increased brain expression of interleukin-6 (IL-6), activation of the complement system, and higher microglial activation, which is consistent with these findings [34]. Cyclooxygenase-2 (COX-2) expression has also been found to be higher in brain areas of people who have been subjected to elevated concentrations of air pollution [42]. Exposure to PM_{2.5} may activate the NLRP3 inflammasome, amplifying inflammatory signaling and releasing pro-inflammatory cytokines [16]. Collectively, these changes may create a persistent neuroinflammatory milieu that promotes progressive neuronal malfunction and neurodegeneration.

4.3 Amyloidogenic Processing and Tau Hyperphosphorylation

Oxidative stress and neuroinflammation can accelerate pathogenic processes in Alzheimer's disease, such as aberrant Aβ buildup and tau hyperphosphorylation. Exposure to nanoparticulate matter in transgenic mouse models has been demonstrated to raise cerebral Aβ levels, with a more prominent impact reported in mice expressing the APOE ε4 allele [5]. Similarly, diesel exhaust exposure has been linked to increased amyloid plaque development in AD models [36].

Clinical data suggest a link between PM_{2.5} exposure and elevated cerebral amyloid load, as measured by positron emission tomography (PET) [16]. Post-mortem brain tissue from persons persistently to high levels of air pollution, including younger

populations, has shown A β deposition and tau-related neuropathological changes [41,42]. These data imply that long-term pollution exposure may increase or accelerate AD-related proteinopathies by causing oxidative and inflammatory cellular damage.

4.4 Blood–Brain Barrier and Neurovascular Dysfunction

Exposure to PM_{2.5} might reduce the expression of tight-junction proteins needed for endothelial barrier function, potentially compromising BBB integrity [23,45,46]. Disruption of the BBB may enhance the permeability of the neurovascular interface, allow circulating inflammatory mediators and toxic chemicals to enter the CNS, and induce further oxidative and inflammatory harm. Pericyte dysfunction and cerebral amyloid angiopathy have also been intertwined with chronic particle pollution exposure [23,45,46]. Pericytes are crucial for maintaining the structural soundness of the blood-brain barrier, controlling cerebral microvascular blood flow, and promoting neurovascular homeostasis. Therefore, pollution-induced pericyte dysfunction may promote AD-associated neurodegeneration by altering cerebral perfusion, impairing vascular function, and reducing the clearance of neurotoxic metabolites.

4.5 Mitochondrial Dysfunction and Epigenetic Alterations

Chronic exposure to environmental pollutants can cause mitochondrial dysfunction, including decreased oxidative phosphorylation, altered mitochondrial bioenergetics, and increased ROS production [22]. These alterations may impair neural energy metabolism and increase neuronal vulnerability to oxidative stress. Pollutant insults have also been associated with epigenetic modification, manifested as alterations in DNA methylation and gene expression, which can modulate inflammatory responses, oxidative stress pathways, and neurodegenerative processes [22]. These prolonged alterations yield detrimental consequences for neurological homeostasis.

4.6 Impairment of Glymphatic-Mediated Amyloid- β Clearance

Exposure to diesel exhaust may disrupt the glymphatic system, which removes soluble metabolites and neurotoxic proteins from the brain [37]. It also promotes A β formation and aggregation. Glymphatic clearance dysfunction can lead to increased soluble A β buildup outside the cell. Impaired A β clearance can boost cerebral A β deposition and accelerate AD-related neuropathology, both independently and synergistically with enhanced amyloidogenic processing [37].

4.7 Modulatory Role of the APOE ϵ 4 Genotype

The APOE ϵ 4 genotype seems to enhance vulnerability to the negative neurological consequences of air pollution. Research suggests that APOE ϵ 4 carriers may experience higher levels of oxidative stress, A β accumulation, neuroinflammatory responses, and cognitive decline after chronic pollutant exposure [5, 44]. APOE ϵ 4 carriers may have impaired lipid transport, reduced A β clearance, altered neurovascular function, and decreased cellular resilience to oxidative and inflammatory injury. As a result, the APOE ϵ 4 allele may increase the risk or severity of AD-related pathological changes by amplifying the neurotoxic effects of environmental pollutants

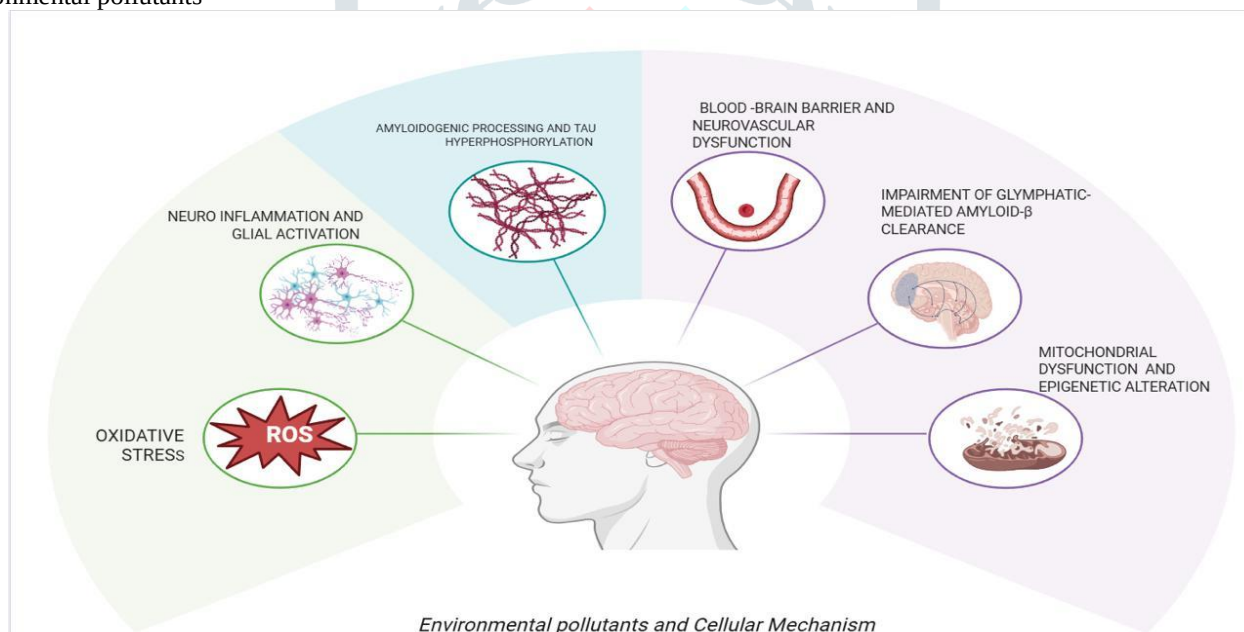


Figure 3: Molecular and cellular mechanism

V. EPIDEMIOLOGICAL EVIDENCE

The epidemiological research is what eventually bases this in actual human danger; mechanistic biology merely provides a portion of the narrative. A similar finding is reached by a number of large cohort studies that include various nations and exposure measurements.

Table 2: Summary of epidemiological evidence linking air pollution with dementia/Alzheimer's disease risk

Study / Region	Population	Exposure Metric	Key Finding
Ontario, Canada	~2.2 million adults, ages 55–85	Proximity to roadways	The risk of dementia is greater for residents living 50 meters or less from major roads than for those living more than 300 meters away; this impact is largest among urban dwellers; Parkinson's disease and multiple sclerosis do not show a similar effect.[1]
WHIMS, USA	Older women	Residential PM (EPA standard)	Increased dementia risk and global cognitive impairment; APOE ϵ 4 carriers are more affected.[5]

Study / Region	Population	Exposure Metric	Key Finding
Västerbotten, Sweden	>70,000 residents	Modelled traffic and wood-burning PM exposure	Dementia risk was increased by both pollution sources separately; the greatest risk was observed in the top exposure quartile of home wood stove owners.[2,3]
London, UK	Cohort study	Air pollution combined with noise exposure	Results are generally in line with the Swedish and Canadian cohorts.[4]
Taiwan	~30,000 individuals	National insurance registry data (NO ₂ , CO)	Dose-dependent rise in dementia risk across exposure quartiles.[31]

Beyond these individual cohorts, a pooled analysis covering PM_{2.5}, PM₁₀, SO₂ and ozone confirms a statistically significant link between exposure to air pollution and cognitive impairment across the wider literature [28]. Neuroimaging evidence is thinner but points the same way: higher PM_{2.5} exposure correlates with greater amyloid burden on PET scans in clinical populations [16], and diesel exhaust exposure produces measurable white-matter injury on MRI and diffusion tensor imaging in animal models [34,35]. Every cohort with graded exposure data — whether measured in distance bands or exposure quartiles — shows a clear dose-response relationship [1,3,31].

VI. AIR POLLUTION DOESN'T ACT ALONE

Treating air pollution as a stand-alone danger factor that is unrelated to everything else we know about AD would be incorrect. In reality, it interacts with the risk factors that are already well-established in the area and occasionally works through them. Consider APOE ϵ 4. The WHIMS cohort, a transgenic mouse model, and human autopsy tissue are three distinct and quite diverse lines of data that all lead to the same conclusion: the detrimental consequences of pollution are consistently amplified in ϵ 4 carriers. Instead of two separate hazards that just happen to sum together, that pattern of amplification shows a true gene–environment synergy [5,44].

Additionally, there is significant overlap with cardiovascular risk pathways: PM_{2.5}-induced damage to the blood-brain barrier and tight junctions contributes to cerebral amyloid angiopathy [23,45,46], PM pollution independently drives cerebrovascular disease, including ischemic stroke [11], and established modifiable danger factors, such as obesity, diabetes, and hypertension, act through shared vascular, metabolic, and inflammatory pathways [20].

Finally, some groups seem to be disproportionately exposed to this combined risk: the elderly, for whom pollution exacerbates an already elevated age-related risk [1,5]; those with lower socioeconomic status in low- and middle-income nations, who typically face both more exposure and fewer care resources [11]; and urban dwellers near major roads, who exhibit the strongest correlation in cohort data [1].

VII. THE BIGGER PICTURE: GLOBAL BURDEN AND WHAT POLICY COULD DO

The scope of the issue is quite startling when you zoom out. Every year, ambient air pollution is thought to be responsible for 4.2 million early demise, and about 99% of the world's population breathes air that exceeds WHO guideline limits for PM_{2.5} [12]. Low- and middle-income nations bear a disproportionate amount of that load [11,12]. Additionally, it exacerbates the already growing dementia issue, which has 55 to 57 million cases now and is anticipated to increase 150 to 191 million by 2050 [9,10]. Unlike air pollution, this demographic trend cannot be easily changed by legislation [24,25].

Three directions for policy follow reasonably naturally from the evidence reviewed here. First, given both road emissions and home wood-burning are independently implicated throughout the cohort evidence, stricter and better-enforced air quality regulations should be implemented [1,2]. Second, risk-stratified guidelines that give priority to the groups identified in Section 6 as having disproportionate risk, such as APOE ϵ 4 carriers, individuals with pre-existing cardiovascular risk, the elderly, and urban dwellers. Third, official incorporation of air quality into current frameworks for dementia prevention, in addition to the management of diabetes and hypertension that are currently included in the majority of these frameworks [20,24,25].

VIII. CURRENT GAPS AND LIMITATIONS

- **Geographic gap** - Despite being among the world's most polluted regions, mainland China, India, and Sub-Saharan Africa are largely absent from this evidence base; cohort evidence is heavily concentrated in Canada, Sweden, and the UK, with only Taiwan representing Asia [1,12,31].
- **Narrow gene–environment scope** — APOE ϵ 4 remains the only genetic variant studied for its interaction with pollution exposure to date [5,44].
- **Animal-to-human translation** - Transgenic mice provide a significant amount of the mechanistic data. The Mexico City autopsy series, the most convincing human confirmation, is cross-sectional rather than longitudinal [5,36,41].
- **No safe threshold established** - This limits the accuracy with which AD-specific air quality objectives may be defined [12]
- **Observational design** - All of the cohort studies examined here are, by definition, observational. Although the mechanistic and autopsy evidence does give the results more biological plausibility, residual confounding from socioeconomic position, healthcare access, and diagnostic practice cannot be completely eliminated [5,6,45].
- **Thin neuroimaging base** — The evidence here is currently limited to one large amyloid-PET analysis alongside animal DTI studies [16,34,35].
- **Diagnostic heterogeneity** - Instead of using amyloid-confirmed AD, most cohorts use a wide clinical diagnosis of dementia, which runs the risk of confusing AD-specific pathways with vascular dementia [2,29,31].

IX. CONCLUSION AND FUTURE DIRECTIONS

When considered collectively, the data show that air pollution is an unevenly distributed, mechanistically reasonable, and epidemiologically established risk factor for AD. Through the olfactory route and blood-brain barrier rupture, fine and ultrafine particles enter the brain [38,40,46], causing oxidative stress, neuroinflammation, accelerated deposition of tau and amyloid, and reduced clearance [6,16,37,42]. Convergent cohort, imaging, and autopsy evidence collected over three continents supports this

approach [1,28,31,44]. Furthermore, the risk is not fairly distributed: APOE $\epsilon 4$ carriers, those with pre-existing heightened cardiovascular risk, the elderly, people from poorer socioeconomic backgrounds, and urban dwellers are all at higher risk [5,11,20]. Given how widespread this exposure already is and the lack of a safe threshold [12], air pollution should be considered a changeable, mainstream part of the entire AD risk picture rather than a specialized environmental problem. Sharper threshold and dose-response modeling [12], biomarker-confirmed rather than purely clinical AD diagnosis within cohort designs [11,29,31], geographically representative cohorts in mainland China, India, and Sub-Saharan Africa [11,12], and a more comprehensive gene-environment research agenda that looks beyond APOE $\epsilon 4$ alone [5,44] should all be prioritized in future research.

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