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Air Pollution as an Environmental Risk Factor for Alzheimer's Disease and Related Dementias

Heui Hye Park[1], **Matthew J. Armstrong**[1], **Fredric A. Gorin**[2], **Pamela J. Lein**[1,*]

[1]Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, CA 95616, USA.

[2]Department of Molecular Biosciences, School of Veterinary Medicine, and Department of Neurology, School of Medicine, University of California, Davis, CA 95616, USA.

Abstract

Alzheimer's disease and related dementias are a leading cause of morbidity in our aging populations. Although influenced by genetic factors, fewer than 5% of Alzheimer's disease and related dementia cases are due solely to genetic causes. There is growing scientific consensus that these dementias arise from complex gene by environment interactions. The 2020 Lancet Commission on dementia prevention, intervention, and care identified 12 modifiable risk factors of dementia, including lifestyle, educational background, comorbidities, and environmental exposures to environmental contaminants. In this review, we summarize the current understanding and data gaps regarding the role(s) of environmental pollutants in the etiology of Alzheimer's disease and related dementias with a focus on air pollution. In addition to summarizing findings from epidemiological and experimental animal studies that link airborne exposures to environmental contaminants to increased risk and/or severity of Alzheimer's disease and related dementias, we discuss currently hypothesized mechanism(s) underlying these associations, including peripheral inflammation, neuroinflammation and epigenetic changes. Key data gaps in this rapidly expanding investigative field and approaches for addressing these gaps are also addressed.

Introduction

Alzheimer's disease (AD) and AD-related dementia (ADRD) are global public health concerns. The worldwide prevalence of ADRD is projected to rise from 57.4 million affected individuals in 2019 to 152.8 million by 2050[1]. Alzheimer's disease and related dementias are the most prevalent type of progressive neurodegenerative disease that is pathologically characterized by amyloid beta plaques (Aβ), phosphorylated neurofibrillary tau tangles (NFT), and persistent neuroinflammation[2–5]. Clinical studies have identified that AD pathology develops years and often decades prior to the onset of AD symptoms[6,7].

* pjlein@ucdavis.edu .

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Mild cognitive impairment is a transitional phase of cognitive decline that progresses to dementia in approximately 30% of cases[8,9]. Currently, there are no definitive preventative or therapeutic interventions that effectively mitigate AD and ADRD risks or that prevent or reverse cognitive impairment. Given the increasing awareness that much of AD/ADRD, particularly late-onset forms, arises from complex gene × environmental (G × E) interactions, significant research effort is being devoted to identifying environmental risk factors for AD/ADRD and understanding how they modify disease risk and/or severity[10–12]. This is because currently it is much easier to modify our environment than our genes.

HETEROGENEITY OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Alzheimer's disease was initially described as a presenile dementia occurring in individuals between 45 and 65 years old, but in 1977 it was determined that the neuropathological findings of amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs), which are the hallmark pathologies of AD were very similar in AD of early- and late-onset. However, it became increasingly recognized that with aging, late-onset AD brains frequently exhibited additional neuropathological findings, and these became categorized as ADRD. Before discussing environmental and genetic risk factors that contribute to AD and ADRD, it is important to explain terminologies used in this field.

Dementia describes a range of neurological conditions causing progressive deterioration of cognition and can be accompanied by additional neurological dysfunction. Alzheimer's disease and related dementias are distinguished from other dementing illness by clinical assessment, neuroradiology, neuropathology, and biomarkers. Clinical assessment based on neurological and cognitive functional testing is least sensitive and least accurate at early stages of AD, and clinical confirmation utilizes other diagnostic tools including brain imaging modalities and blood and/or cerebrospinal fluid biomarker testing for amyloid and phosphorylated tau isoforms[13]. The current evolution of increasingly selective and sensitive biomarkers for AD is necessary to accurately distinguish AD from other dementias and to evaluate treatments for AD/ADRD whose pathology develops decades before clinical symptomatology[14]. Biomarker selectivity that distinguish between the different types of dementias will greatly assist with the identification of genetic and other specific risk factors, but currently consensus has not been reached on future AD/ADRD classifications. For this review, we are summarizing prior literature based on current AD/ADRD classifications and guidelines.

In the current U.S. National plan to address AD, ADRD includes frontotemporal dementia, Lewy body dementia, vascular contributions to cognitive impairment and dementia, and mixed dementias (including cerebrovascular disease or Lewy bodies)[15]. Each of these dementias share progressive neuronal loss, cognitive and behavioral decline, impaired daily function, and aberrant protein accumulation (e.g., Aβ, tau, or α-synuclein)[16,17]. The heterogeneity of AD/ADRD complicates the task of identifying the interplay between specific genetic and environmental risk factors. While it has been easier to include ADRDs with AD when identifying environmental risk factors, it is acknowledged that this inclusive categorization increases the likelihood of "masking" specific G × E interactions that drive individual risk for specific forms of AD/ADRD.

GENETICS OF EARLY AND LATE ONSET ALZHEIMER'S DISEASE

Broadly speaking, there are two age-based classifications of AD: early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD). Early-onset Alzheimer's disease is a less common form of AD diagnosed in individuals under the age of 65, often in their 40s and 50s. Late-onset Alzheimer's disease, which is the more common form of AD is diagnosed after age 65 and frequently includes additional neuropathology. While both forms of AD are highly heritable (~92–100%, and ~70–80%, respectively), they differ in their inheritance pattern[18,19] Roughly 90% of EOAD is inherited in an autosomal recessive fashion, and 10% follows an autosomal dominant inheritance pattern. Additional subclassifications for EOAD have emerged, including Mendelian, non-Mendelian or sporadic EOAD; however, in many studies of EOAD, the inheritance patterns are not delineated[19]. Common autosomal dominant forms of EOAD are due to mutations in APP, PSEN1, and PSEN2, and autosomal recessive AD is linked to mutations in approximately 27 genes, including APOE4, BIN1, TREM2, MAPT, APP, UNC5C, and CLU (Table 1). While genome-wide association studies (GWAS) have identified multiple genes associated with increased risk of AD, the relationship of many of these risk loci to pathogenic mechanisms that drive disease progression have yet to be elucidated. Importantly, the differing clinical profiles of individuals carrying these high-risk alleles is consistent with a role for environmental factors interacting with genetic risks to determine individual outcomes.

The genetic contributions to LOAD are significantly more complex and include roughly 117 associated genes (Table 1). Overall, the heritability of LOAD is less than that of EOAD and findings from twin studies indicate a greater contribution of environmental factors in the development and progression of disease. A significant number of individuals with LOAD have co-morbid medical conditions, such as cardiovascular disease, type 2 diabetes[20], autoimmune disorder[21], or head trauma[22], each of which is separately associated with cognitive decline and each of which is heavily influenced by environmental factors. In addition to age-dependent increases in Aβ plaques and NFT, as many as 50% of LOAD brains contain pathologies of cerebral amyloid angiopathy, TDP-43 inclusions (LATE-NC) and/or Lewy body pathology (α-synuclein), which increase with age and AD progression[23]. The presence of cerebrovascular cerebral amyloid angiopathy correlates with both Aβ plaques and NFT and is associated with expression of the APOE ε4 allele independent of dementia status. Cerebral amyloid angiopathy, like AD, is a consequence of Aβ accumulation, but the intracerebral vascular accumulation produces a separate disorder with increased risk of stroke, cerebral hemorrhages, and inflammatory encephalopathies[24,25] with its own distinct genetic risk factors[26] and diagnostic and potential clinical therapeutics. Given the modest risks conferred by each of these genetic mutations, it has been argued that LOAD, as well as most of ADRD, are driven by multifactorial influences, including multiple genes interacting with diverse environmental factors. Interestingly, many of the pathogenic mechanisms associated with these genetic risk alleles have been shown to be independently modified by environmental factors.

GENE BY ENVIRONMENT INTERACTION IN ALZHEIMER's DISEASE AND RELATED DEMENTIAS ETIOLOGY

Twin studies have provided further evidence in support of the contribution of environmental factors to AD/ADRD etiology[27,28]. Specifically, genetically identical monozygotic twins have been compared to explore the effects of non-shared environmental risk factors. In one twin study, positron emission tomography (PET) imaging to quantify tau deposition in the entorhinal cortex and neocortical brain regions, revealed similar intensity and deposition of tau pathology[27], suggesting that genetics was the predominant driver. However, when non-shared environmental risk factors were compared in twin pairs, differences in tau deposition strongly correlated with differences in depressive behaviors, social isolation, and physical inactivity[27]. Similarly, another study of monozygotic twins found that individuals exposed to higher levels of air pollution had lower structural integrity of the locus coeruleus, which is a brain region involved in the early stages of AD[28]. These results suggest that while similarities in the development of AD-relevant pathologies between monozygotic twin pairs may be explained by identical genetic composition, different trajectories of ADRD pathologies may arise from exposure to non-shared environmental factors. In a different study, analysis of the AD polygenic risk score in monozygotic and dizygotic twins suggested that total genetic contribution to AD risk accounted for 71%, while the remaining 29% was attributed to environmental factors[29]. This finding can help explain cases of discordant development of ADRD pathologies in monozygotic twins despite their genetic uniformity[30] and highlights the importance of identifying and studying the impact of environmental risk factors that can modify ADRD outcomes (Figure 1).

Environmental risk factors for Alzheimer's disease and related dementias

The 2020 Lancet Commission on dementia prevention, intervention, and care identified 12 modifiable environmental AD/ADRD risk factors based on meta-analyses and systemic reviews of the available literature[12]. The report highlighted that these 12 modifiable risk factors contributed to 40% of global prevalence of dementia, suggesting that 40% of dementia cases worldwide might potentially be prevented or slowed by modifying individual exposures[12]. The risk factors identified by the Lancet Commission included various comorbid medical conditions (hypertension, diabetes, hearing impairment, obesity, depression, and traumatic brain injury), lifestyles (physical inactivity, excessive alcohol consumption, social isolation, smoking), less educational background, and exposure to air pollution. Medical and public health strategies targeting comorbidity or lifestyles heavily depend on individual motivation, and these applications have been limited in success at the population level[31]. Many of these factors are strongly influenced by environmental contaminants, and environmental exposures represent a class of risk factors that can be changed by public policy, and thus have population-level impacts[31].

The contribution of environmental contaminants to the development of neurodegenerative diseases has been primarily studied in the context of occupational exposure to pesticides among agricultural workers.[32] Individuals occupationally exposed to pesticides, such as organophosphate insecticides[33–35] and fungicides that contain manganese[36–38], were reported to have lower cognitive function and increased risk of developing

neurodegenerative diseases, including AD[33,39]. Other synthetic persistent organic pollutants like per-and polyfluoroalkyl substances (PFAS) have also been associated with increased AD-relevant pathology and cognitive impairment in ADRD patients[40]. More recently, air pollution (Box 1) has garnered significant interest due to increasing evidence from epidemiological and experimental animal studies of a strong association between air pollution and AD/ADRD. Additionally, while air pollution is directly linked to increased risk for AD/ADRD, it is also linked to a number of other ADRD risk factors, such as cardiovascular disease[41–46], metabolic dysfunction[47], and physical inactivity[48]. The links between air pollution, AD/ADRD, and other risk factors suggest that air pollution may be an upstream environmental modifier that influences AD/ADRD onset and progression. It has been argued that targeting causative upstream environmental modifiers will have a broader and more significant impact on reducing the AD burden than modifying proximal individual-level risk factors[49]. This review focuses on current understanding and findings regarding the association between air pollution and increased risk and/or severity of AD/ADRD and discusses prevailing hypotheses regarding the mechanisms underlying these links.

Epidemiological evidence linking air pollution with progressive cognitive impairment and Alzheimer's disease and related dementias

Over 80 epidemiological studies investigating an association between air pollution and AD/ADRD were published in the peer-reviewed literature during the last six years (Table 2). Recent studies have focused on correlations between independent and combined effects of specific air pollutants and AD/ADRD risk. Zip code-based residential exposure levels of fine and course particulate matter ($PM_{2.5}$, PM_{10}), nitrogen oxides (NO_x), and ground-level ozone (O_3), have been leveraged to calculate odds ratios or hazard ratios to assess the risk for AD/ADRD conferred by exposure to air pollutants, with increasing risk associated with increasing levels of each air pollutant. Longitudinal monitoring studies of average air pollution exposure levels have also been leveraged to measure the time-lagged effects of long-term exposure to air pollution on cognitive decline and AD/ADRD[50–54]. The cohort sizes ranged from small population-based studies (n=150–8,000) to nationwide studies (n=4–12 million) of midlife to aged participants (age > 45). The main ADRD outcomes that were measured against air pollution exposure levels were risks of incident ADRD determined by clinical records of diagnosis, hospitalization, pathology of AD-relevant biomarkers, cognitive assessment, and mortality.

SUMMARY OF FINDINGS

In line with earlier epidemiology studies[55–57], the main consensus of current epidemiological findings is that there is a strong association between exposure to air pollution and AD/ADRD; however, there were mixed results regarding associations between air pollutant type and increased risk of AD/ADRD. The majority of studies found a positive correlation between risk of all-cause dementia and exposure to $PM_{2.5}$[50–52,58–90] and NO_x[50,58,59,61–63,66,67,69–73,76–80,82–87,90–93] but not to O_3[58,61,76,87,94,95] (table 2). A few studies reported no significant association between risk of dementia and levels of $PM_{2.5}$[95–99]

and NO_x[52,75,94–99]; and a small number of studies found a positive association between O_3 level and risk of dementia[58,82,93].

When records of dementia diagnoses are more specifically stratified, differential correlations between various types of air pollutants and subtypes of dementia emerge. In an analysis of data from the UK Biobank, authors reported that exposure to combined levels of NO_x, $PM_{2.5}$, and PM_{10} were significantly associated with all-cause dementia, AD, vascular dementia (VaD), and mild cognitive impairment. Yet, when each air pollutant was compared separately, VaD was no longer associated with $PM_{2.5,10}$ but only influenced by NO_x, while all-cause dementia, AD, and mild cognitive impairment remained significantly associated with both $PM_{2.5,10,}$ and NO_x[83]. Another study leveraging the UK Biobank data found similar associations of $PM_{2.5,10}$, and NO_x with all-cause dementia and AD but not with VaD[66]. In line with these findings, other studies reported the association of $PM_{2.5}$ to be more pronounced with AD than with non-AD or VaD[61,64,65,74], but contrary results showed more significant association with non-AD or VaD than with AD[82,84,100]. These mixed findings may reflect differences across studies in modeling methods, cohort characteristics, exposure duration, confounding co-exposures, source of air pollution data, and dementia ascertainments. Due to the heterogeneity of dementia etiology and disease progression, inconsistent clinical diagnoses and records may have been used across different studies with participants from a wide range of cohorts. Additionally, the outcome measurements mainly derived from medical records may not be an accurate representation of the entire population because of underlying socioeconomic disparities in quality and accessibility of medical care[101,102]. This could be a critical confounding factor because studies have shown that social disadvantage can increase vulnerability to air pollution and air pollution-mediated risk of AD/ADRD[101,103].

Despite these mixed results, long-term exposure to higher levels of $PM_{2.5}$ and NO_x was still consistently found to be associated with increased risk of AD and ADRD in most studies (Table 3). Long-term exposure to higher levels of $PM_{2.5}$ and NO_x was associated with greater extent of AD-relevant structural changes in the brain, which were assessed using PET and magnetic resonance imaging (MRI) to quantify amyloid deposition and cortical atrophy[28,53,104–107]. Individuals who were exposed to higher levels of $PM_{2.5}$ and NO_2 exhibited higher amyloid PET positivity and cortical atrophy[53,104–107]. In smaller cohorts, AD-relevant biomarkers, such as Aβ 42/40 and neurofilament light levels in the plasma and cerebrospinal fluid, were positively associated with $PM_{2.5}$ and NO_x exposure levels[54,104,108]. There were a few post-mortem autopsy studies that reported increased expression of histological biomarkers of AD/ADRD, including hyperphosphorylated tau, Aβ deposition, nanoparticle inclusions, and glial activation in the hippocampus, cortex, and olfactory bulbs of young and old individuals who lived in areas with high levels of air pollution[109–113]. Another outcome measurement was cognitive performance, which was assessed by a battery of cognitive tests to quantify memory, verbal fluency, and executive functions[114–118]. While some studies reported an inverse correlation between cognitive test scores and exposure to $PM_{2.5}$ and NO_x in cognitively unimpaired and impaired populations[106,115–124], other studies found the relationship to be not significant[98,105,114,125].

LIMITATIONS

All epidemiological studies are limited by several factors. In the studies described, synergistic effects between air pollution and other genetic[59,126], lifestyle[87,101,122,126–129], and environmental[65,78,101,103,105,128,130–133] risk factors may not have been completely adjusted for in the analyses. Although carrying the APOE ε4 gene is a significant AD risk factor[134–136], results from studies assessing whether it has a modifying effects on the association between air pollution and AD are inconclusive: some showed the AD/ADRD risk associated with air pollution exposure to be more pronounced in APOE ε4 carriers[59,72,104,116,119,121] while others did not[62,66,73,77,104,105]. Genetic susceptibilities other than APOE ε4 status that can change the trajectory of AD pathogenesis were not taken into consideration for most studies. Moreover, other lifestyle factors, such as physical activity, exposure to traffic noise, sleeping patterns, and socioeconomic status, all of which are known to influence AD etiology[87,129,137–140] may not have been well reflected or adjusted for in most studies. Since the G × E interactions that lead to AD/ADRD progression are complicated and not well understood, it is challenging for epidemiological studies to fully capture the true impact of air pollution on AD/ADRD. Nevertheless, consistent epidemiological findings across different cohorts and countries that show a robust association between air pollution and ADRD provide strong justification for further experimental investigation of the underlying mechanisms by which air pollution increases AD/ADRD risk.

Experimental animal studies: The challenge of replicating human exposures to air pollution

To investigate the impact of air pollution on AD/ADRD pathogenesis, experimental animal studies have primarily used wildtype or transgenic rodent models that express human AD risk genes to determine whether exposure to air pollution decreases the time to onset or the severity of AD-relevant phenotypes.

A major challenge of studying air pollution toxicology in an experimental animal model is replicating human-relevant exposures to air pollution[141,142]. Most earlier studies employed acute exposures to high concentrations of diesel exhaust particles (DEP) or $PM_{2.5}$ administered to rodents via intratracheal[143] or intranasal[144] instillation, or, alternatively, oropharyngeal aspiration[145] of ambient $PM_{2.5}$ samples extracted from filtered media and resuspended in a delivery vehicle. The advantages of these instillation or aspiration exposure routes are that the composition of particles, dosage, and site of delivery are easier to control in testing the toxicity of a known amount and composition of air pollutants in a cost-effective way[146]. However, there are several critical shortcomings of these exposure paradigms in terms of replicating human exposure, including: (1) inaccurate reproduction of human-relevant exposure route, composition, pattern, and dosage of air pollutants[142]; and (2) omission of gaseous co-pollutants[141]. These factors can influence the toxicity of air pollutants and induce inconsistent biological responses even to the same air pollutants[142,147,148]. Hence, many recent studies have utilized *in vivo* whole-body inhalation exposures to aerosols of air pollutants to test toxicity in a manner that more closely replicates human exposure[149–161]. Some studies exposed animals to laboratory-generated

aerosols of concentrated $PM_{2.5}$, UFPM, or O_3[149–154], while other studies implemented variations of concentrated ambient particle (CAP) systems to collect real-world ambient air and concentrate $PM_{2.5}$ or UFPM for direct delivery to animals[155–158]. The CAP systems allow more accurate representation of real-world compositions of PM, yet because CAPs methodology only concentrates particles and not gases, understanding combined effects of PM and gases on biological outcomes is not possible[141,159]. Lastly, both laboratory-generated and CAP-generated aerosols do not effectively emulate chronic real-life exposure dynamics, which vary hourly, weekly, monthly and seasonally[141].

A few *in vivo* studies have developed methods for collecting ambient polluted air and delivering it to animals unchanged and in real-time at ambient concentrations via whole-body inhalation[141,160–162]. For example, in one study, ambient traffic-related air pollution (TRAP) was collected from a heavily trafficked freeway tunnel in northern California, USA, for subsequent delivery in real-time to animals housed in an adjacent vivarium[141]. This study demonstrated that chronic life-time exposure to ambient TRAP exacerbated AD-relevant phenotypes in wildtype Fischer rats and transgenic TgF344-AD rats that expressed human AD risk genes[160]. Another study in Taipei, Taiwan used the Taipei Air Pollutant Exposure System (TAPES) to sample and deliver outdoor ambient air mixture directly to 3xTg-AD mice housed in an exposure chamber. Transgenic mice exposed to ambient air pollution exhibited increased AD neuropathologies relative to filtered air controls[161]. These novel exposure methods in rodent models increase the translational value of experimental animal studies and provide corroborative evidence to support the epidemiological findings.

Experimental animal studies: Chronic exposure to air pollution exacerbates Alzheimer's disease pathology

A number of experimental animal studies have quantified Aβ plaques, NFT, tau phosphorylation, neuronal cell loss, and cognitive behavior deficits in both wildtype and transgenic rodent models after exposure to air pollution (Table 4). In most of these studies, the exposure paradigms were short-term or subchronic exposures to $PM_{2.5}$ and UFPM that ranged from 2–13 weeks[149–152,155–158,161]. Only a few studies examined the neurological impacts of chronic exposures, ranging from 5–14 months[109,153,154,160,162]. Results from these studies are mixed depending on the exposure paradigm and animal model. Studies with more chronic exposure durations (Table 4) more consistently reported air pollution-induced increases in Aβ/NFT loads, tau hyperphosphorylation, microgliosis, astrogliosis, and neuronal atrophy. Exposures longer than 3 months at either concentrated or ambient levels of UFPM, $PM_{2.5}$, or O_3 were shown to increase Aβ plaque load, tau phosphorylation, gliosis, and worsen learning and memory in transgenic AD rodent models[109,150,153,157,158,160]. Some short-term exposure studies (2–3 weeks) in rodents reported increased Aβ plaques, tau phosphorylation, neuronal atrophy, and memory deficits[153,155,163], while others did not observe those changes[149,161,164] or observed contrary results of reduced Aβ plaques with increased microgliosis[156]. The mixed results may be partially attributed to varying degrees of neuroinflammation caused by air pollution, as discussed below.

Prevailing hypothesis: Air pollution promotes Alzheimer's disease-related dementias phenotypes via inflammatory mechanisms

CHRONIC NEUROINFLAMMATION IN ALZHEIMER'S DISEASE PATHOGENESIS

Persistent neuroinflammation has been posited as a key mechanism responsible for progressive neurodegenerative diseases, including ADRD[165], based on accumulating evidence from human post-mortem[166–168] and experimental animal studies[169,170]. Aggregates of misfolded proteins like Aβ and NFT, which are neurotoxic, have been shown to trigger neuroinflammation[171,172]. Neuroinflammatory responses are mainly orchestrated by resident brain immune cells – microglia and astrocytes – that protect the brain microenvironment not only by phagocytosing cellular damage, but also regulating neurogenesis and synapse number[173,174]. While microglia-mediated amyloid clearance[169,175] and pruning of axosomatic inhibitory synapses following injuries[176,177] likely provide neuroprotection, dysregulation of these microglial functions is observed in AD/ADRD, and an increasing number of studies report that pro-inflammatory or disease-associated microglial phenotypes are associated with worse neurotoxic outcomes and increased severity of AD/ADRD neuropathology[169,178–182].

EXPOSURE TO AIR POLLUTION PROMOTES NEUROINFLAMMATION

Glial activation in response to PM exposure has been quantified by immunohistochemical analyses in many experimental animal studies. Most studies used IBA-1 as a biomarker of microglia[183,184] and GFAP as a biomarker of astrocytes[185,186], and some studies colocalized IBA-1 with CD68, a marker of phagocytic cells. Numerous studies have reported that PM induced recruitment of microglia and astrocytes to the olfactory bulb and hippocampus of rodents[158,160,187]. However, PM-induced microglial activation varied across different studies depending on the exposure paradigm, sex, age, genotype, and brain region. In one study, wildtype mice exhibited increased IBA-1$^+$ expression with more amoeboid microglial morphology in the olfactory bulb after 4–8 weeks of exposure to concentrated $PM_{2.5}$[187], whereas in another study, APP/PS1 mice, but not wildtype mice, exhibited increased microglial activation in the hippocampus following a 3-month exposure[158]. A more chronic exposure to ambient TRAP induced microglial phagocytosis (increased ratio of CD68$^+$/IBA-1$^+$) in the hippocampus of both wildtype and TgF344-AD female rats after 2 months of exposure, while male wildtype and TgF344-AD rats did not exhibit TRAP-induced microglial activation until after 14 months of exposure[160]. Interestingly, in contrast to male rats, female rats exhibited a dampened microglial phagocytic response to TRAP after 14 months of exposure[160]. A different study reported that 2 weeks of UFPM exposure reduced microglial activation with more ramified microglial morphology in 3xTgAD mice compared to filtered air-exposed controls[156]. Like microglia, observations regarding the impacts of PM on astrocytic activation (GFAP$^+$ immunoreactivity) varied across studies. While some studies reported PM-induced astrocytic recruitment and activation in the hippocampus[152,158,188], hypothalamus[189], and striatum[190], other studies reported no significant effects of PM on astrocytic activation in any of the brain regions examined[156,160].

These variable observations suggest that the glial responses to air pollution are complex. The functional impact of these changes also is not clear since it is now appreciated that

glial activation may either exacerbate[169,178–182] or protect[169,191–193] against synapse loss and neurodegeneration. To better understand how air pollution disrupts neuroinflammatory homeostasis, more recent studies have distinguished glial phenotypes using molecular biomarkers of pro- vs. anti-inflammatory phenotypes or biomarkers of disease-associated microglia (DAM). Following 12 weeks of exposure to UFPM, TMEM119^{+} microglia, which are considered homeostatic, that were not associated with amyloid plaques were reduced, while ferritin^{+} DAM microglia, which are associated with senescence and reactive oxygen species (ROS), were increased in both wildtype and App$^{NL\text{-}G\text{-}F/+}$-KI mice[157]. The same study also showed that UFPM increased the number of highly inflammatory, neurotoxic C3^{+} DAM astrocytes in the cortex of both genotypes[157]. *In vitro* studies also have characterized glial phenotypes after PM treatment. Primary coculture of microglia and astrocytes exhibited upregulated expression of DAM astrocytic markers (C3 protein and DAM-specific transcripts) in response to $PM_{2.5}$ treatment[194]. In addition, $PM_{2.5}$ altered interactions between neurons and glial cells in a triculture of neuron, astrocyte, and microglia human cell lines by promoting polarization of DAM microglia characterized by CD11b, CD86, and iNOS expression[195]. Based on these results, the type of glial activation or polarization following PM exposure may be important in either resolving inflammation or driving it towards persistent neuroinflammation and glial dysfunction, which can further exacerbate AD pathologies and neuronal atrophy.

These observations raise important questions regarding the mechanism(s) by which air pollutants alter glial phenotypes. Microglia and astrocytes are activated by autocrine and paracrine signals in the forms of: (1) cytokines and chemokines, which are small immune signaling molecules[196], and (2) reactive oxygen or nitrogen species (ROS/RNS), which are byproducts of cellular oxidative metabolism that carry unstable oxygen radicals[197]. Reactive oxygen/nitrogen species, such as H_2O_2, NO_x, and superoxides, serve as short-lived paracrine signals that play important physiological roles in immune defense and maintenance of cellular homeostasis[197]. Due to the highly reactive property of ROS, the cellular and extracellular levels of ROS are tightly regulated by cellular and enzymatic antioxidants that reduce and stabilize ROS to maintain homeostatic levels of ROS[197]. However, an imbalanced and persistent increase of ROS beyond the physiological range depletes the normal antioxidant capacity, resulting in oxidative stress when ROS react with cellular components to cause lipid peroxidation, mitochondrial damage, protein oxidative damage, DNA damage, and cellular death[197]. Additionally, subtler changes in cellular ROS levels can alter physiological redox signaling and consequently, result in cellular dysfunctions in microglia[198].

In vitro, short-term (2–3 weeks) exposure to concentrated PM or subchronic (3 months) exposure to ambient level of $PM_{2.5}$ was sufficient to cause oxidative stress in the olfactory bulb and hippocampus of rodents as evidenced by increased lipid peroxidation[152,161,199–201], dysregulated antioxidant metabolism[149,152,202], DNA damage and epigenetic modifications consistent with oxidative stress[109]. These findings demonstrate that air pollution can cause oxidative stress that may trigger neuroinflammation via microglia activation. In tissue culture models, $PM_{2.5}$ or DEP has been shown to increase ROS followed by microglial activation and release of proinflammatory cytokines in microglial monoculture[201,203,204], neuron-glia coculture[195,205] and microglia-endothelial cell coculture[206]. Interestingly, it has

been reported that complement 3 (C3)-mediated microglial activation resulted in aggravated Aβ deposition, synaptic loss, and neuronal degeneration[182,207–210] via NADPH oxidase activation[208,209], which increases ROS production. In an independent study, NADPH oxidase activation was found to induce DAM microglial polarization[211].

Exposure to air pollution has also been shown to cause proinflammatory cytokine release in the rodent hippocampus[149,150,152,158,162,164,200,212–214]. Across different studies, the main proinflammatory cytokines that were consistently upregulated by PM exposure were TNF-α, IL-1β, IL-6, and IFN-γ. However, whether and how PM-induced proinflammatory cytokines mediate DAM glial polarization and neuronal cell death are still poorly understood. Several recent *in vitro* studies suggest several potential mechanisms. For example, in a neuron-astrocyte coculture of human cell lines, $PM_{2.5}$ treatment caused the release of chemokines (CCL1, CCL2) that can recruit microglia, as well as cytokines (IL-1β, IFN-γ, IL-5, IL-8) that can polarize microglia into DAM phenotypes[195]. Monocultured microglia were polarized to the DAM phenotype ($CD86^+$, $iNOS^+$ with increased NO release) when exposed to conditioned media from astrocyteneuron coculture exposed to $PM_{2.5}$; and antibody neutralization of IL-1β, IFN-γ, CCL1, and CCL2 in the conditioned media significantly reduced DAM polarization. Interestingly, when monocultured microglia were directly exposed to $PM_{2.5}$ they did not polarize to a DAM phenotype, but instead became phagocytic and anti-inflammatory ($TREM2^+$, $LC3b^+$, $CD86^-$), which resulted in effective clearance of $PM_{2.5}$. These authors further demonstrated that microglia and astrocytes both contributed to PM-induced synaptic impairment while DAM microglia primarily drove PM-induced neuronal cell death and tau-phosphorylation[195]. These findings suggest that PM-induced glial polarization occurs through bidirectional crosstalk between microglia and astrocytes in which cytokines act as mediators to not only shift glial responses, but also to cause neuronal atrophy. An independent study further confirmed these results by showing that $PM_{0.2}$-induced neuronal synaptic atrophy was mainly driven via C3 signals released by DAM astrocytes that were polarized by activated microglia. Disease-associated astrocyte polarization was reversed when microglia were inhibited by minocycline even with the $PM_{0.2}$ treatment, and this further reduced synaptic damages[194].

The role of IL-1β has also been investigated in the context of inflammasome activation. The inflammasome is a multiprotein intracellular immune signaling complex that detects pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) to initiate proinflammatory responses and has been increasingly reported and discussed as a pathogenic mechanism of AD[215]. In a neuron-microglia coculture, co-exposure to oligomeric Aβ and $PM_{2.5}$ augmented the microglial response to lipopolysaccharide (LPS), evidenced as increased ROS and IL-1β production, resulting in activation of the NLRP3 inflammasome and subsequent neuronal apoptosis. Pretreating the coculture with the antioxidant N-acetyl-cysteine and/or caspase-1 inhibitor before oligomeric Aβ and $PM_{2.5}$ exposure significantly ameliorated neuronal apoptosis, suggesting that oxidative stress and NLRP3 inflammasome activation mediate the neurotoxic effects of oligomeric Aβ and $PM_{2.5}$[205].

Results from animal studies and *in vitro* studies corroborate epidemiological findings and provide a better understanding of the molecular and cellular responses to air pollution

that include oxidative stress, neuroinflammation, neurodegeneration, and aggravation of AD/ADRD pathologies. While there is ongoing progression towards identifying how air pollutants perturb brain health, mechanistic links that integrate the neuropathological processes triggered by air pollution need further investigation. It is experimentally challenging to recreate realistic air pollution exposure paradigms, but recent development of exposure systems that allow better recapitulation of human-relevant exposures will enable significant advancements in the field of air pollution and ADRD research possible. Nevertheless, discrepancies in exposure paradigms and animal models between studies has led to large variabilities in neurologic outcomes. Therefore, follow-up studies with more standardized exposures using genetically modified animal models with inclusion of both sexes are necessary to validate observations reported across different studies.

Outstanding data gap: Direct vs. indirect effects of air pollution on the brain

While *in vitro* studies demonstrate that PM from polluted air can directly trigger responses in neurons and glial cells, whether and how gases associated with air pollution directly affect these cell types is largely unknown. Similarly, there remains considerable uncertainty as to whether *in vivo* brain responses to air pollution arise from direct interactions with air pollutants or rather are the indirect consequence of air pollution effects on peripheral organs. There is experimental evidence, albeit limited, to support both possibilities, which likely are not mutually exclusive.

DIRECT PATHWAY

The direct pathway infers translocation of PM to the brain, where it can directly activate microglia. Translocation of PM to brain parenchyma may occur through retrograde transport of PM from olfactory epithelium to the olfactory cortex via olfactory nerves or via the trigeminal nerve to the brain[216–218] (Figure 3A). Particulate matter inclusions in the olfactory bulbs and prefrontal cortex have been observed and associated with impaired olfactory function in both mice and humans[109,110,112,113,155,160,161,187,219,220]. Alternatively, PM may enter the brain by crossing the blood-brain barrier (BBB) from the systemic circulation. Inhaled fine particles that are deposited in the distal airways and alveoli can readily cross the air-blood barrier to enter the systemic circulation and cross other biological barriers like the BBB[221–225]. Studies using a 3-D human BBB organotypic chip have shown that PM can cross the BBB[225]. Moreover, an *in vivo* study in which transgenic AD animals were exposed to ambient levels of PM, extensive PM deposition was observed in the hippocampus, which is vulnerable to BBB leakage in AD, with minimal PM detected in the frontal cortex[160], supporting this as the primary mechanism by which inhaled PM may be reaching the brain under conditions of exposure to ambient TRAP levels. Blood-brain barrier impairment is a known AD pathology[226–228] that may be both a causal factor and a result of air pollution-induced AD exacerbation because PM and circulating mediators can cross an impaired BBB[229] and air pollution can break down components of the neurovascular unit that forms the BBB[199,230,231]. Phagocytosis of PM by activated microglia has been well characterized in many *in vitro* studies[195,205,206,232–234], and neurotoxic materials, such as metals, endotoxins, and polycyclic aromatic hydrocarbons, adhered to PM have been shown to cause neuroinflammation in the brain parenchyma[115,235–237]. Although

there are less studies on PM-induced astrocytic activation[189,194,195], results indicate that the microglia-astrocyte crosstalk can lead to bidirectional responses in both glial cells to promote neuroinflammation[194,195,210,238,239].

INDIRECT PATHWAY

The indirect pathway infers that air pollution-associated neuroinflammation is a consequence of inflammation induced by air pollution in peripheral targets. The respiratory toxicology of air pollution has been extensively studied, and it is well-established that inhaled air pollutants reduce lung function and increase respiratory disease susceptibility and mortality by inducing and disrupting pulmonary inflammatory responses[240–243]. Air pollution also causes consequent systemic inflammation, and increased serum levels of proinflammatory cytokines, dysfunctional fibrinolysis, oxidative stress, and activation of circulating immune cells[41,244–248]. With growing evidence suggesting that systemic inflammation can promote neuroinflammation[249–254] and that higher risks of dementia and cognitive deficits are associated with impaired lung function[255–258], the lung-brain axis has been proposed as a potential indirect pathway by which chronic exposure to air pollution induces persistent neuroinflammation that promotes AD/ADRD pathogenesis (Figure 3B). While the direct pathway proposes a valid explanation for PM-induced neuroinflammation, it does not adequately explain neuroinflammatory effects of gaseous components like NO_x and O_3[150]. A research group from Indiana University has conducted a series of studies demonstrating how O_3-induced systemic circulating factors regulate microglial and astrocytic activation[150,151,259]. An acute exposure to O_3 caused persistent microglial activation in rats 24 hours post-exposure, and the same study showed that the addition of serum from O_3-exposed animals can prime microglia *in vitro* to augment their response to LPS treatment.[259] The group's more recent studies show that O_3 reduced the number of peri-plaque $TREM2^+$ microglia but increased peri-plaque colocalization of microglia and astrocytes[151] with altered transcriptomic profiles shifting glial cells to more disease-associated states (lower *Trem2* and higher *Serpinea3n* gene expressions) in 5xFAD mice[150]. They also reported that O_3 increased the level of circulating high mobility group box 1 (HMGB1), which is a DAMP signal that enhances both innate and adaptive immune responses[150]. Deleting HMGB1 only in peripheral myeloid cells, but not in microglia by using *Hmgb1*$^{fl/fl}$*LysM-Cre*$^+$ mouse strain, reversed O_3-induced changes in glial expressions and returned *Trem2* and *Serpinea3n* transcript levels back to the filtered air control baseline[150,151]. An *in vitro* study from a different group showed that in comparison to directly adding DEP alone to microglia, adding conditioned medium from DEP-stimulated alveolar macrophages caused a higher activation of microglial CD14, which is a pattern recognition receptor that induces DAMP signaling[234]. These findings and those from other studies[260–262] with similar results suggest that the lung-brain axis may indirectly mediate neuroinflammatory effects of air pollution independent of the direct pathway. However, more experimental studies are needed to further investigate the lung-brain axis in different exposure paradigms that not only test acute effects of exclusive air pollutants, but also test long-term effects of exposure to combined air pollutants.

Epigenetics, Environment, and Alzheimer's disease and related dementias

Epigenetic factors, which mediate gene and environment interactions, may serve as a mechanism underlying G × E interactions and explain a portion of the missing heritability of AD/ADRD.[83] Epigenetic control is highly complex, with at least 28 known histone, 53 DNA, and 160 RNA modifications, as well as non-coding RNAs, that work in concert to regulate chromatin accessibility, gene expression, mRNA stability, and mRNA translation[263–265]. The location and context-dependent function of these modifications further adds to their complexity but also enables their targeted use as biomarkers and targeted therapeutics[266–268]. Here, while we do not cover the full breadth of epigenetic modifications and their functions, we do summarize recent findings related to their association with and potential functional link between air pollution and AD/ADRD pathogenicity.

Prior experimental and population-based epigenetic studies characterizing G × E interactions identified dynamic and disease-associated epigenetic modifications and transcriptional profiles that varied in response to environmental factors[268]. The modifiable nature of epigenetic modifications and their control over gene expression positions them as prime tools and targets for therapeutic intervention. Additionally, their dynamism makes them well suited to function as biomarkers indicative of disease predisposition, pathological outcomes and disease susceptibility, or of environmental exposures.

Generally, epigenetic modifications, whether located on histones, DNA, or RNA, are regulated by writer and erasers and interpreted by reader proteins or protein/RNA complexes. The expression of these regulatory factors enables fine control over tissue and cell-type specific spatiotemporal expressional programming[269–272]. Dysregulation of epigenetic control, either through the alteration of specific markers or the abundance of the readers/writers/erasers serves as an additional mechanism of control and potential contributor towards disease state.

DNA MODIFICATIONS

Recent work characterizing the relative contributions of genetic and environmental factors in the development and progression of AD highlighted epigenetic modifications as critical mediators of G × E interactions. In a cohort of older women from the Women's Health Initiative Memory Study (WHIMS), it was found that nanoparticles exposure increased the risk of cognitive decline by 81% and all-cause dementia by 92% in a dose-dependent manner for *APOE ε4* carriers[273]. Following up on these findings, the authors utilized the 5xFAD mouse model and found that exposure to nanoparticles was associated with greater AD pathology and the APOE status of the exposed individual functioned as a response modifier. In the 5xFAD mouse model, over the course of 15 weeks of nanoparticles exposure, the presence of $ApoE\ \varepsilon4^{+/+}$ over $ApoE\ \varepsilon3^{+/+}$ alleles significantly increased amyloid plaque pathology, reduced hippocampal CA1 neurites, and decreased the glutamate GluR1 subunit. In a similar study investigating the G × E interaction between cadmium exposure and *ApoE ε4* dosage, 14 weeks of cadmium exposure in the ApoE knock-in mouse model identified accelerated cognitive impairment and reduced hippocampal neurogenesis in *ApoE ε4* carriers relative to their *ApoE ε3* counterparts, indicating G × E interactions

modulate AD pathogenicity[274]. In effort to explore the missing heritability observed in AD, Panitch, et al. recently investigated the relationship between *APOE* DNA methylation (5-methylcytosine; 5mC) and ε4 carrier status and found differential methylation at 25 CpG sites in the dorsolateral prefrontal cortex and 36 CpG sites in blood, with the majority of sites being hypomethylated[275]. Furthermore, this group identified seven CpG sites in the APOE region (including *TOMM40, APOE*, and *APOC1* genes) that significantly differed between *APOE ε4* carriers and non-carriers in brain and blood ($P<5\times10^{-8}$), with three sites in the *APOE* gene showing hypermethylation in ε4 carriers and a nominal association with *APOE* expression in the brain ($P<10^{-5}$)[275]. One of the three genes that contained differentially methylated CpG sites in *APOE ε4* carriers relative to control was *TET1*, a 5mC eraser and DNA hydroxymethylation (5-hydroxymethylcytosine, 5hmC) writer. In the same family of Ten-Eleven Translocation proteins, *TET2*, a 5mC eraser and 5hmC writer, was also found to be moderately differentially methylated in *APOE ε4* carriers relative to control ($p = 7.6\times10^{-6}$)[275]. Interestingly, both TET1 and TET2 function in similar but distinct capacities, and prior sequencing studies have identified an enrichment of *TET1* and *TET2* variants associated with EOAD/frontotemporal dementia[276,277]. Lastly, utilizing an APP mouse model, tethering the *de novo* 5mC writer, Dnmt3a, to dCas9 targeted to *APP* was sufficient to methylate the APP gene, reduce APP expression and amyloid pathology, and ameliorate cognitive and behavioral impairment[278].

HISTONE MODIFICATIONS

In addition to DNA modifications, histone modifications have emerged as crucial players in the pathogenesis of AD and often function with DNA modifications to regulate gene expression[279,280]. Recent studies reveal links between air pollution and histone modifications. Zheng et al. explored how different components of air pollution ($PM_{2.5}$, PM_{10}, black carbon, and elemental components (potassium, sulfur, iron, silicon, aluminum, zinc, calcium, and titanium)) influenced various histone modifications (H3K9ac, H3K9me3, H3K27me3, and H3K36me3) in the blood leukocytes of exposed truck drivers and office workers in Beijing[281]. Their group identified differential associations between pollutants and various histone markers. Specifically, they noted an increase in ambient PM_{10} associated with lower H3K27me3 and H3K36me3 levels. They also observed that office workers had a stronger association between black carbon and H3K9ac and H3K36me3 than truck drivers, and that the association between black carbon exposure and H3K9ac and H3K9me3 status was sex-dependent[281].

Similarly, exposure to air pollutants, particularly $PM_{2.5}$ and PM_{10}, induced significant epigenetic alterations in rat blood and lung tissue in a dose-dependent manner[282]. This study revealed that increased exposure to $PM_{2.5}$ and PM_{10} generally led to decreased DNA methylation of *LINE-1* and *iNOS*, while simultaneously increasing histone acetylation (H3K9ac) in both blood and lung tissue. Interestingly, $PM_{2.5}$ exposure was also associated with increased methylation of *p16CDKN2A* and *APC* promoters. The effects of NO_x were more variable, showing mixed impacts on methylation patterns. Notably, these epigenetic changes were often more pronounced in blood compared to lung tissue, with H3K9ac consistently increasing in response to $PM_{2.5}$and PM_{10} exposure in both tissue types[282].

RNA MODIFICATIONS

RNA N6-methyladenosine (m^6A) is the most studied and prevalent RNA modification, it is highly enriched in the brain, and associated with a suite of neurodevelopmental and neurodegenerative diseases, including AD. m^6A influences transcript splicing, stability, translation, nuclear export, and RNA structure[283,284]. There is evidence that environmental exposure influences RNA modifications and subsequently, AD pathophysiology[285] Li et al., 2023 found that exposure to $PM_{2.5}$ is associated with a greater prevalence of m^6A modifications, a global increase in gene expression, and a significant increase in the expression of prostaglandin-endoperoxide synthase 2 (PTGS2), which is involved in synthesizing the prostaglandin inflammation signaling molecules[286].

Recent research shed light on the molecular mechanisms underlying the effects of $PM_{2.5}$ exposure on lung cells[287]. In the A549 lung cell line, $PM_{2.5}$ exposure upregulated m^6A RNA methylation coincident with increased expression of *TGF-β, SMAD3*, and the methyltransferases *METTL3* and *METTL14* (m^6A writers). Importantly, inhibition of TGF-β reversed the $PM_{2.5}$ -induced changes, suggesting a pivotal role for the TGF-β signaling pathway in regulating m^6A RNA methylation following $PM_{2.5}$ exposure[287]. These findings revealed a potential mechanism by which lung inflammation triggered by $PM_{2.5}$ exposure leads to m^6A modifications observed in AD.

Using postmortem AD patient data, another study identified significantly reduced expression and soluble protein levels of METTL3, and no significant changes for METTL14 in the hippocampus[288]. Notably, insoluble fractions of AD brain samples had accumulated METTL3 that positively correlated with insoluble tau protein levels, although no direct interaction between METTL3 and tau was observed[288]. This research suggests that while tau pathology is a better predictor of disrupted m^6A signaling than Aβ load, it likely does not directly cause the altered *METTL3* expression seen in AD hippocampal neurons.

These findings were corroborated in a study of individuals diagnosed with AD vs. controls that reported a marked decrease in m^6A modifications and METTL3, METTL14, WTAP, FTO, and YTHDF protein levels in cortex and hippocampus tissue with AD. The functional significance of this observation is suggested by experimental animal studies: knockdown of *METTL3* in mouse hippocampus significantly increased memory loss, neurodegeneration, gliosis, oxidative stress, and apoptotic processes[289]. Knocking down *METTL3, METTL14*, and *YTHDF* in flies expressing *TauR406W* was found to worsen eye phenotype and reduce motor function, highlighting that reduced expression of m^6A or the ability to read m^6A is associated with worsened AD-associated phenotypes[290].

Collectively, these studies suggest that the regulation of RNA writers, readers and erasers is a critical component for mediating G × E interactions, and aberrant regulation of these proteins has a large knock-on effect, influencing pathological outcomes.

NON-CODING RNA

A separate class of RNAs, non-coding RNAs, exert epigenetic control via control of transcription, transcript stability, and translation efficiency. These molecules are highly

dynamic, and their expression and stability can be influenced by exposure to environmental factors[291–294].

To determine whether DEP induces pulmonary inflammatory response, Wang and colleagues explored the involvement of RNA binding protein LIN28B and non-coding microRNA Iet7 axis in the inflammatory response to DEP exposure in mice[295]. Let7-d and Iet7-g were significantly downregulated, while LIN28B protein levels were elevated from 6 to 24 hours after DEP exposure. Furthermore, they found that LIN28B is responsible for the downregulation of Iet7, subsequently increasing expression of the pro-inflammatory cytokine IL-6[295]. A study involving a protein of the same class, LIN28A, in a VaD rat model, where VaD was introduced by bilateral common carotid artery occlusion, found that treatment with *Lin28a* siRNA ameliorated cognitive impairment, as well as upregulated expression of GFAP, and IBA-1 glial markers[296]. Moreover, treatment with siRNA alleviated BBB damage as measured by expression of PECAM-1, PDGFRβ, occludin, claudin-9, and ZO-1, and *Ccr6*[296].

Furthering the link between environmental exposure, non-coding RNAs and modulation of inflammation, microarray analyses of blood samples from foundry workers exposed to metal-rich PM identified significantly increased expression of miR-421, miR-146a, miR-29a, and let-7g after 3 days of work exposure relative to baseline (first day of the work week after two days off).[297] In addition to sampling miRNA expression, PCR was performed on 18 inflammatory genes, including *TGFß1, TGFß2, TNF, ITGA2, ITGAX, NFKB1, NOS2, CCL2, CCL5*. Significant differences were found in individual miRNAs and inflammatory genes that have differing targets and regulatory activity. This included miR-421 associated with *NOS2* expression; miR-146a with *TGFß1, CCL2* and *CCL5* expression; and let-7g with *TGFß1, ITGAX*, and *NFKß1* expression[297].

Additional research exploring the relationship between $PM_{2.5}$ exposure and expression of non-coding RNAs has identified increased expression of the long non-coding RNA, HCG18, in the lung. HCG18 suppresses miR-195 expression and leads to upregulated *ATG14* expression and increased autophagy and progression of lung adenocarcinoma[298]. In addition to playing a significant role in the development of lung pathologies, reduced mir-195 expression is observed with human aging and in AD progression, while increased mir-195 prevalence is associated with improved cognitive performance and negatively correlated with cerebrospinal fluid tau levels. Human expression patterns of mir-195 are mirrored in *ApoE ε4*$^{+/+}$ mice when compared with *ApoE ε3*$^{+/+}$ mice. Furthermore, elevating miR-195 levels was found to reduce amyloid burden and tau hyper-phosphorylation and improve cognitive impairment. Lastly, when cortical neurons and astrocytes generated from inducible pluripotent stem cells derived from *ApoE ε4*$^{+/+}$ mice were co-cultured, miR-195 inhibition exacerbated AD-associated lysosomal phenotypes[299].

In this section, we highlighted epigenetic mechanisms by which air pollutants may contribute to cognitive impairment and AD-associated pathologies. These studies underscore the crucial role of epigenetics as a mediator of G × E interactions in AD. Importantly, they indicate that the development of epigenetic markers of air pollution exposure may advance the identification of specific air pollutants that promote AD/ADRD-associated risk and

progression. Epigenetic analyses also hold the promise of providing targets for therapeutic interventions, offering modifiable pathways to potentially reduce AD pathophysiology.

Conclusions

Consistent with previous epidemiological findings regarding the association between air pollution and ADRD, recent epidemiological studies have largely reported positive correlations between air pollution and AD/ADRD. This association is mostly substantiated by experimental animal studies. Although there is general consensus that air pollution is an environmental risk factor for AD/ADRD, associations between specific air pollutants and ADRD subtypes are variable across different studies. This variability in part stems from the complexity of mixed ADRD pathologies and equivocal etiological links between genetic status, pathological manifestation, cognitive impairment, and clinical diagnoses. Currently, the field is reassessing diagnostic criteria utilizing biomarkers that more accurately delineate between AD and related dementias to better characterize pathology-specific disease progression. These refinements in diagnostic precision will improve efforts to identify environmental factors that modify risk and severity of AD/ADRD. Elucidating ADRD stratification and G × E contributions implicated in the development of ADRD will inform effective public health regulations and guidelines for air pollution and other environmental contaminants, with the aim of preventing and minimizing adverse neurological health outcomes.

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List of abbreviations

5hmC	5-hydroxymethylcytosine
5mC	5-methylcytosine
AD	Alzheimer’s disease
ADRD	Alzheimer’s disease-related dementias
Aβ	Amyloid beta plaques
BBB	Blood-brain barrier
BC	Black carbon
C3	Complement 3
CAP	Concentrated ambient particle

CO	Carbon monoxide
CSF	Cerebrospinal fluid
DAM	Disease-associated molecular biomarkers
DAMP	Damage-associated molecular pattern
DEP	Diesel exhaust particles
EOAD	Early-onset Alzheimer's disease
G × E	Gene by environment interaction
HMGB1	High mobility group box 1
LOAD	Late-onset Alzheimer's disease
LPS	Lipopolysaccharide
m^6A	N6-methyladenosine
MRI	Magnetic resonance imaging
NFL	Neurofilament light
NFT	Neurofibrillary tau tangles
NO_x	Nitrogen oxides
O_3	Ground-level ozone
PAMP	Pathogen-associated molecular pattern
PET	Positron emission tomography
PFAS	Per-and polyfluoroalkyl substances
PM	Particulate matter
PTGS2	prostaglandin-endoperoxide synthase 2
ROS/RNS	Reactive oxygen or nitrogen species
SO_2	Sulfur dioxide
TRAP	Traffic-related air pollution
UFPM	Ultrafine particulate matter
VaD	Vascular dementia

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Box 1.

Air pollution composition, toxicology and regulations

Six criteria air pollutants are monitored and regulated by the U.S. Environmental Protection Agency National Ambient Air Quality Standards and the World Health Organization Air Quality Guidelines. These include: (1) coarse and fine particulate matter (PM_{10}, PMzs); (2) nitrogen dioxide (NOz); (3) ground-level ozone (03): (4) carbon monoxide (CO); (5) sulfur dioxide (SO_2); and (6) lead (Pb) (Figure 2). The composition and toxicity of these pollutants are determined in large part by their sources.[222] Sources of these pollutants include industrial pollution, near roadway traffic-related air pollution (TRAP), wildfire, and agriculture[51,60,317,318].

Amongst the six criteria air pollutants, PM has been most intensively monitored and studied as a health hazard because it deposits in the respiratory system, and the finer particles can enter the systemic circulation and be distributed to all organs in the body, including the brain[219,222,224,319–321]. Particulate matter ranges in size from coarse (PM_{10} with an aerodynamic diameter <10 μm) to fine ($PM_{2.5,}$ diameter <2.5 μm) to ultrafine (UFPM, diameter <0.1 μm) (Figure 2). Fine $PM_{0.1–2.5}$ are considered more toxic than coarse PM_{10} because of a higher penetrance into the lung parenchyma with smaller sizes. Fine $PM_{2.5}$ from agriculture, TRAP, coal combustion and wildfire were found to be significant risk modifiers for dementia, including AD[49,51,221,318,322,323]. A wide range of organic and inorganic compounds from different sources of agriculture, wildfire, and TRAP can adsorb to $PM_{2.5}$ and cause negative health outcomes in the lung and the brain.[124,324,325] Likewise, the composition of gases in polluted air also depends on the source of emission. Traffic-related air pollution is one of the main sources of NO_x, CO, benzene, and other volatile organic compounds (Figure 2), yet industrial boilers, gas stoves, and other fuel combustion processes also contribute to emissions of these gases. Traffic-related air pollution as a source of SO_2 emissions has declined with the global transition to using low sulfur fuels for automobiles[326]. Yet, other sources like wildfire smoke, industrial sources, and ship emissions still contribute to the release of SO_2[327]. Ground-level O_3 is a gaseous secondary air pollutant that forms from photochemical reactions with radicals derived from NO_x and volatile organic compounds in the warm ambient atmosphere[328].

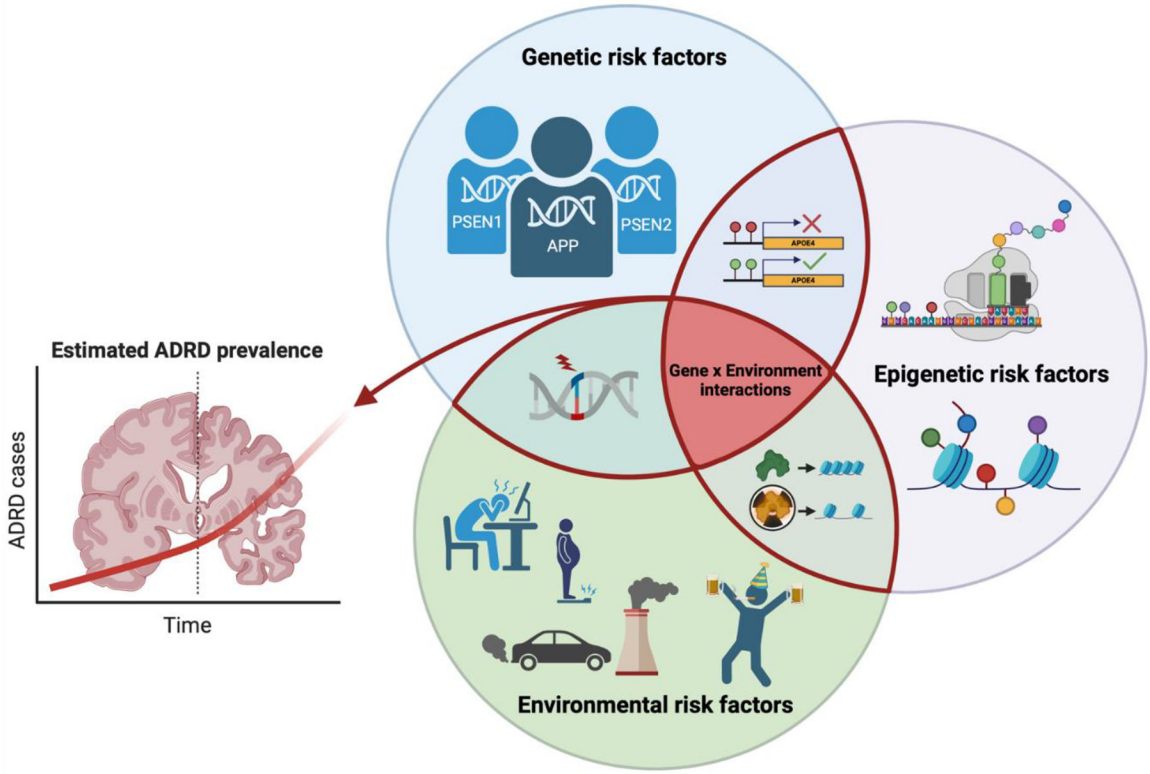

Figure 1. Gene by environment interactions.

Genetic, epigenetic, and environmental risk factors interact to promote ADRD etiology and disease progression. NOTE: ADRD, Alzheimer's disease-related dementias. Created with BioRender.com.

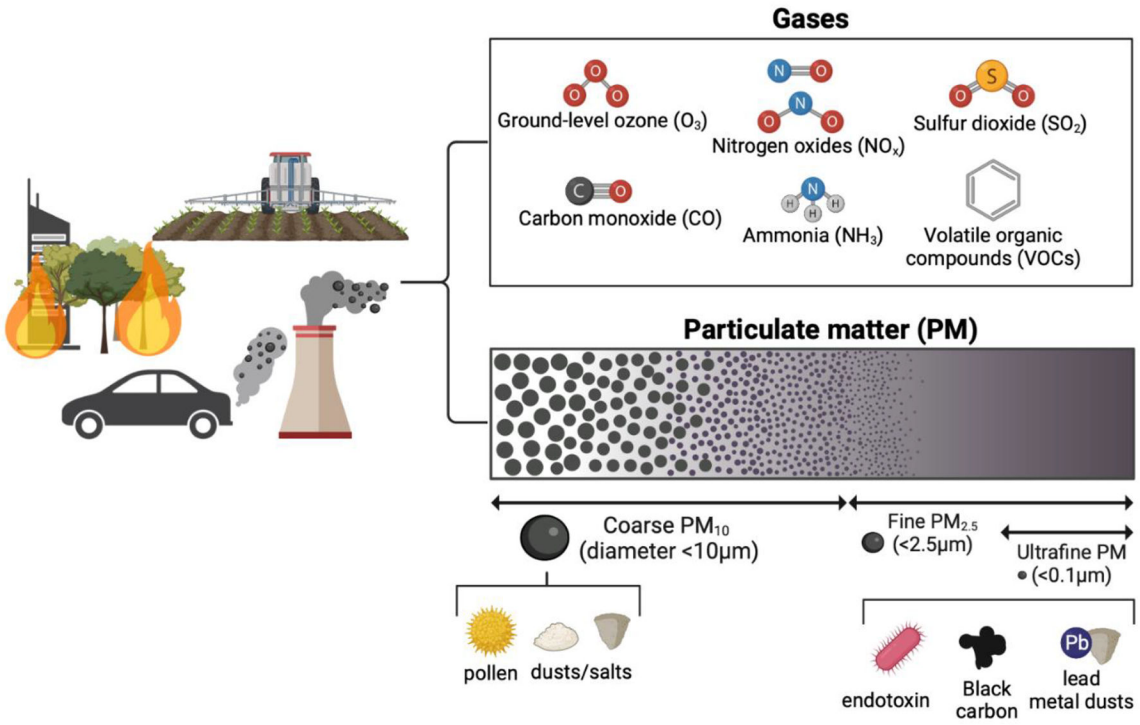

Figure 2. Composition of air pollutants.

Air pollutants consist of gaseous and particulate matter (PM) fractions with heterogenous sources, compositions, and sizes, all of which influence toxicity to the respiratory system and the brain. Created with BioRender.com.

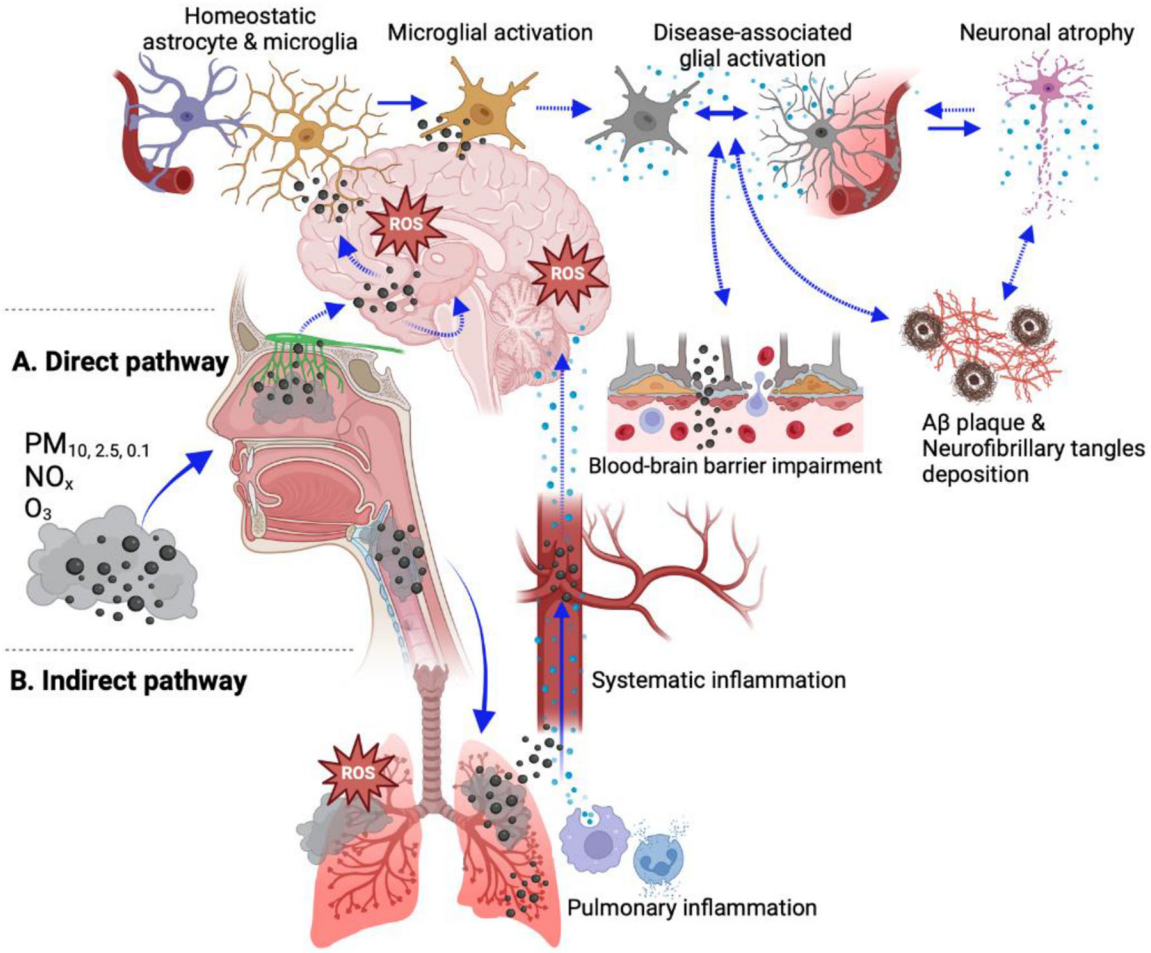

Figure 3. Potential mechanisms by which air pollutants promote neuroinflammation.

Schematic summary of potential pathways by which air pollutants mediate neuroinflammation. **A. Direct pathway:** Inhaled air pollutants infiltrate the brain parenchyma via retrograde transportation from olfactory nerve terminals into the olfactory cortex or by crossing the blood-brain barrier from the systemic circulation to directly activate microglia. **B. Indirect pathway:** Inhaled air pollutants cause neuroinflammation via the lung-brain axis. It is hypothesized that air pollutant-induced pulmonary inflammation leads to neuroinflammation via increased systemic inflammation and release of inflammatory mediators into the systemic circulation, which are then delivered to the brain and cross the blood brain barrier to activate innate immune cells in the brain. *NOTE:* ROS, reactive oxygen species; dotted arrows indicate hypothesized modes of actions; solid arrows indicate modes of actions supported by experimental evidence. Created with BioRender.com.

Table 1:

Alzheimer's disease risk genes

Early-Onset Alzheimer's disease (EOAD)		Late-Onset Alzheimer's disease (LOAD)			
Autosomal Dominant EOAD	Autosomal Recessive/Sporadic EOAD	ABCA7[135,307,311–314]	TMEM106B[311,313,314]	PRKD3[313,314]	NTN5[311]
		BIN1[135,307,311–314]	TNIP1[311,313,314]	RASGEF1C[313,314]	NYAP1[307]
		CASS4[135,307,311–314]	ABCA1[313,314]	RBCK1[313,314]	LINC02705[307]
		CD2AP[135,307,311–314]	ADAM17[313,314]	RHOH[313,314]	LINC02695[307]
APP[300]	APOE4[302,303]	CR1[135,307,311–314]	ADAMTS1[313,314]	SCIMP[135,314]	RNU6–560P[307]
PSEN1[300,301]	TREM2[304,305]	SORL1[135,307,311–314]	ANK3[313,314]	SCIMP/RABEP[311,313]	USP6NL-AS1[307]
PSEN2[300,301]	SORL1[302]	TREM2[135,307,311–314]	ANKH[313,314]	SEC61G[313,314]	ADAMTS4[135]
	PRNP[301]	CLU[307,311–314]	BLNK[313,314]	SIGLEC11[313,314]	HESX1[135]
	MAPT[306]	EPHA1[135,307,312–314]	COX7C[313,314]	SLC2A4RG[313,314]	HS3ST1[135]
	GRN[307]	FERMT2[307,311–314]	CTSB[313,314]	SNX1[313,314]	CNTNAP2[135]
	C9orf72[308]	ABI3[135,311,313,314]	CTSH[313,314]	SORT1[313,314]	CLU/PTK2B[135]
	NOTCH3[309]	ADAM10[311–313]	DOC2A[313,314]	SPI1[307,314]	BZRAP1-AS1[135]
	PARK2[306]	APH1B[135,311,313,314]	FOXF1[313,314]	SPPL2A[313,314]	
	PLCG2[300]	INPP5D[307,312–314]	HS3ST5[313,314]	TPCN1[313,314]	SUZ12P1[135]
	ABI3[300]	PICALM[135,311–313]	ICA1[313,314]	TSPAN14[313,314]	ALPK2[135]
	APP[300]	PTK2B[307,312–314]	IDUA[313,314]	TSPOAP1[313,314]	AC074212.3[135]
	PSEN1[300,301]	ACE[311,313,314]	IL34[313,314]	UMAD1[313,314]	CLNK/HS3ST1[313]
	PSEN2[300,301]	APOE[135,307,311]	INPPD5[311]	WDR12[313,314]	
	SORL1[300,302]	APP[311,313,314]	JAZF1[313,314]	WDR81[313,314]	HLA[313]
	ABCA7[300]	CD33[135,311,312]	KAT8[313]	ZCWPW1[135,312]	CELF1/SPI1[313]
	TREM2[300]	CLNK[135,311,314]	KLF16[313,314]	ZCWPW1/NYAP1[311,313]	HLA-DQA1[314]
	BIN1[300]	ECHDC3[135,313]	MAF[313,314]		UNC5CL[314]
	UNC5C[300]	GRN[311,313,314]	MME[313,314]	AGRN[311]	TREML2[314]
	AKAP9[300]	HLA-DRB1[135,311]	MS4A4A[313,314]	HAVCR2[311]	EPDR1[314]
	NOTCH3[300]	LILRB2[311,313,314]	MYO15A[313,314]	EPHA1-AS[311]	SPDYE3[314]
	12s rRNA[300]	MS4A6A[135,312]	NME8[313,314]	USP6NL/ECHDC3[311]	USP6NL[314]
	CLU[300]	NCK2[311,313,314]	PLCG[313,314]	CCDC6[311]	EED[314]

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Early-Onset Alzheimer's disease (EOAD)		Late-Onset Alzheimer's disease (LOAD)			
	PLCG2[300]	SHARPIN[311,313,314]	PLEKHA1[313,314]	MADD/SPI1[311]	MINDY2[314]
	ABI3[300]	SLC24A4[135,311,314]	PRDM7[313,314]	RIN3[311]	BCKDK[314]
	APOE[300]			TSPOAP1-AS1[311]	WNT3[314]
	TET1[310]				AKAP9[312]
	TET2[276]				UNC5C[312]

Table 2:

Summary of epidemiological studies testing the association between air pollutants and Alzheimer's disease-related dementias

Air pollutant	AD-relevant clinical pathology	Cognitive impairment	ADRD risk
$PM_{2.5}$	↑ 5 studies reported positive association[53,54,104,106,111] ∅ 1 study reported no association[105]	↑13 studies reported positive association[51,81,106,115–121,124,314,315] ∅ 4 studies reported no association[98,105,114,125]	↑ 36 studies reported positive association[50–52,58–90] ∅ 5 studies reported no association[95–99]
PM_{10}	↑ 4 studies reported positive association[54,104–106]	↑ 4 studies reported positive association[106,121,123,314] ∅ 3 studies reported no association[98,105,125]	↑ 9 studies reported positive association[67,70–72,80,82,85,87,100] ∅ 1 study reported no association[98]
NO_x	↑ 4 studies reported positive association[54,104–106]	↑ 6 studies reported positive association[106,118,121,123,314,315] ∅ 4 studies reported no association[98,105,114,125]	↑ 28 studies reported positive association[50,58,59,61–63,66,67,69–73,76–80,82–87,90–93] ∅ 8 studies reported no association[52,75,94–99]
O_3	∅ 1 study reported no association[53]	↑ 1 study reported positive association[120] ∅ 1 study reported no association[123]	↑ 3 studies reported positive association[58,82,93] ∅ 6 studies reported no association[58,61,76,87,94,95]
Black carbon			↑ 4 studies reported positive association[76,79,87,90] ∅ 4 studies reported no association[52,96,97,99]

NOTE: AD, Alzheimer's Disease; ADRD, Alzheimer's disease-related dementias; AD-relevant clinical pathology includes Aβ 42/40 and neurofilament light levels in the blood and cerebrospinal fluid, and brain PET/MRI scans for amyloid, tau, and cortical thickness detection.

↑: positive association reported; ∅: no association reported.

Table 3:

Epidemiological studies studying air pollution as a risk factor for Alzheimer's disease-related dementias

Air pollutant levels	Participant follow-up duration	Study results	Cohort type/size	Citation/location
Annual mean: $PM_{2.5}$ = 9.3 μg/m^3 NO_2 = 17.1 ppb O_3 = 42.6 ppb	2000–2018	$PM_{2.5}$, NO_2∝↑ incident AD/ADRD O3 ∅ incident AD/ADRD	Medicare Chronic Conditions Warehouse Age ≥ 65yrs n=12,233,371	Shi, *et al.*[58] United States
Annual median: $PM_{2.5}$ = 10.6 μg/m^3 NO_2 = 18.26 ppb O_3 = 46.68 ppb	2000–2016	$PM_{2.5}$, NO_2 exposure 8–10yrs prior to diagnosis ∝↑first ADRD hospitalization	Medicare FFS beneficiaries Age > 65yrs n=8,507,437	Mork, *et al.*[50] United States
2010 median: $PM_{2.5}$ = 10 μg/m^3 PM_{10} = 16.1 μg/m^3 NO_x = 43.4 μg/m^3	Median 12.01yrs	$PM_{2.5}$, NO_x∝↑ all-cause dementia risk NO_x∝↑ AD risk in individuals with higher genetic risk scores	UK Biobank Study Age ≥ 50yrs n=437,932	Yuan, *et al.*[59] United Kingdom
10-year median: $PM_{2.5}$ = 11.2 μg/m^3	1998–2016	PM2.5 ∝↑ incident dementia	Health and Retirement Study Age > 50yrs n=27,857	Zhang, *et al.*[51]
10-year median: $PM_{2.5}$ = 21.3 μg/m^3 NO_2 = 32.8 μg/m^3 BC = 2.3 10^{-5}/m	1999–2011	$PM_{2.5}$∝↑ all-cause dementia, AD, and VaD risks NO_2, BC ∅ dementia risk	Three-City Study Age ≥ 65yrs n=7,066	Mortamias, *et al.*[52] France
Annual mean: TRAP $PM_{2.5}$ = 0.18 μg/m^3 Wood-burning $PM_{2.5}$ = 0.77 μg/m^3	1993–2010	All sources of $PM_{2.5}$∝↑dementia incidence	Betula Study Age > 55yrs n=1,806	Oudin, *et al.*[60] Sweden
Biennial median $PM_{2.5}$ range: 2002–2003: 10.09–12.65 μg/m^3 2015–2016: 7.4–8.34 μg/m^3	2016–2018	$PM_{2.5}$∝↑ amyloid PET scan positivity O_3∅ amyloid PET scan positivity	IDEAS Study (Imaging DementiaEvidence For Amyloid Scanning) Age ≥ 65yrs n=18,178	laccarino, *et al.*[53] United States
1- to 20-year average range: $PM_{2.5}$ = 5–25 μg/m^3 PM_{10} = 10–40 μg/m^3 NO_2 = 5–40 ppb	2000–2008	$PM_{2.5}$, PM_{10}, NO_2∝↑ plasma Aβ1–40, Aβ1–42, Aβ 1–42/1–40 ratios	Ginkgo Evaluation of Memory Study Age ≥ 75yrs n=3,044	Hajat, *et al.*[54] United States
5-year mean: $PM_{2.5}$ = 25.9 μg/m^3 PM_{10} = 49.7 μg/m^3 NO_2 = 27.0 ppb	2014–2017	PM_{10}, NO_2∝↑ MRI AD-like cortical atrophy, $PM_{2.5}$∅ MRI AD-like cortical atrophy, $PM_{2.5}$, PM_{10}, NO_2∝↑MRI non-AD-like cortical atrophy, PM_{10}, NO_2∝↓ MoCA cognitive score	EPINEF Study (Environmental Pollution-Induced Neurological EFfects) Age ≥ 50yrs n=640	Cho, *et al.*[106] Korea

Air pollutant levels	Participant follow-up duration	Study results	Cohort type/size	Citation/location
Annual mean: $PM_{2.5}$ = 17.2 μg/m^3 PM_{10} = 37.7μg/m^3 NO_2 = 57.3 μg/m^3 NO_x = 99.1 μg/m^3	2013–2014	PM_{10}, NO_2 ∝↓ MRI cortical thickness, $PM_{2.5}$ ∅ MRI cortical thickness, $PM_{2.5}$, PM_{10}, NO_2 ∅ cognitive function	ALFA+ Study (Alzheimer and Families) Cognitively unimpaired adults Age 45–74yrs n=958 (cognition) n=228 (MRI)	Crous-Bou, *et al.*[105] Spain
Annual mean: $PM_{2.5}$ = 17.3 μg/m^3 PM_{10} = 37.9 μg/m^3 NO_2 = 57.6 μg/m^3	2013–2014	$PM_{2.5}$, NO_2 ∝↑ PET amyloid, $PM_{2.5}$, PM_{10} ∝↑ CSF NFL stronger in APOE-ε4 carriers	ALFA+ Study Cognitively unimpaired adults Age 57yrs n=156	Alemany, *et al.*[104] Spain

NOTE: AD, Alzheimer's Disease; ADRD, Alzheimer's disease-related dementias; VaD, vascular dementia; BC, black carbon; PM, particulate matter; NO_2, nitrogen dioxide; NO_X, nitrogen oxides; CSF, cerebrospinal fluid; NFL, neurofilament light; MoCA, Montreal Cognitive Assessment; PET, positron emission tomography; MRI, magnetic resonance imaging.

∝↑: positively correlated to, ∝↓: inversely correlated to, ∅: not correlated to.

Orange cells indicate studies that assessed ADRD risks as outcomes; green cells indicate studies that assessed AD-relevant biomarkers as outcomes.

Table 4:

Summaries of **in vivo** studies of the effects of air pollution on Alzheimer's disease neuropathology

Exposure system	Exposure paradigm	Animal model	Study results	Citation
System: Caldecott Tunnel Exposure Facility (CTFE) Source: TRAP drawn from tunnel bores in Oakland, CA, USA	Whole-body exposure for 2, 5, 9, and 14 months (7days/week, 24h/day) $PM_{2.5}$ = 15.6 ± 3.7 μg/m^3	Male & female TgF344-AD & WT rats (Fisher344) 1-month-old	↑ Refractive particle deposition in HIP after 5 months ↑ p-Tau in HIP after 14 months ↑ Aβ deposition in CO after 10 months ↑ Neuronal cell death in EC after 14 months ↑ Neuroinflammation in HIP, EC (microglia activation, IL-1 β, TNF-α,) ↓ Learning, memory after 14 months ∅ Serum cytokine	Patten, *et al.*[160,162]
System: Taipei Air Pollutant Exposure System (TAPES) Source: Outdoor ambient air drawn from Taipei, Taiwan	Whole-body exposure for 3 months (7days/week, 24h/day) $PM_{2.5}$ = 11.38 μg/m^3	Female 3xTg-AD mice 6-month-old	↑ p-Tau, oxidative stress (MDA) in HIP, OB ↑ Neuronal cell death in EC ∅ Aβ−42 deposition, learning	Lee, *et al.*[161]
System: Harvard ultrafine concentrated ambient particle system (HUCAPS) Source: TRAP UFPM drawn from Rochester, NY, USA	Whole-body exposure for 2 weeks (4days/week, 4h/day) UFPM = 57 μg/m^3 Mean UFPM size = 79 nm	Male 3xTgAD & WT mice 12.5-month-old	↓ Learning, memory ↓ olfactory discrimination	Jew, *et al.*[155]
System: Harvard ultrafine concentrated ambient particle system (HUCAPS) Source: Ambient UFPM drawn from street	Whole-body exposure for 2 weeks (4days/week, 4h/day) UFPM = 42 ± 15.7 μg/m^3	Male 3xTgAD & WT mice 12.5–14-month-old	↑ p-Tau (pT205) in HIP ∅ Aβ deposition in HIP ↓ Aβ deposition in subiculum ↑ Microglial ramification in HIP	Herr, *et al.*[156]
System: Versatile Aerosol Concentration and Enrichment System (VACES) Source: TRAP UFPM drawn from Orange County, CA, USA	Whole-body exposure for 12 weeks (4days/week, 5h/day) UFPM = 65.4 μg/m^3	Male and female $APP^{NL\text{-}G\text{-}f/+}$-KI & WT mice (C57/BL6) 3-, 9-month-old	↓ Learning, memory in both young and aged mice ↑ Aβ deposition in CO, HIP ↑ Neuroinflammation in CO only in old mice (microglia & astrocyte activation) ∅ Neuronal atrophy	Kilian, *et al.*[157]
System: Versatile Aerosol Concentration and Enrichment System (VACES) Source: $PM_{2.5}$ from Columbus, OH, USA	Whole-body exposure for 3 months (5days/week, 6h/day) $PM_{2.5}$ = 25.8 μg/m^3	Male APP/PS1 & WT mice (C57BU6;C3H) 12-month-old	↑ Neuroinflammation in HIP (microglia & astrocyte activation; TNF-α, IL-1β, IL-6, MIP-3α, IFN-γ) ↑ Aβ deposition, β-secretase, γ-secretase	Sahu, *et al.*[158]
System: Chambers housed outdoor Source: Ambient outdoor air in Santiago, Chile	Whole-body exposure for 7 months (7days/week, 24h/day) $PM_{2.5}$ > 55 μg/m^3	Female C57/BL6 mice 2-month-old	↑ DNA double-strand break marker (γ-H2AX) ↑ p-Tau in CO	Calderon-Garciduenas, *et al.*[109]

Exposure system	Exposure paradigm	Animal model	Study results	Citation
System/source: Soot UFPM generated by a Combustion Aerosol Standard burner	Whole-body exposure for 2 weeks (5days/week, 4h/day) UFPM = 7.0×10^5 particles/cm^3 Mean UFPM size = 39 nm	Female 5xFAD & WT mice (C57BL/6J) 6-month-old	↑ Inflammation (IFN-γ in plasma, OB, HIP) ↑ Oxidative stress in HIP (SOD2 protein) ∅ Aβ deposition or microglial and astrocytic activation in HIP and CO	Saveleva, *et al.*[149]
System/source: UFPM generated by a PM generator	Whole-body exposure for 3 weeks (5days/week, 8h/day) UFPM = 1000 μg/m^3 Mean UFPM size = 178 ± 65 nm	Male WT mice (C58BL6) 12-month-old	↑ Oxidative stress (4-HNE) in HIP ↑ Aβ deposition, neuroinflammation (TNF-a) in HIP ∅ Neuronal cell death in HIP	Park, *et al.*[152]
System/source: O_3 generated by an HFL-10 O_3 generator	Whole-body exposure for 13 weeks (3days/week, 4h/day) O_3 = 1.0 ppm	Male 5xFAD & WT mice (C57BL/6J) 10–11-week-old	↑ Aβ deposition in HIP and CO ↓ Plaque-associated microglia, ↓ TREM2 on plaque-associated microglia in CO ↑ Neuroinflammation in CO (NLRP3, IL-1 β) ↑ Neurite dystrophy (↑LAMP1, ↓VaChT, ChAT, AChE) in CO	Greve, *et al.*[150]
System/source: O_3 generated by an HFL-10 O_3 generator	Whole-body exposure for 13 weeks (3days/week, 4h/day) O_3 = 1.0 ppm	Male 5xFAD mice (C57BL/6J) 10–11-week-old	↑ Aβ deposition in CO ↑ Astrocyte, astrocyte-microglia interaction in peri-plaque regions ↑ Neuroinflammation in CO (DAM astrocytic profile)	Ahmed, *et al.*[151]
System/source: O_3 generated by a flux ozone generator	Whole-body exposure for 7, 15, 30, 60, and 90 days (7days/week, 4h/day) O_3 = 0.25ppm	Male WT rats (Wistar) 250–300g	↑ Aβ structural destabilization overtime (↓a-helix, ↑β-sheet) ↑ Intracellular Aβ 1–42 after 60–90 days ↑ Lipid peroxidation, microglial and astrocytic activation in HIP after 15–90 days ↑ Neuronal cell death in HIP after 90 days	Rivas-Arancibia, *et al.*[153,154]

NOTE: HIP, hippocampus; CO, cortex; EC, entorhinal cortex; p-Tau, phosphorylated tau; WT, wildtype.

↑: increase in measurement; ↓: decrease in measurement; ∅: no change in measurement.

Blue cells indicate studies that used air pollutants collected from real-world sources; yellow cells indicate studies that used air pollutants generated in the laboratory.