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] and 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.

*pjlein@ucdavis.edu

OPEN ACCESS

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]. 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 *x* environmental (G *x* 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 *x* 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.

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				
APP[300]	APOE4[302,303]	ABCA7[135,307,311-314]	TMEM106B[311,313,314]	PRKD3[313,314]	NTN5[311]
PSEN1[300,301]	TREM2[304,305]	BIN1[135,307,311-314]	TNIP1[311,313,314]	RASGEF1C[313,314]	NYAP1[307]
PSEN2[300,301]	SORL1[302]	CASS4[135,307,311-314]	ABCA1[313,314]	RBCK1[313,314]	LINC02705[307]
	PRNP[301]	CD2AP[135,307,311-314]	ADAM17[313,314]	RHOH[313,314]	LINC02695[307]
	MAPT[306]	CR1[135,307,311-314]	ADAMTS1[313,314]	SCIMP[135,314]	RNU6-560P[307]
	GRN[307]	SORL1[135,307,311-314]	ANK3[313,314]	SCIMP/RABEP[311,313]	USP6NL-AS1[307]
	C9orf72[308]	TREM2[135,307,311-314]	ANKH[313,314]	SEC61G[313,314]	ADAMTS4[135]
	NOTCH3[309]	CLU[307,311-314]	BLNK[313,314]	SIGLEC11[313,314]	HESX1[135]
	PARK2[306]	EPHA1[135,307,312-314]	COX7C[313,314]	SLC2A4RG[313,314]	HS3ST1[135]
	PLCG2[300]	FERMT2[307,311-314]	CTSB[313,314]	SNX1[313,314]	CNTNAP2[135]
	ABI3[300]	ABI3[135,311,313,314]	CTSH[313,314]	SORT1[313,314]	CLU/PTK2B[135]
	APP[300]	ADAM10[311-313]	DOC2A[313,314]	SPI1[307,314]	BZRAP1-AS1[135]
	PSEN1[300,301]	APH1B[135,311,313,314]	FOXF1[313,314]	SPPL2A[313,314]	SUZ12P1[135]
	PSEN2[300,301]	INPP5D[307,312-314]	HS3ST5[313,314]	TPCN1[313,314]	ALPK2[135]
	SORL1[300,302]	PICALM[135,311-313]	ICA1[313,314]	TSPAN14[313,314]	AC074212.3[135]
	ABCA7[300]	PTK2B[307,312-314]	IDUA[313,314]	TSPOAP1[313,314]	CLNK/HS3ST1[313]
	TREM2[300]	ACE[311,313,314]	IL34[313,314]	UMAD1[313,314]	HLA[313]
	BIN1[300]	APOE[135,307,311]	INPPD5[311]	WDR12[313,314]	CELF1/SPI1[313]
	UNC5C[300]	APP[311,313,314]	JAZF1[313,314]	WDR81[313,314]	HLA-DQA1[314]
	AKAP9[300]	CD33[135,311,312]	KAT8[313]	ZCWPW1[135,312]	UNC5CL[314]
	NOTCH3[300]	CLNK[135,311,314]	KLF16[313,314]	ZCWPW1/NYAP1[311,313]	TREML2[314]
	12s rRNA[300]	ECHDC3[135,313]	MAF[313,314]	AGRN[311]	EPDR1[314]
	CLU[300]	GRN[311,313,314]	MME[313,314]	HAVCR2[311]	SPDYE3[314]
	PLCG2[300]	HLA-DRB1[135,311]	MS4A4A[313,314]	EPHA1-AS[311]	USP6NL[314]
	ABI3[300]	LILRB2[311,313,314]	MYO15A[313,314]	USP6NL/ECHDC3[311]	EED[314]
	APOE[300]	MS4A6A[135,312]	NME8[313,314]	CCDC6[311]	MINDY2[314]
	TET1[310]	NCK2[311,313,314]	PLCG[313,314]	MADD/SPI1[311]	BCKDK[314]
	TET2[276]	SHARPIN[311,313,314]	PLEKHA1[313,314]	RIN3[311]	WNT3[314]
		SLC24A4[135,311,314]	PRDM7[313,314]	TSPOAP1-AS1[311]	AKAP9[312]
					UNC5C[312]

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).
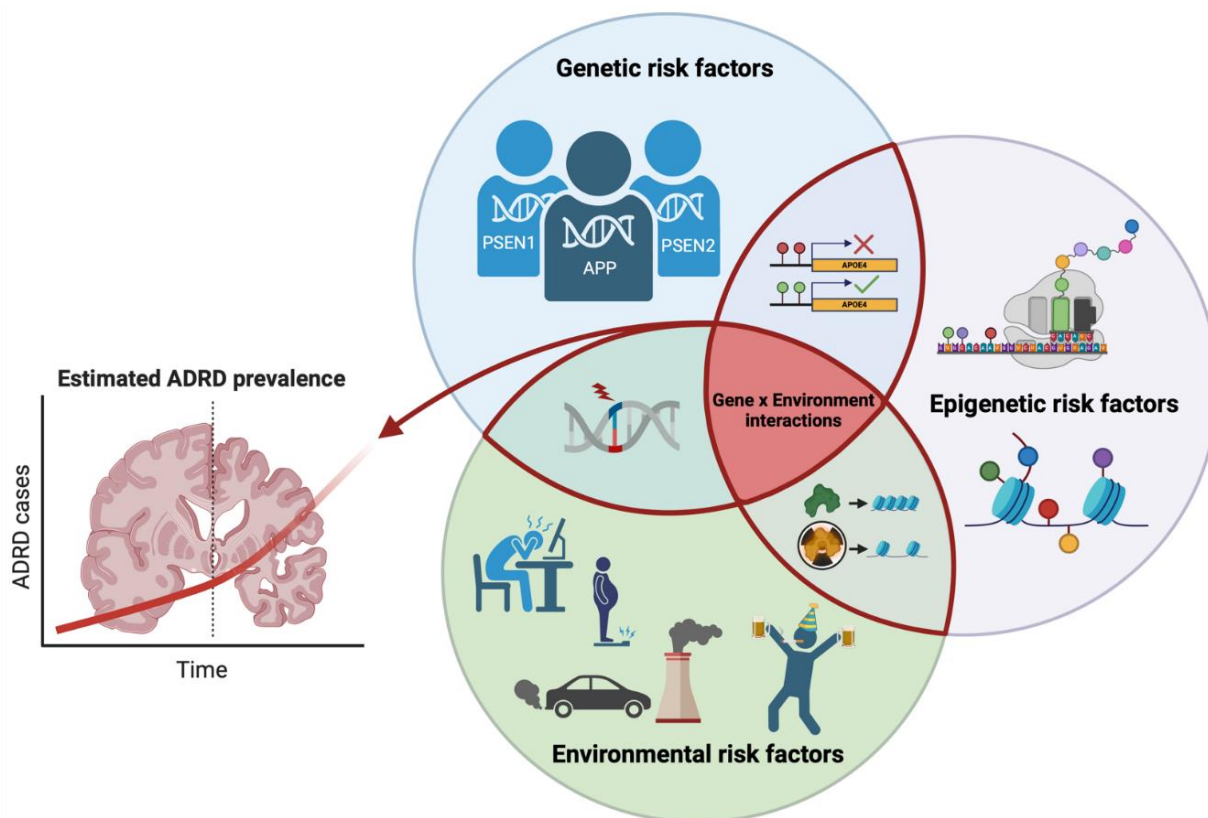

Figure 1. Gene by environment interactions. Genetic, epigenetic, and environmental risk factors interact to promote ADRD etiology and disease progression. *NOTE:* ADRD, Alzheimer's disease-related dementias. *Created with BioRender.com.*

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.

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}, $PM_{2.5}$); (2) nitrogen dioxide (NO_2); (3) ground-level ozone (O_3): (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].
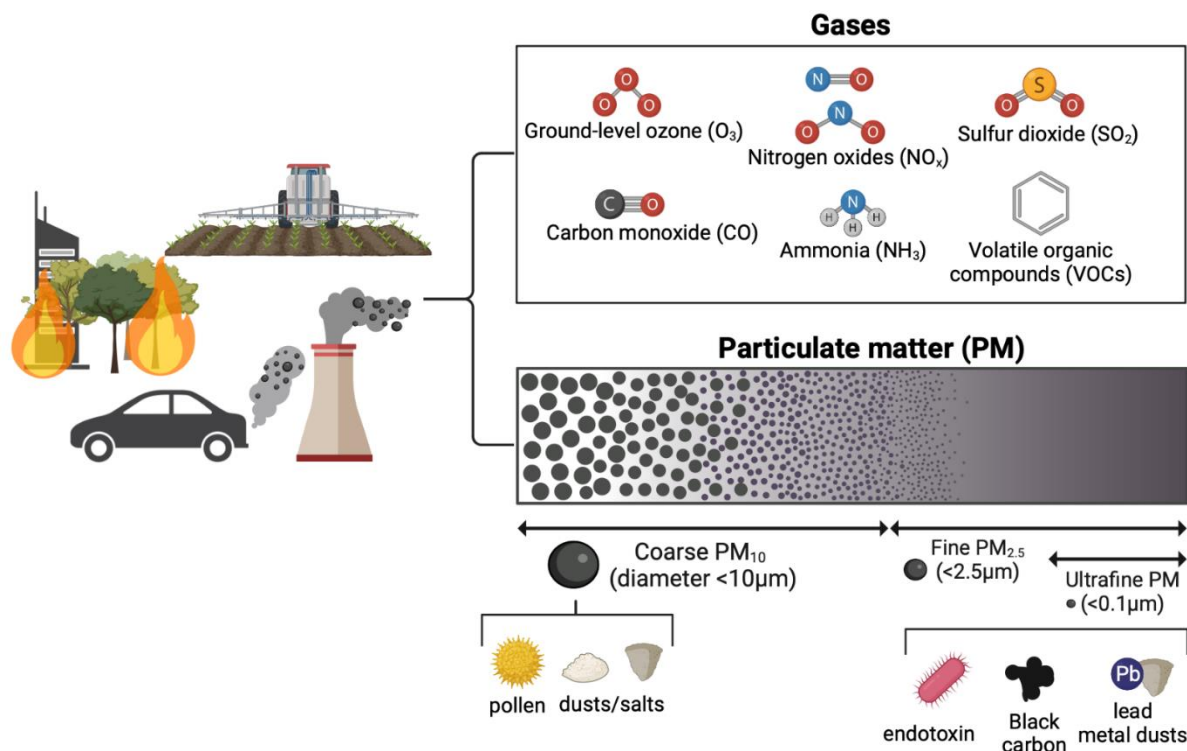
Figure 2. Composition of air pollutants. Air pollutants consist of gaseous and particulate matter (PM) fractions with heterogenous sources, compositions, and sizes, all of which influence toxicity to the respiratory system and the brain. *Created with BioRender.com.*

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.

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[66,70-72,80,82,85,87,100] ∅ 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.

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].

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/m³ NO_2 = 17.1 ppb O_3 = 42.6 ppb	2000-2018	$PM_{2.5}$, NO_2 ∝↑ incident AD/ADRD O_3 ∅ 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/m³ 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/m³ PM_{10} = 16.1 µg/m³ NO_x = 43.4 µg/m³	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

Air pollutant levels	Participant follow-up duration	Study results	Cohort type/size	Citation/location
10-year median: $PM_{2.5}$= 11.2 µg/m³	1998-2016	$PM_{2.5}$ ∝↑ incident dementia	Health and Retirement Study Age > 50yrs n=27,857	Zhang, *et al.*[51] United States
10-year median: $PM_{2.5}$ = 21.3 µg/m³ NO_2 = 32.8 µg/m³ 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/m³ Wood-burning $PM_{2.5}$ = 0.77 µg/m³	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/m³ 2015-2016: 7.4-8.34 µg/m³	2016-2018	$PM_{2.5}$ ∝↑ amyloid PET scan positivity O_3 ∅ amyloid PET scan positivity	IDEAS Study (Imaging Dementia-Evidence For Amyloid Scanning) Age ≥ 65yrs n=18,178	Iaccarino, *et al.*[53] United States
1- to 20-year average range: $PM_{2.5}$ = 5-25 µg/m³ PM_{10} = 10-40 µg/m³ 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/m³ PM_{10} = 49.7 µg/m³ 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
Annual mean: $PM_{2.5}$ = 17.2 µg/m³ PM_{10} = 37.7µg/m³ NO_2 = 57.3 µg/m³ NO_x = 99.1 µg/m³	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/m³ PM_{10} = 37.9 µg/m³ NO_2 = 57.6 µg/m³	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.

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 x 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.

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 (CTEF) 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-1β, TNF-α,) ↓ Learning, memory after 14 months ∅ Serum cytokine	Patten, *et al.*[160,162]
System: Taipei Air Pollutant Exposure System (TAPES)	Whole-body exposure for 3 months (7days/week, 24h/day)	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]

Exposure system	Exposure paradigm	Animal model	Study results	Citation
Source: Outdoor ambient air drawn from Taipei, Taiwan	$PM_{2.5}$ = 11.38 µg/m³			
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/m³ 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/m³	Male 3xTgAD & WT mice 12.5-14-month-old	↑ p-Tau (pT205) in HIP Ø 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/m³	Male and female APP$^{NL-G-f/+}$-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) Ø 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/m³	Male APP/PS1 & WT mice (C57BL/6;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/m³	Female C57/BL6 mice 2-month-old	↑ DNA double-strand break marker (γ-H2AX) ↑ p-Tau in CO	Calderon-Garciduenas, et al.[109]
System/source: Soot UFPM generated by a Combustion Aerosol Standard burner	Whole-body exposure for 2 weeks (5days/week, 4h/day) UFPM = 7.0×10⁵ particles/cm³ 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) Ø 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/m³ 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 Ø Neuronal cell death in HIP	Park, et al.[152]

Exposure system	Exposure paradigm	Animal model	Study results	Citation
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; Ø: 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.

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$^{NL-G-F/+}$-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$_2$O$_2$, 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 vivo, 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 astrocyte-neuron 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).
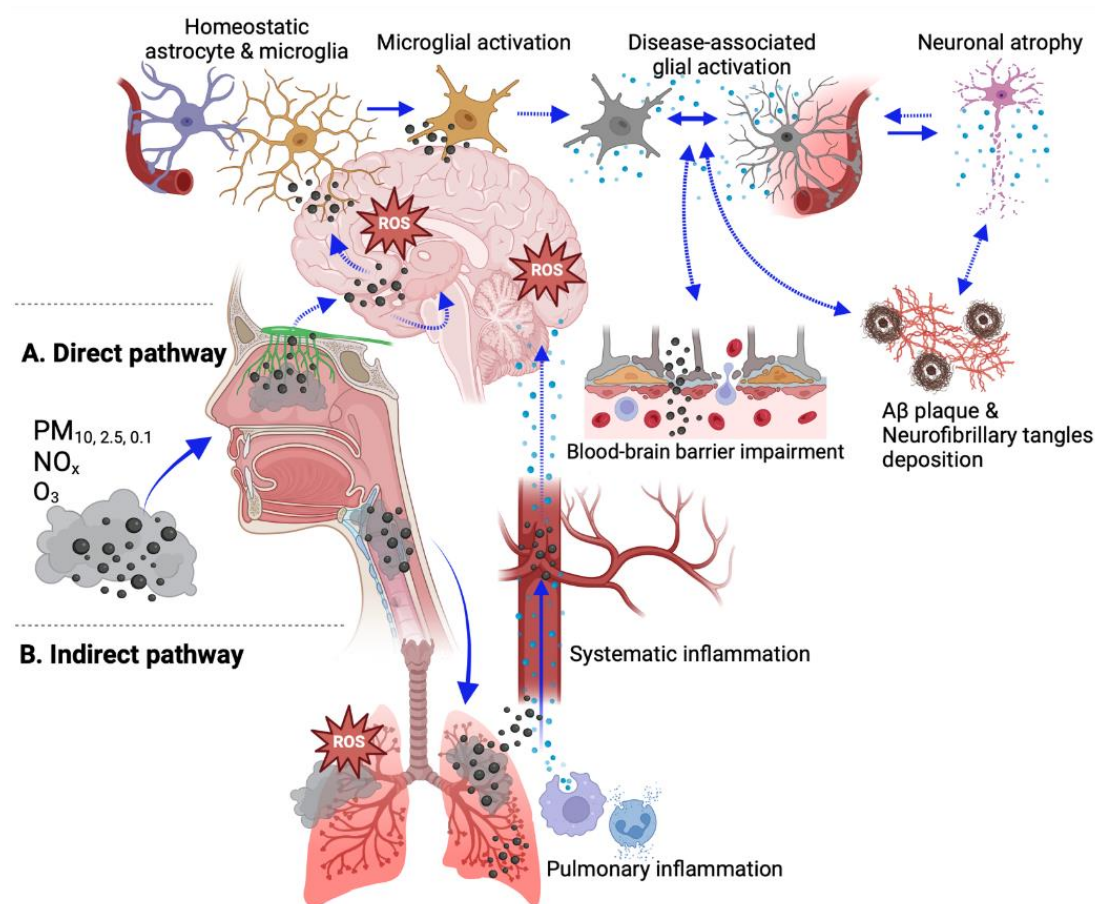

Figure 3. Potential mechanisms by which air pollutants promote neuroinflammation. Schematic summary of potential pathways by which air pollutants mediate neuroinflammation. A. Direct pathway: Inhaled air pollutants infiltrate the brain parenchyma via retrograde transportation from olfactory nerve terminals 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.

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 x 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 x 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 x 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 ε4*$^{+/+}$ over *ApoE ε3*$^{+/+}$ alleles significantly increased amyloid plaque pathology, reduced hippocampal CA1 neurites, and decreased the glutamate GluR1 subunit. In a similar study investigating the G x 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 x 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 ($P < 5 \times 10^{-8}$), 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 e4* carriers relative to control (p = 7.6x10^{-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 (m⁶A) 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. m⁶A 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 m⁶A 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 m⁶A RNA methylation coincident with increased expression of *TGF-β*, *SMAD3*, and the methyltransferases *METTL3* and *METTL14* (m⁶A 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 m⁶A 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 m⁶A 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 m⁶A 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 m⁶A 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 m⁶A or the ability to read m⁶A 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 x 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 let7 axis in the inflammatory response to DEP exposure in mice[295]. Let7-d and let7-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 let7, 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 *TGFβ1*, *TGFβ2*, *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 *TGFβ1*, *CCL2* and *CCL5* expression; and let-7g with *TGFβ1*, *ITGAX*, and *NFKβ1* 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 *x* 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 *x* 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.

List of abbreviations

Abbreviation	Definition
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 x E	Gene by environment interaction
HMGB1	High mobility group box 1
LOAD	Late-onset Alzheimer's disease
LPS	Lipopolysaccharide
m^{6}A	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

References:

1. Collaborators GBDDF. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. Feb 2022;7(2):e105-e125. doi:10.1016/S2468-2667(21)00249-8

2. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med*. Jun 2016;8(6):595-608. doi:10.15252/emmm.201606210

3. Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. Apr 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018

4. Khan SS, Bloom GS. Tau: The Center of a Signaling Nexus in Alzheimer's Disease. *Front Neurosci*. 2016;10:31. doi:10.3389/fnins.2016.00031

5. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. May 2024;20(5):3708-3821. doi:10.1002/alz.13809

6. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers Dement*. Mar 2016;12(3):292-323. doi:10.1016/j.jalz.2016.02.002

7. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. May 2011;7(3):280-92. doi:10.1016/j.jalz.2011.03.003

8. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med*. Mar 2014;275(3):214-28. doi:10.1111/joim.12190

9. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. Jan 16 2018;90(3):126-135. doi:10.1212/WNL.0000000000004826

10. Dunn AR, O'Connell KMS, Kaczorowski CC. Gene-by-environment interactions in Alzheimer's disease and Parkinson's disease. *Neurosci Biobehav Rev*. Aug 2019;103:73-80. doi:10.1016/j.neubiorev.2019.06.018

11. Eid A, Mhatre I, Richardson JR. Gene-environment interactions in Alzheimer's disease: A potential path to precision medicine. *Pharmacol Ther*. Jul 2019;199:173-187. doi:10.1016/j.pharmthera.2019.03.005

12. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. Aug 8 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6

13. Schindler SE, Galasko D, Pereira AC, et al. Acceptable performance of blood biomarker tests of amyloid pathology - recommendations from the Global CEO Initiative on Alzheimer's Disease. *Nat Rev Neurol*. Jul 2024;20(7):426-439. doi:10.1038/s41582-024-00977-5

14. Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev*. Mar 22 2017;3(3):CD010803. doi:10.1002/14651858.CD010803.pub2

15. National Plan to Address Alzheimer's Disease: 2023 Update. Updated 2024, April 22. https://aspe.hhs.gov/reports/national-plan-2023-update

16. Schneider JA. Neuropathology of Dementia Disorders. *Continuum (Minneap Minn)*. Jun 1 2022;28(3):834-851.doi:10.1212/CON.0000000000001137

17. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. *JAMA*. Oct 22 2019;322(16):1589-1599. doi:10.1001/jama.2019.4782

18. Caldwell AB, Anantharaman BG, Ramachandran S, et al. Transcriptomic profiling of sporadic

Alzheimer's disease patients. *Mol Brain.* Oct 12 2022;15(1):83. doi:10.1186/s13041-022-00963-2

19. Reitz C, Rogaeva E, Beecham GW. Late-onset vs nonmendelian early-onset Alzheimer disease: A distinction without a difference? *Neurol Genet.* Oct 2020;6(5):e512.doi:10.1212/NXG.0000000000000512

20. Dao L, Choi S, Freeby M. Type 2 diabetes mellitus and cognitive function: understanding the connections. *Curr Opin Endocrinol Diabetes Obes.* Feb 1 2023;30(1):7-13. doi:10.1097/MED.0000000000000783

21. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *Lancet Neurol.* Oct 2020;19(10):860-871. doi:10.1016/S1474-4422(20)30277-5

22. McInnes K, Friesen CL, MacKenzie DE, Westwood DA, Boe SG. Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. *PLoS One.* 2017;12(4):e0174847. doi:10.1371/journal.pone.0174847

23. Robinson JL, Richardson H, Xie SX, et al. The development and convergence of co-pathologies in Alzheimer's disease. *Brain.* Apr 12 2021;144(3): 953-962. doi:10.1093/brain/awaa438

24. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. *Nat Rev Neurol.* Jan 2020;16(1):30-42. doi:10.1038/s41582-019-0281-2

25. Grasso D, Castorani G, Borreggine C, Simeone A, De Blasi R. Cerebral amyloid angiopathy related inflammation: A little known but not to be underestimated disease. *Radiol Case Rep.* Sep 2021;16(9):2514-2521. doi:10.1016/j.radcr.2021.05.080

26. Hereditary cerebral amyloid angiopathy (2022).

27. Coomans EM, Tomassen J, Ossenkoppele R, et al. Genetically identical twins show comparable tau PET load and spatial distribution. *Brain.* Oct 21 2022;145(10):3571-3581. doi:10.1093/brain/awac004

28. Puckett OK, Fennema-Notestine C, Hagler DJ, Jr., et al. The Association between Exposure to Fine Particulate Matter and MRI-Assessed Locus Coeruleus Integrity in the Vietnam Era Twin Study of Aging (VETSA). *Environ Health Perspect.* Jul 2024;132(7):77006. doi:10.1289/EHP14344

29. Karlsson IK, Escott-Price V, Gatz M, et al. Measuring heritable contributions to Alzheimer's disease: polygenic risk score analysis with twins. *Brain Commun.* 2022;4(1):fcab308. doi:10.1093/braincomms/fcab308

30. Varjonen A, Schwarz C, Vuoksimaa E. Co-twin design in brain imaging-review on biomarkers of Alzheimer's disease. *Cereb Cortex.* Jul 5 2023;33(14):9054-9066. doi:10.1093/cercor/bhad181

31. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet.* Dec 16 2017;390(10113):2673-2734. doi:10.1016/S0140-6736(17)31363-6

32. Gunnarsson LG, Bodin L. Occupational Exposures and Neurodegenerative Diseases-A Systematic Literature Review and Meta-Analyses. *Int J Environ Res Public Health.* Jan 26 2019;16(3)doi:10.3390/ijerph16030337

33. Sarailoo M, Afshari S, Asghariazar V, Safarzadeh E, Dadkhah M. Cognitive Impairment and Neurodegenerative Diseases Development Associated with Organophosphate Pesticides Exposure: a Review Study. *Neurotox Res.* Oct 2022;40(5):1624-1643. doi:10.1007/s12640-022-00552-0

34. Kim JY, Park SJ, Kim SK, et al. Pesticide exposure and cognitive decline in a rural South Korean population. *PLoS One.* 2019;14(3):e0213738. doi:10.1371/journal.pone.0213738

35. Hayden KM, Norton MC, Darcey D, et al. Occupational exposure to pesticides increases the risk of incident AD: the Cache County study. *Neurology.* May 11 2010;74(19):1524-30. doi:10.1212/WNL.0b013e3181dd4423

36. Sturm ET, Castro C, Mendez-Colmenares A, et al. Risk Factors for Brain Health in Agricultural Work: A Systematic Review. *Int J Environ Res Public Health.* Mar 13 2022;19(6)doi:10.3390/ijerph19063373

37. Palzes VA, Sagiv SK, Baker JM, et al. Manganese exposure and working memory-

related brain activity in smallholder farmworkers in Costa Rica: Results from a pilot study. *Environ Res.* Jun 2019;173:539-548. doi:10.1016/j.envres.2019.04.006

38. Liu CH, Huang CY, Huang CC. Occupational neurotoxic diseases in taiwan. *Saf Health Work.* Dec 2012;3(4):257-67. doi:10.5491/SHAW.2012.3.4.257

39. Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues JF, Brochard P. Neurodegenerative diseases and exposure to pesticides in the elderly. *Am J Epidemiol.* Mar 1 2003;157(5):409-14. doi:10.1093/aje/kwf216

40. Delcourt N, Pouget AM, Grivaud A, et al. First Observations of a Potential Association Between Accumulation of Per- and Polyfluoroalkyl Substances in the Central Nervous System and Markers of Alzheimer's Disease. *J Gerontol A Biol Sci Med Sci.* Mar 1 2024;79(3)doi:10.1093/gerona/glad208

41. Lederer AM, Fredriksen PM, Nkeh-Chungag BN, et al. Cardiovascular effects of air pollution: current evidence from animal and human studies. *Am J Physiol Heart Circ Physiol.* Apr 1 2021;320(4):H1417-H1439. doi:10.1152/ajpheart.00706.2020

42. Anderson JO, Thundiyil JG, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. *J Med Toxicol.* Jun 2012;8(2):166-75. doi:10.1007/s13181-011-0203-1

43. Bennett M, Nault I, Koehle M, Wilton S. Air Pollution and Arrhythmias. *Can J Cardiol.* Sep 2023;39(9):1253-1262. doi:10.1016/j.cjca.2023.03.023

44. Brook RD, Rajagopalan S, Pope CA, 3rd, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation.* Jun 1 2010;121(21):2331-78. doi:10.1161/CIR.0b013e3181dbece1

45. Fiordelisi A, Piscitelli P, Trimarco B, Coscioni E, Iaccarino G, Sorriento D. The mechanisms of air pollution and particulate matter in cardiovascular diseases. *Heart Fail Rev.* May 2017;22(3):337-347. doi:10.1007/s10741-017-9606-7

46. Miller MR, Newby DE. Air pollution and cardiovascular disease: car sick. *Cardiovasc Res.* Feb 1 2020;116(2):279-294. doi:10.1093/cvr/cvz228

47. Rajagopalan S, Brook RD, Salerno P, et al. Air pollution exposure and cardiometabolic risk. *Lancet Diabetes Endocrinol.* Mar 2024;12(3):196-208. doi:10.1016/S2213-8587(23)00361-3

48. Tainio M, Jovanovic Andersen Z, Nieuwenhuijsen MJ, et al. Air pollution, physical activity and health: A mapping review of the evidence. *Environ Int.* Feb 2021;147:105954. doi:10.1016/j.envint.2020.105954

49. Paul KC, Haan M, Mayeda ER, Ritz BR. Ambient Air Pollution, Noise, and Late-Life Cognitive Decline and Dementia Risk. *Annu Rev Public Health.* Apr 1 2019;40:203-220. doi:10.1146/annurev-publhealth-040218-044058

50. Mork D, Braun D, Zanobetti A. Time-lagged relationships between a decade of air pollution exposure and first hospitalization with Alzheimer's disease and related dementias. *Environ Int.* Jan 2023;171:107694. doi:10.1016/j.envint.2022.107694

51. Zhang B, Weuve J, Langa KM, et al. Comparison of Particulate Air Pollution From Different Emission Sources and Incident Dementia in the US. *JAMA Intern Med.* Aug 14 2023;doi:10.1001/jamainternmed.2023.3300

52. Mortamais M, Gutierrez LA, de Hoogh K, et al. Long-term exposure to ambient air pollution and risk of dementia: Results of the prospective Three-City Study. *Environ Int.* Mar 2021;148:106376. doi:10.1016/j.envint.2020.106376

53. Iaccarino L, La Joie R, Lesman-Segev OH, et al. Association Between Ambient Air Pollution and Amyloid Positron Emission Tomography Positivity in Older Adults With Cognitive Impairment. *JAMA Neurol.* Feb 1 2021;78(2):197-207. doi:10.1001/jamaneurol.2020.3962

54. Hajat A, Park C, Adam C, et al. Air pollution and plasma amyloid beta in a cohort of older adults: Evidence from the Ginkgo Evaluation of Memory study. *Environ Int.* Feb 2023;172:107800. doi:10.1016/j.envint.2023.107800

55. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med.* Feb 13 2012;172(3):219-27. doi:10.1001/archinternmed.2011.683

56. Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. *Environ Res.* Nov 2009;109(8):1004-11. doi:10.1016/j.envres.2009.08.003

57. Jung CR, Lin YT, Hwang BF. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. *J Alzheimers Dis.* 2015;44(2):573-84. doi:10.3233/JAD-140855

58. Shi L, Steenland K, Li H, et al. A national cohort study (2000-2018) of long-term air pollution exposure and incident dementia in older adults in the United States. *Nat Commun.* Nov 19 2021;12(1):6754. doi:10.1038/s41467-021-27049-2

59. Yuan S, Huang X, Zhang L, et al. Associations of air pollution with all-cause dementia, Alzheimer's disease, and vascular dementia: a prospective cohort study based on 437,932 participants from the UK biobank. *Front Neurosci.* 2023;17:1216686. doi:10.3389/fnins.2023.1216686

60. Oudin A, Segersson D, Adolfsson R, Forsberg B. Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. *PLoS One.* 2018;13(6):e0198283. doi:10.1371/journal.pone.0198283

61. Carey IM, Anderson HR, Atkinson RW, et al. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. *BMJ Open.* Sep 11 2018;8(9):e022404. doi:10.1136/bmjopen-2018-022404

62. Parra KL, Alexander GE, Raichlen DA, Klimentidis YC, Furlong MA. Exposure to air pollution and risk of incident dementia in the UK Biobank. *Environ Res.* Jun 2022;209:112895. doi:10.1016/j.envres.2022.112895

63. Zhang H, Shi L, Ebelt ST, et al. Short-term associations between ambient air pollution and emergency department visits for Alzheimer's disease and related dementias. *Environ Epidemiol.* Feb 2023;7(1):e237. doi:10.1097/EE9.0000000000000237

64. Rhew SH, Kravchenko J, Lyerly HK. Exposure to low-dose ambient fine particulate matter PM2.5 and Alzheimer's disease, non-Alzheimer's dementia, and Parkinson's disease in North Carolina. *PLoS One.* 2021;16(7):e0253253. doi:10.1371/journal.pone.0253253

65. Wu J, Jackson L. Greenspace Inversely Associated with the Risk of Alzheimer's Disease in the Mid-Atlantic United States. *Earth (Basel).* Feb 28 2021;2(1):140-150. doi:10.3390/earth2010009

66. Zhang Z, Chen L, Wang X, et al. Associations of Air Pollution and Genetic Risk With Incident Dementia: A Prospective Cohort Study. *Am J Epidemiol.* Feb 1 2023;192(2):182-194. doi:10.1093/aje/kwac188

67. Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. Association Between Cardiovascular Disease and Long-term Exposure to Air Pollution With the Risk of Dementia. *JAMA Neurol.* Jul 1 2020;77(7):801-809. doi:10.1001/jamaneurol.2019.4914

68. Grande G, Hooshmand B, Vetrano DL, et al. Association of Long-term Exposure to Air Pollution and Dementia Risk: The Role of Homocysteine, Methionine, and Cardiovascular Burden. *Neurology.* Jul 13 2023;doi:10.1212/WNL.0000000000207656

69. Ilango SD, Chen H, Hystad P, et al. The role of cardiovascular disease in the relationship between air pollution and incident dementia: a population-based cohort study. *Int J Epidemiol.* Feb 1 2020;49(1):36-44. doi:10.1093/ije/dyz154

70. Ilango SD, Leary CS, Ritchie E, et al. An Examination of the Joint Effect of the Social Environment and Air Pollution on Dementia Among US Older Adults. *Environ Epidemiol.* Jun 2023;7(3):e250. doi:10.1097/EE9.0000000000000250

71. Liu T, Zhou Y, Wei J, et al. Association between short-term exposure to ambient air

pollution and dementia mortality in Chinese adults. *Sci Total Environ*. Nov 25 2022;849:157860. doi:10.1016/j.scitotenv.2022.157860

72. Ma H, Li X, Zhou T, Wang M, Heianza Y, Qi L. Long-term exposure to low-level air pollution, genetic susceptibility and risk of dementia. *Int J Epidemiol*. Jun 6 2023;52(3):738-748. doi:10.1093/ije/dyac146

73. Oudin A, Andersson J, Sundstrom A, et al. Traffic-Related Air Pollution as a Risk Factor for Dementia: No Clear Modifying Effects of APOEvarepsilon4 in the Betula Cohort. *J Alzheimers Dis*. 2019;71(3):733-740. doi:10.3233/JAD-181037

74. Shi L, Zhu Q, Wang Y, et al. Incident dementia and long-term exposure to constituents of fine particle air pollution: A national cohort study in the United States. *Proc Natl Acad Sci U S A*. Jan 3 2023;120(1):e2211282119. doi:10.1073/pnas.2211282119

75. Smargiassi A, Sidi EAL, Robert LE, et al. Exposure to ambient air pollutants and the onset of dementia in Quebec, Canada. *Environ Res*. Nov 2020;190:109870. doi:10.1016/j.envres.2020.109870

76. So R, Andersen ZJ, Chen J, et al. Long-term exposure to air pollution and mortality in a Danish nationwide administrative cohort study: Beyond mortality from cardiopulmonary disease and lung cancer. *Environ Int*. Jun 2022;164:107241. doi:10.1016/j.envint.2022.107241

77. Wang X, Younan D, Millstein J, et al. Association of improved air quality with lower dementia risk in older women. *Proc Natl Acad Sci USA*. Jan 11 2022;119(2)doi:10.1073/pnas.2107833119

78. Yu Y, Su J, Jerrett M, et al. Air pollution and traffic noise interact to affect cognitive health in older Mexican Americans. *Environ Int*. Mar 2023;173:107810. doi:10.1016/j.envint.2023.107810

79. Yuchi W, Sbihi H, Davies H, Tamburic L, Brauer M. Road proximity, air pollution, noise, green space and neurologic disease incidence: a population-based cohort study. *Environ Health*. Jan 21 2020;19(1):8. doi:10.1186/s12940-020-0565-4

80. Zhu Z, Yang Z, Yu L, et al. Residential greenness, air pollution and incident neurodegenerative disease: A cohort study in China. *Sci Total Environ*. Jun 20 2023;878:163173. doi:10.1016/j.scitotenv.2023.163173

81. Tzivian L, Dlugaj M, Winkler A, et al. Long-Term Air Pollution and Traffic Noise Exposures and Mild Cognitive Impairment in Older Adults: A Cross-Sectional Analysis of the Heinz Nixdorf Recall Study. *Environ Health Perspect*. Sep 2016;124(9):1361-8. doi:10.1289/ehp.1509824

82. Cerza F, Renzi M, Gariazzo C, et al. Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study. *Environ Health*. Aug 9 2019;18(1):72. doi:10.1186/s12940-019-0511-5

83. Ge R, Wang Y, Zhang Z, Sun H, Chang J. Association of long-term exposure to various ambient air pollutants, lifestyle, and genetic predisposition with incident cognitive impairment and dementia. *BMC Public Health*. Jan 15 2024;24(1):179. doi:10.1186/s12889-024-17702-y

84. Peters S, Bouma F, Hoek G, Janssen N, Vermeulen R. Air pollution exposure and mortality from neurodegenerative diseases in the Netherlands: A population-based cohort study. *Environ Res*. Jul 2 2024;259:119552. doi:10.1016/j.envres.2024.119552

85. Tian F, Qian Z, Zhang Z, et al. Air pollution, APOE genotype and risk of dementia among individuals with cardiovascular diseases: A population-based longitudinal study. *Environ Pollut*. Apr 15 2024;347:123758. doi:10.1016/j.envpol.2024.123758

86. Wang J, Hu X, Yang T, et al. Ambient air pollution and the dynamic transitions of stroke and dementia: a population-based cohort study. *EClinicalMedicine*. Jan 2024;67:102368. doi:10.1016/j.eclinm.2023.102368

87. Tuffier S, Zhang J, Bergmann M, et al. Long-term exposure to air pollution and road traffic noise and incidence of dementia in the Danish Nurse Cohort. *Alzheimers Dement*. Jun 2024;20(6):4080-4091. doi:10.1002/alz.13814

88. Zhang B, Langa KM, Weuve J, et al. Hypertension and Stroke as Mediators of Air Pollution Exposure and Incident Dementia. *JAMA Netw Open*. Sep 5 2023;6(9):e2333470. doi:10.1001/jamanetworkopen.2023.33470

89. Shaffer RM, Blanco MN, Li G, et al. Fine Particulate Matter and Dementia Incidence in the Adult Changes in Thought Study. *Environ Health Perspect*. Aug 2021;129(8):87001. doi:10.1289/EHP9018

90. Wu QZ, Zeng HX, Andersson J, et al. Long-term exposure to major constituents of fine particulate matter and neurodegenerative diseases: A population-based survey in the Pearl River Delta Region, China. *J Hazard Mater*. May 15 2024;470:134161. doi:10.1016/j.jhazmat.2024.134161

91. Paul KC, Haan M, Yu Y, et al. Traffic-Related Air Pollution and Incident Dementia: Direct and Indirect Pathways Through Metabolic Dysfunction. *J Alzheimers Dis*. 2020;76(4):1477-1491. doi:10.3233/JAD-200320

92. Andersson J, Oudin A, Sundstrom A, Forsberg B, Adolfsson R, Nordin M. Road traffic noise, air pollution, and risk of dementia - results from the Betula project. *Environ Res*. Oct 2018;166:334-339. doi:10.1016/j.envres.2018.06.008

93. Fania A, Monaco A, Amoroso N, et al. Machine learning and XAI approaches highlight the strong connection between O3 and NO2 pollutants and Alzheimer's disease. *Sci Rep*. Mar 5 2024;14(1):5385. doi:10.1038/s41598-024-55439-1

94. He F, Tang J, Zhang T, et al. Impact of air pollution exposure on the risk of Alzheimer's disease in China: A community-based cohort study. *Environ Res*. Apr 1 2022;205:112318. doi:10.1016/j.envres.2021.112318

95. Wood D, Evangelopoulos D, Beevers S, Kitwiroon N, Katsouyanni K. Exposure to Ambient Air Pollution and the Incidence of Dementia in the Elderly of England: The ELSA Cohort. *Int J Environ Res Public Health*. Nov 29 2022;19(23)doi:10.3390/ijerph192315889

96. Trevenen ML, Heyworth J, Almeida OP, et al. Ambient air pollution and risk of incident dementia in older men living in a region with relatively low concentrations of pollutants: The Health in Men Study. *Environ Res*. Dec 2022;215(Pt 2):114349. doi:10.1016/j.envres.2022.114349

97. Andersen ZJ, Zhang J, Jorgensen JT, et al. Long-term exposure to air pollution and mortality from dementia, psychiatric disorders, and suicide in a large pooled European cohort: ELAPSE study. *Environ Int*. Dec 2022;170:107581. doi:10.1016/j.envint.2022.107581

98. de Crom TOE, Ginos BNR, Oudin A, Ikram MK, Voortman T, Ikram MA. Air Pollution and the Risk of Dementia: The Rotterdam Study. *J Alzheimers Dis*. 2023;91(2):603-613. doi:10.3233/JAD-220804

99. Blanco MN, Shaffer RM, Li G, et al. Traffic-related air pollution and dementia incidence in the Adult Changes in Thought Study. *Environ Int*. Jan 2024;183:108418. doi:10.1016/j.envint.2024.108418

100. Shim JI, Byun G, Lee JT. Long-term exposure to particulate matter and risk of Alzheimer's disease and vascular dementia in Korea: a national population-based Cohort Study. *Environ Health*. Apr 14 2023;22(1):35. doi:10.1186/s12940-023-00986-9

101. Li Z, Christensen GM, Lah JJ, et al. Neighborhood characteristics as confounders and effect modifiers for the association between air pollution exposure and subjective cognitive functioning. *Environ Res*. Sep 2022;212(Pt A):113221. doi:10.1016/j.envres.2022.113221

102. McMaughan DJ, Oloruntoba O, Smith ML. Socioeconomic Status and Access to Healthcare: Interrelated Drivers for Healthy Aging. *Front Public Health*. 2020;8:231. doi:10.3389/fpubh.2020.00231

103. Frndak S, Deng Z, Ward-Caviness CK, Gorski-Steiner I, Thorpe RJ, Dickerson AS. Risk of dementia due to Co-exposure to air pollution and neighborhood disadvantage. *Environ Res*. Jun 15 2024;251(Pt 2):118709. doi:10.1016/j.envres.2024.118709

104. Alemany S, Crous-Bou M, Vilor-Tejedor N, et al. Associations between air pollution and biomarkers of Alzheimer's disease in cognitively unimpaired individuals. *Environ Int*. Dec 2021;157:106864. doi:10.1016/j.envint.2021.106864

105. Crous-Bou M, Gascon M, Gispert JD, et al. Impact of urban environmental exposures on cognitive performance and brain structure of healthy individuals at risk for Alzheimer's dementia. *Environ Int.* May 2020;138:105546. doi:10.1016/j.envint.2020.105546

106. Cho J, Jang H, Park H, et al. Alzheimer's disease-like cortical atrophy mediates the effect of air pollution on global cognitive function. *Environ Int.* Jan 2023;171:107703. doi:10.1016/j.envint.2022.107703

107. Falcon C, Gascon M, Molinuevo JL, et al. Brain correlates of urban environmental exposures in cognitively unimpaired individuals at increased risk for Alzheimer's disease: A study on Barcelona's population. *Alzheimers Dement (Amst).* 2021;13(1):e12205. doi:10.1002/dad2.12205

108. Casey E, Li Z, Liang D, et al. Association between Fine Particulate Matter Exposure and Cerebrospinal Fluid Biomarkers of Alzheimer's Disease among a Cognitively Healthy Population-Based Cohort. *Environ Health Perspect.* Apr 2024;132(4):47001. doi:10.1289/EHP13503

109. Calderon-Garciduenas L, Herrera-Soto A, Jury N, et al. Reduced repressive epigenetic marks, increased DNA damage and Alzheimer's disease hallmarks in the brain of humans and mice exposed to particulate urban air pollution. *Environ Res.* Apr 2020;183:109226. doi:10.1016/j.envres.2020.109226

110. Calderon-Garciduenas L, Gonzalez-Maciel A, Reynoso-Robles R, et al. Alzheimer's disease and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults </= 40 years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology. *Environ Res.* Oct 2018;166:348-362. doi:10.1016/j.envres.2018.06.027

111. Shaffer RM, Li G, Adar SD, et al. Fine Particulate Matter and Markers of Alzheimer's Disease Neuropathology at Autopsy in a Community-Based Cohort. *J Alzheimers Dis.* 2021;79(4):1761-1773. doi:10.3233/JAD-201005

112. Calderon-Garciduenas L, Stommel EW, Torres-Jardon R, et al. Alzheimer and Parkinson diseases, frontotemporal lobar degeneration and amyotrophic lateral sclerosis overlapping neuropathology start in the first two decades of life in pollution exposed urbanites and brain ultrafine particulate matter and industrial nanoparticles, including Fe, Ti, Al, V, Ni, Hg, Co, Cu, Zn, Ag, Pt, Ce, La, Pr and W are key players. Metropolitan Mexico City health crisis is in progress. *Front Hum Neurosci.* 2023;17:1297467. doi:10.3389/fnhum.2023.1297467

113. Vanbrabant K, Van Dam D, Bongaerts E, et al. Accumulation of Ambient Black Carbon Particles Within Key Memory-Related Brain Regions. *JAMA Netw Open.* Apr 1 2024;7(4):e245678. doi:10.1001/jamanetworkopen.2024.5678

114. Cullen B, Newby D, Lee D, et al. Cross-sectional and longitudinal analyses of outdoor air pollution exposure and cognitive function in UK Biobank. *Sci Rep.* Aug 14 2018;8(1):12089. doi:10.1038/s41598-018-30568-6

115. Calderon-Garciduenas L, Chavez-Franco DA, Luevano-Castro SC, et al. Metals, Nanoparticles, Particulate Matter, and Cognitive Decline. *Front Neurol.* 2021;12:794071. doi:10.3389/fneur.2021.794071

116. Lee YG, Yoon SJ, Yoon SH, et al. Air pollution is associated with faster cognitive decline in Alzheimer's disease. *Ann Clin Transl Neurol.* Jun 2023;10(6):964-973. doi:10.1002/acn3.51779

117. Yang L, Wan W, Yu C, Xuan C, Zheng P, Yan J. Associations between PM(2.5) exposure and Alzheimer's Disease prevalence Among elderly in eastern China. *Environ Health.* Nov 29 2022;21(1):119. doi:10.1186/s12940-022-00937-w

118. Younan D, Wang X, Millstein J, et al. Air quality improvement and cognitive decline in community-dwelling older women in the United States: A longitudinal cohort study. *PLoS Med.* Feb 2022;19(2):e1003893. doi:10.1371/journal.pmed.1003893

119. Franz CE, Gustavson DE, Elman JA, et al. Associations Between Ambient Air Pollution and Cognitive Abilities from Midlife to Early Old Age: Modification by APOE Genotype. *J Alzheimers Dis.* 2023;93(1):193-209. doi:10.3233/JAD-221054

120.Ilango SD, Gonzalez K, Gallo L, et al. Long-Term Exposure to Ambient Air Pollution and Cognitive Function Among Hispanic/Latino Adults in San Diego, California. *J Alzheimers Dis.* 2021;79(4):1489-1496. doi:10.3233/JAD-200766

121.Kulick ER, Elkind MSV, Boehme AK, et al. Long-term exposure to ambient air pollution, APOE-epsilon4 status, and cognitive decline in a cohort of older adults in northern Manhattan. *Environ Int.* Mar 2020;136:105440. doi:10.1016/j.envint.2019.105440

122.Lo CC, Liu WT, Lu YH, et al. Air pollution associated with cognitive decline by the mediating effects of sleep cycle disruption and changes in brain structure in adults. *Environ Sci Pollut Res Int.* Jul 2022;29(35):52355-52366. doi:10.1007/s11356-022-19482-7

123.Park SY, Han J, Kim SH, Suk HW, Park JE, Lee DY. Impact of Long-Term Exposure to Air Pollution on Cognitive Decline in Older Adults Without Dementia. *J Alzheimers Dis.* 2022;86(2):553-563. doi:10.3233/JAD-215120

124.Ard K, Thomas J, Bullock C. Toxic air pollution and cognitive decline: Untangling particulate matter. *Health Place.* Aug 16 2024;89:103330. doi:10.1016/j.healthplace.2024.103330

125.Wang X, Younan D, Petkus AJ, et al. Ambient Air Pollution and Long-Term Trajectories of Episodic Memory Decline among Older Women in the WHIMS-ECHO Cohort. *Environ Health Perspect.* Sep 2021;129(9):97009. doi:10.1289/EHP7668

126.Younan D, Wang X, Gruenewald T, et al. Racial/Ethnic Disparities in Alzheimer's Disease Risk: Role of Exposure to Ambient Fine Particles. *J Gerontol A Biol Sci Med Sci.* May 5 2022;77(5):977-985. doi:10.1093/gerona/glab231

127.Raichlen DA, Furlong M, Klimentidis YC, et al. Association of Physical Activity with Incidence of Dementia Is Attenuated by Air Pollution. *Med Sci Sports Exerc.* Jul 1 2022;54(7):1131-1138. doi:10.1249/MSS.0000000000002888

128.Yu Y, Haan M, Paul KC, et al. Metabolic dysfunction modifies the influence of traffic-related air pollution and noise exposure on late-life dementia and cognitive impairment: A cohort study of older Mexican-Americans. *Environ Epidemiol.* Dec 2020;4(6):e122. doi:10.1097/EE9.0000000000000122

129.Zhang Y, Fu Y, Guan X, et al. Associations of ambient air pollution exposure and lifestyle factors with incident dementia in the elderly: A prospective study in the UK Biobank. *Environ Int.* Jul 4 2024;190:108870. doi:10.1016/j.envint.2024.108870

130.Hu HY, Ma YH, Deng YT, et al. Residential greenness and risk of incident dementia: A prospective study of 375,342 participants. *Environ Res.* Jan 1 2023;216(Pt 3):114703. doi:10.1016/j.envres.2022.114703

131.Astell-Burt T, Navakatikyan MA, Feng X. Urban green space, tree canopy and 11-year risk of dementia in a cohort of 109,688 Australians. *Environ Int.* Dec 2020;145:106102. doi:10.1016/j.envint.2020.106102

132.Rodriguez-Loureiro L, Gadeyne S, Bauwelinck M, Lefebvre W, Vanpoucke C, Casas L. Long-term exposure to residential greenness and neurodegenerative disease mortality among older adults: a 13-year follow-up cohort study. *Environ Health.* May 7 2022;21(1):49. doi:10.1186/s12940-022-00863-x

133.Yu Y, Mayeda ER, Paul KC, et al. Traffic-related Noise Exposure and Late-life Dementia and Cognitive Impairment in Mexican-Americans. *Epidemiology.* Nov 1 2020;31(6):771-778. doi:10.1097/EDE.0000000000001249

134.Fortea J, Pegueroles J, Alcolea D, et al. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. *Nat Med.* May 2024;30(5):1284-1291. doi:10.1038/s41591-024-02931-w

135.Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet.* Mar 2019;51(3):404-413. doi:10.1038/s41588-018-0311-9

136.Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. *Neuron*. Aug 13 2009;63(3):287-303. doi:10.1016/j.neuron.2009.06.026

137.Klimentidis YC, Raichlen DA, Bea J, et al. Genome-wide association study of habitual physical activity in over 377,000 UK Biobank participants identifies multiple variants including CADM2 and APOE. *Int J Obes (Lond)*. Jun 2018;42(6):1161-1176. doi:10.1038/s41366-018-0120-3

138.Nuzum H, Stickel A, Corona M, Zeller M, Melrose RJ, Wilkins SS. Potential Benefits of Physical Activity in MCI and Dementia. *Behav Neurol*. 2020;2020:7807856. doi:10.1155/2020/7807856

139.Shi L, Chen SJ, Ma MY, et al. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. *Sleep Med Rev*. Aug 2018;40:4-16. doi:10.1016/j.smrv.2017.06.010

140.Zhang Y, Chen SD, Deng YT, et al. Identifying modifiable factors and their joint effect on dementia risk in the UK Biobank. *Nat Hum Behav*. Jul 2023;7(7):1185-1195. doi:10.1038/s41562-023-01585-x

141.Bein KJ, Wallis CD, Silverman JL, Lein PJ, Wexler AS. Emulating Near-Roadway Exposure to Traffic-Related Air Pollution via Real-Time Emissions from a Major Freeway Tunnel System. *Environ Sci Technol*. Mar 2 2022;doi:10.1021/acs.est.1c07047

142.Shang Y, Sun Q. Particulate air pollution: major research methods and applications in animal models. *Environ Dis*. Jul-Sep 2018;3(3):57-62. doi:10.4103/ed.ed_16_18

143.Bendtsen KM, Gren L, Malmborg VB, et al. Particle characterization and toxicity in C57BL/6 mice following instillation of five different diesel exhaust particles designed to differ in physicochemical properties. *Part Fibre Toxicol*. Aug 8 2020;17(1):38. doi:10.1186/s12989-020-00369-9

144.Moon KY, Park MK, Leikauf GD, Park CS, Jang AS. Diesel exhaust particle-induced airway responses are augmented in obese rats. *Int J Toxicol*. Jan-Feb 2014;33(1):21-8. doi:10.1177/1091581813518355

145.Daniel S, Phillippi D, Schneider LJ, Nguyen KN, Mirpuri J, Lund AK. Exposure to diesel exhaust particles results in altered lung microbial profiles, associated with increased reactive oxygen species/reactive nitrogen species and inflammation, in C57Bl/6 wildtype mice on a high-fat diet. *Part Fibre Toxicol*. Jan 8 2021;18(1):3. doi:10.1186/s12989-020-00393-9

146.Zavala J, Freedman AN, Szilagyi JT, et al. New Approach Methods to Evaluate Health Risks of Air Pollutants: Critical Design Considerations for In Vitro Exposure Testing. *Int J Environ Res Public Health*. Mar 23 2020;17(6)doi:10.3390/ijerph17062124

147.Lakatos HF, Burgess HA, Thatcher TH, et al. Oropharyngeal aspiration of a silica suspension produces a superior model of silicosis in the mouse when compared to intratracheal instillation. *Exp Lung Res*. May 2006;32(5):181-99. doi:10.1080/01902140600817465

148.Silva RM, Doudrick K, Franzi LM, et al. Instillation versus inhalation of multiwalled carbon nanotubes: exposure-related health effects, clearance, and the role of particle characteristics. *ACS Nano*. Sep 23 2014;8(9):8911-31. doi:10.1021/nn503887r

149.Saveleva L, Vartiainen P, Gorova V, et al. Subacute inhalation of ultrafine particulate matter triggers inflammation without altering amyloid beta load in 5xFAD mice. *Neurotoxicology*. Mar 2022;89:55-66. doi:10.1016/j.neuro.2022.01.001

150.Greve HJ, Dunbar AL, Lombo CG, et al. The bidirectional lung brain-axis of amyloid-beta pathology: ozone dysregulates the peri-plaque microenvironment. *Brain*. Mar 1 2023;146(3):991-1005. doi:10.1093/brain/awac113

151.Ahmed C, Greve HJ, Garza-Lombo C, et al. Peripheral HMGB1 is linked to O(3) pathology of disease-associated astrocytes and amyloid. *Alzheimers Dement*. May 2024;20(5):3551-3566. doi:10.1002/alz.13825

152. Park SJ, Lee J, Lee S, et al. Exposure of ultrafine particulate matter causes glutathione redox imbalance in the hippocampus: A neurometabolic susceptibility to Alzheimer's pathology. *Sci Total Environ*. May 20 2020;718:137267. doi:10.1016/j.scitotenv.2020.137267

153. Rivas-Arancibia S, Rodriguez-Martinez E, Badillo-Ramirez I, Lopez-Gonzalez U, Saniger JM. Structural Changes of Amyloid Beta in Hippocampus of Rats Exposed to Ozone: A Raman Spectroscopy Study. *Front Mol Neurosci*. 2017;10:137. doi:10.3389/fnmol.2017.00137

154. Rivas-Arancibia S, Guevara-Guzman R, Lopez-Vidal Y, et al. Oxidative stress caused by ozone exposure induces loss of brain repair in the hippocampus of adult rats. *Toxicol Sci*. Jan 2010;113(1):187-97. doi:10.1093/toxsci/kfp252

155. Jew K, Herr D, Wong C, et al. Selective memory and behavioral alterations after ambient ultrafine particulate matter exposure in aged 3xTgAD Alzheimer's disease mice. *Part Fibre Toxicol*. Nov 26 2019;16(1):45. doi:10.1186/s12989-019-0323-3

156. Herr D, Jew K, Wong C, et al. Effects of concentrated ambient ultrafine particulate matter on hallmarks of Alzheimer's disease in the 3xTgAD mouse model. *Neurotoxicology*. May 2021;84:172-183. doi:10.1016/j.neuro.2021.03.010

157. Kilian JG, Mejias-Ortega M, Hsu HW, et al. Exposure to quasi-ultrafine particulate matter accelerates memory impairment and Alzheimer's disease-like neuropathology in the AppNL-G-F knock-in mouse model. *Toxicol Sci*. May 31 2023;193(2):175-191. doi:10.1093/toxsci/kfad036

158. Sahu B, Mackos AR, Floden AM, Wold LE, Combs CK. Particulate Matter Exposure Exacerbates Amyloid-beta Plaque Deposition and Gliosis in APP/PS1 Mice. *J Alzheimers Dis*. 2021;80(2):761-774. doi:10.3233/JAD-200919

159. Jung HA, C.; Zhao, Y.; Paulson, S,; Anastasio, C.; Wexler, A. Impact of the Versatile Aerosol Concentration Enrichment System (VACES) on Gas Phase Species. *Aerosol Science and Technology*. 2010;44(12):1113–1121.doi:https://doi.org/10.1080/02786826.2010.512028

160. Patten KT, Valenzuela AE, Wallis C, et al. The Effects of Chronic Exposure to Ambient Traffic-Related Air Pollution on Alzheimer's Disease Phenotypes in Wildtype and Genetically Predisposed Male and Female Rats. *Environ Health Perspect*. May 2021;129(5):57005. doi:10.1289/EHP8905

161. Lee SH, Chen YH, Chien CC, et al. Three month inhalation exposure to low-level PM2.5 induced brain toxicity in an Alzheimer's disease mouse model. *PLoS One*. 2021;16(8):e0254587. doi:10.1371/journal.pone.0254587

162. Patten KT, Valenzuela AE, Wallis C, et al. Hippocampal but Not Serum Cytokine Levels Are Altered by Traffic-Related Air Pollution in TgF344-AD and Wildtype Fischer 344 Rats in a Sex- and Age-Dependent Manner. *Front Cell Neurosci*. 2022;16:861733. doi:10.3389/fncel.2022.861733

163. Fu P, Zhao Y, Dong C, Cai Z, Li R, Yung KKL. An integrative analysis of miRNA and mRNA expression in the brains of Alzheimer's disease transgenic mice after real-world PM(2.5) exposure. *J Environ Sci (China)*. Dec 2022;122:25-40. doi:10.1016/j.jes.2021.10.007

164. Ehsanifar M, Yavari Z, Rafati M. Exposure to urban air pollution particulate matter: neurobehavioral alteration and hippocampal inflammation. *Environ Sci Pollut Res Int*. Jul 2022;29(33):50856-50866. doi:10.1007/s11356-022-19367-9

165. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. *Signal Transduct Target Ther*. Jul 12 2023;8(1):267. doi:10.1038/s41392-023-01486-5

166. Hopperton KE, Mohammad D, Trepanier MO, Giuliano V, Bazinet RP. Markers of microglia in post-mortem brain samples from patients with Alzheimer's disease: a systematic review. *Mol Psychiatry*. Feb 2018;23(2):177-198. doi:10.1038/mp.2017.246

167. Wetering JV, Geut H, Bol JJ, et al. Neuroinflammation is associated with Alzheimer's disease co-pathology in dementia with Lewy

bodies. *Acta Neuropathol Commun.* May 7 2024;
12(1):73. doi:10.1186/s40478-024-01786-z

168.Liu WS, Zhang YR, Ge YJ, Wang HF, Cheng W,
Yu JT. Inflammation and Brain Structure in
Alzheimer's Disease and Other Neurodegenerative
Disorders: a Mendelian Randomization Study. *Mol
Neurobiol.* Mar 2024;61(3):1593-1604. doi:10.100
7/s12035-023-03648-6

169.Rangaraju S, Dammer EB, Raza SA, et al.
Identification and therapeutic modulation of a pro-
inflammatory subset of disease-associated-microglia
in Alzheimer's disease. *Mol Neurodegener.* May 21
2018;13(1):24. doi:10.1186/s13024-018-0254-8

170.Saito T, Saido TC. Neuroinflammation in
mouse models of Alzheimer's disease. *Clin Exp
Neuroimmunol.* Nov 2018;9(4):211-218. doi:10.11
11/cen3.12475

171.Mucke L, Selkoe DJ. Neurotoxicity of amyloid
beta-protein: synaptic and network dysfunction.
Cold Spring Harb Perspect Med. Jul 2012;2(7)
:a006338. doi:10.1101/cshperspect.a006338

172.Chen Y, Yu Y. Tau and neuroinflammation in
Alzheimer's disease: interplay mechanisms and
clinical translation. *J Neuroinflammation.* Jul 14
2023;20(1):165. doi:10.1186/s12974-023-02853-3

173.Rauti R, Cellot G, D'Andrea P, et al. BDNF
impact on synaptic dynamics: extra or intracellular
long-term release differently regulates cultured
hippocampal synapses. *Mol Brain.* Mar 17 2020
;13(1):43. doi:10.1186/s13041-020-00582-9

174.Stevens B, Allen NJ, Vazquez LE, et al. The
classical complement cascade mediates CNS
synapse elimination. *Cell.* Dec 14 2007;131(6):1
164-78. doi:10.1016/j.cell.2007.10.036

175.Jantti H, Sitnikova V, Ishchenko Y, et al.
Microglial amyloid beta clearance is driven by
PIEZO1 channels. *J Neuroinflammation.* Jun 15
2022;19(1):147. doi:10.1186/s12974-022-02486-y

176.Chen Z, Jalabi W, Shpargel KB, et al.
Lipopolysaccharide-induced microglial activation
and neuroprotection against experimental brain
injury is independent of hematogenous TLR4. *J

Neurosci.* Aug 22 2012;32(34):11706-15. doi:10.15
23/JNEUROSCI.0730-12.2012

177.Fan J, Dong X, Tang Y, et al. Preferential
pruning of inhibitory synapses by microglia
contributes to alteration of the balance between
excitatory and inhibitory synapses in the hippocampus
in temporal lobe epilepsy. *CNS Neurosci Ther.* Oct
2023;29(10):2884-2900. doi:10.1111/cns.14224

178.Taddei RN, Perbet R, Mate de Gerando A, et
al. Tau Oligomer-Containing Synapse Elimination
by Microglia and Astrocytes in Alzheimer Disease.
JAMA Neurol. Nov 1 2023;80(11):1209-1221.
doi:10.1001/jamaneurol.2023.3530

179.Chung HY, Wickel J, Hahn N, et al. Microglia
mediate neurocognitive deficits by eliminating
C1q-tagged synapses in sepsis-associated
encephalopathy. *Sci Adv.* May 26 2023;9(21):eabq
7806. doi:10.1126/sciadv.abq7806

180.Shu J, Fang XH, Li YJ, Deng Y, Wei WS, Zhang
L. Microglia-induced autophagic death of neurons
via IL-6/STAT3/miR-30d signaling following
hypoxia/ischemia. *Mol Biol Rep.* Aug 2022;49(8):
7697-7707. doi:10.1007/s11033-022-07587-8

181.Liang P, Zhang X, Zhang Y, et al. Neurotoxic
A1 astrocytes promote neuronal ferroptosis via
CXCL10/CXCR3 axis in epilepsy. *Free Radic Biol
Med.* Feb 1 2023;195:329-342. doi:10.1016/j.free
radbiomed.2023.01.002

182.Hong S, Beja-Glasser VF, Nfonoyim BM, et al.
Complement and microglia mediate early synapse
loss in Alzheimer mouse models. *Science.* May 6
2016;352(6286):712-716.
doi:10.1126/science.aad8373

183.Imai Y, Ibata I, Ito D, Ohsawa K, Kohsaka S. A
novel gene iba1 in the major histocompatibility
complex class III region encoding an EF hand
protein expressed in a monocytic lineage. *Biochem
Biophys Res Commun.* Jul 25 1996;224(3):855-62.
doi:10.1006/bbrc.1996.1112

184.Ito D, Imai Y, Ohsawa K, Nakajima K, Fukuuchi
Y, Kohsaka S. Microglia-specific localisation of a
novel calcium binding protein, Iba1. *Brain Res Mol

Brain Res. Jun 1 1998;57(1):1-9. doi:10.1016/s0169-328x(98)00040-0

185.Middeldorp J, Hol EM. GFAP in health and disease. *Prog Neurobiol.* Mar 2011;93(3):421-43. doi:10.1016/j.pneurobio.2011.01.005

186.Eng LF. Glial fibrillary acidic protein (GFAP): the major protein of glial intermediate filaments in differentiated astrocytes. *J Neuroimmunol.* Jun 1985;8(4-6):203-14. doi:10.1016/s0165-5728(85)80063-1

187.Ji X, Liu R, Guo J, et al. Olfactory bulb microglia activation mediated neuronal death in real-ambient particulate matter exposure mice with depression-like behaviors. *Sci Total Environ.* May 15 2022;821:153456. doi:10.1016/j.scitotenv.2022.153456

188.Jang S, Kim EW, Zhang Y, et al. Particulate matter increases beta-amyloid and activated glial cells in hippocampal tissues of transgenic Alzheimer's mouse: Involvement of PARP-1. *Biochem Biophys Res Commun.* Jun 2 2018;500 (2):333-338. doi:10.1016/j.bbrc.2018.04.068

189.Xu MX, Zhu YF, Chang HF, Liang Y. Nanoceria restrains PM2.5-induced metabolic disorder and hypothalamus inflammation by inhibition of astrocytes activation related NF-kappaB pathway in Nrf2 deficient mice. *Free Radic Biol Med.* Oct 2016;99:259-272. doi:10.1016/j.freeradbiomed.2016.08.021

190.Andrade-Oliva MD, Aztatzi-Aguilar OG, Garcia-Sierra F, De Vizcaya-Ruiz A, Arias-Montano JA. Effect of in vivo exposure to ambient fine particles (PM(2.5)) on the density of dopamine D(2)-like receptors and dopamine-induced [(35)S]-GTPgammaS binding in rat prefrontal cortex and striatum membranes. *Environ Toxicol Pharmacol.* Jun 2018;60:58-65. doi:10.1016/j.etap.2018.04.001

191.Zhong L, Sheng X, Wang W, et al. TREM2 receptor protects against complement-mediated synaptic loss by binding to complement C1q during neurodegeneration. *Immunity.* Aug 8 2023;56(8):1794-1808 e8. doi:10.1016/j.immuni.2023.06.016

192.Saha P, Sarkar S, Paidi RK, Biswas SC. TIMP-1: A key cytokine released from activated astrocytes protects neurons and ameliorates cognitive behaviours in a rodent model of Alzheimer's disease. *Brain Behav Immun.* Jul 2020;87:804-819. doi:10.1016/j.bbi.2020.03.014

193.Chen Z, Jalabi W, Hu W, et al. Microglial displacement of inhibitory synapses provides neuroprotection in the adult brain. *Nat Commun.* Jul 22 2014;5:4486. doi:10.1038/ncomms5486

194.Li B, Chang X, Liang X, et al. The role of reactive astrocytes in neurotoxicity induced by ultrafine particulate matter. *Sci Total Environ.* Apr 1 2023;867:161416. doi:10.1016/j.scitotenv.2023.161416

195.Kang YJ, Tan HY, Lee CY, Cho H. An Air Particulate Pollutant Induces Neuroinflammation and Neurodegeneration in Human Brain Models. *Adv Sci (Weinh).* Nov 2021;8(21):e2101251. doi:10.1002/advs.202101251

196.Weaver DF. Amyloid-beta is a cytokine. *Alzheimers Dement.* Sep 2023;19(9):4237-4247. doi:10.1002/alz.13165

197.Bai R, Guo J, Ye XY, Xie Y, Xie T. Oxidative stress: The core pathogenesis and mechanism of Alzheimer's disease. *Ageing Res Rev.* May 2022;77:101619. doi:10.1016/j.arr.2022.101619

198.Vilhardt F, Haslund-Vinding J, Jaquet V, McBean G. Microglia antioxidant systems and redox signalling. *Br J Pharmacol.* Jun 2017;174(12):1719-1732. doi:10.1111/bph.13426

199.Suwannasual U, Lucero J, McDonald JD, Lund AK. Exposure to traffic-generated air pollutants mediates alterations in brain microvascular integrity in wildtype mice on a high-fat diet. *Environ Res.* Jan 2018;160:449-461. doi:10.1016/j.envres.2017.10.029

200.Ehsanifar M, Montazeri Z, Taheri MA, Rafati M, Behjati M, Karimian M. Hippocampal inflammation and oxidative stress following exposure to diesel exhaust nanoparticles in male and female mice. *Neurochem Int.* May 2021;145:104989. doi:10.1016/j.neuint.2021.104989

201. Cacciottolo M, Morgan TE, Saffari AA, et al. Traffic-related air pollutants (TRAP-PM) promote neuronal amyloidogenesis through oxidative damage to lipid rafts. *Free Radic Biol Med*. Feb 1 2020;147: 242-251. doi:10.1016/j.freeradbiomed.2019.12.023

202. Lee SH, Lin CY, Chen TF, et al. Distinct brain lipid signatures in response to low-level PM(2.5) exposure in a 3xTg-Alzheimer's disease mouse inhalation model. *Sci Total Environ*. Sep 10 2022;8 38(Pt 4):156456. doi:10.1016/j.scitotenv.20 22.156456

203. Bai KJ, Chuang KJ, Wu SM, et al. Effects of diesel exhaust particles on the expression of tau and autophagy proteins in human neuroblastoma cells. *Environ Toxicol Pharmacol*. Sep 2018;62:54-59. doi:10.1016/j.etap.2018.06.007

204. Milani C, Corsetto PA, Farina F, et al. Early evidence of stress in immortalized neurons exposed to diesel particles: the role of lipid reshaping behind oxidative stress and inflammation. *Toxicology*. Nov 1 2018;409:63-72. doi:10.1016/j.tox.2018.07.017

205. Wang BR, Shi JQ, Ge NN, et al. PM2.5 exposure aggravates oligomeric amyloid beta-induced neuronal injury and promotes NLRP3 inflammasome activation in an in vitro model of Alzheimer's disease. *J Neuroinflammation*. May 2 2018;15(1):132. doi:10.1186/s12974-018-1178-5

206. Aquino GV, Dabi A, Odom GJ, Zhang F, Bruce ED. Evaluating the endothelial-microglial interaction and comprehensive inflammatory marker profiles under acute exposure to ultrafine diesel exhaust particles in vitro. *Toxicology*. Apr 30 2021;454:152 748. doi:10.1016/j.tox.2021.152748

207. Shi Q, Chowdhury S, Ma R, et al. Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice. *Sci Transl Med*. May 31 2017;9(392)doi:10.1126/scitranslmed.aaf6295

208. Zhang J, Malik A, Choi HB, Ko RW, Dissing-Olesen L, MacVicar BA. Microglial CR3 activation triggers long-term synaptic depression in the hippocampus via NADPH oxidase. *Neuron*. Apr 2 2014;82(1):195-207. doi:10.1016/j.neuron.2014.01.043

209. Hou L, Wang K, Zhang C, et al. Complement receptor 3 mediates NADPH oxidase activation and dopaminergic neurodegeneration through a Src-Erk-dependent pathway. *Redox Biol*. Apr 2018;14:250-260. doi:10.1016/j.redox.2017.09.017

210. Lian H, Litvinchuk A, Chiang AC, Aithmitti N, Jankowsky JL, Zheng H. Astrocyte-Microglia Cross Talk through Complement Activation Modulates Amyloid Pathology in Mouse Models of Alzheimer's Disease. *J Neurosci*. Jan 13 2016;36(2):577-89. doi:10.1523/JNEUROSCI.2117-15.2016

211. Kumar A, Barrett JP, Alvarez-Croda DM, Stoica BA, Faden AI, Loane DJ. NOX2 drives M1-like microglial/macrophage activation and neurodegeneration following experimental traumatic brain injury. *Brain Behav Immun*. Nov 2016;58:291-309. doi:10.1016/j.bbi.2016.07.158

212. Zhang H, Haghani A, Mousavi AH, et al. Cell-based assays that predict in vivo neurotoxicity of urban ambient nano-sized particulate matter. *Free Radic Biol Med*. Dec 2019;145:33-41. doi:10.1016/j.freeradbiomed.2019.09.016

213. Velazquez-Perez R, Rodriguez-Martinez E, Valdes-Fuentes M, Gelista-Herrera N, Gomez-Crisostomo N, Rivas-Arancibia S. Oxidative Stress Caused by Ozone Exposure Induces Changes in P2X7 Receptors, Neuroinflammation, and Neurodegeneration in the Rat Hippocampus. *Oxid Med Cell Longev*. 2021;2021:3790477. doi:10.115 5/2021/3790477

214. Solleiro-Villavicencio H, Hernandez-Orozco E, Rivas-Arancibia S. Effect of exposure to low doses of ozone on interleukin 17A expression during progressive neurodegeneration in the rat hippocampus. *Neurologia (Engl Ed)*. Nov-Dec 202 1;36(9):673-680. doi:10.1016/j.nrleng.2018.08.003

215. Singh J, Habean ML, Panicker N. Inflammasome assembly in neurodegenerative diseases. *Trends Neurosci*. Oct 2023;46(10):814-831. doi:10.1016/j.tins.2023.07.009

216. Bourganis V, Kammona O, Alexopoulos A, Kiparissides C. Recent advances in carrier mediated nose-to-brain delivery of pharmaceutics. *Eur J Pharm Biopharm*. Jul 2018;128:337-362. doi:10.10 16/j.ejpb.2018.05.009

217. Ajmani GS, Suh HH, Pinto JM. Effects of Ambient Air Pollution Exposure on Olfaction: A Review. *Environ Health Perspect.* Nov 2016;124 (11):1683-1693. doi:10.1289/EHP136

218. Gartziandia O, Egusquiaguirre SP, Bianco J, et al. Nanoparticle transport across in vitro olfactory cell monolayers. *Int J Pharm.* Feb 29 2016;499(1-2):81-89. doi:10.1016/j.ijpharm.2015.12.046

219. Elder A, Gelein R, Silva V, et al. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. *Environ Health Perspect.* Aug 2006;114(8):1172-8. doi:10.1289/ehp.9030

220. Liang C, Jiang Y, Zhang T, et al. Atmospheric particulate matter impairs cognition by modulating synaptic function via the nose-to-brain route. *Sci Total Environ.* Jan 20 2023;857(Pt 3):159600. doi:10.1016/j.scitotenv.2022.159600

221. Kilian J, Kitazawa M. The emerging risk of exposure to air pollution on cognitive decline and Alzheimer's disease - Evidence from epidemiological and animal studies. *Biomed J.* Jun 2018;41(3):141-162. doi:10.1016/j.bj.2018.06.001

222. Wang W, Lin Y, Yang H, et al. Internal Exposure and Distribution of Airborne Fine Particles in the Human Body: Methodology, Current Understandings, and Research Needs. *Environ Sci Technol.* Jun 7 2022;56(11):6857-6869. doi:10.1021/acs.est.1c07051

223. You R, Ho YS, Chang RC. The pathogenic effects of particulate matter on neurodegeneration: a review. *J Biomed Sci.* Feb 22 2022;29(1):15. doi:10.1186/s12929-022-00799-x

224. Calderon-Garciduenas L, Perez-Calatayud AA, Gonzalez-Maciel A, et al. Environmental Nanoparticles Reach Human Fetal Brains. *Biomedicines.* Feb 9 2022;10(2)doi:10.3390/biomedicines10020410

225. Li Y, Liu Y, Hu C, et al. Study of the neurotoxicity of indoor airborne nanoparticles based on a 3D human blood-brain barrier chip. *Environ Int.* Oct 2020;143:105598. doi:10.1016/j.envint.2020.105598

226. Yamazaki Y, Shinohara M, Shinohara M, et al. Selective loss of cortical endothelial tight junction proteins during Alzheimer's disease progression. *Brain.* Apr 1 2019;142(4):1077-1092. doi:10.1093/brain/awz011

227. Kurz C, Walker L, Rauchmann BS, Perneczky R. Dysfunction of the blood-brain barrier in Alzheimer's disease: Evidence from human studies. *Neuropathol Appl Neurobiol.* Apr 2022;48(3):e12782. doi:10.1111/nan.12782

228. Cai Z, Qiao PF, Wan CQ, Cai M, Zhou NK, Li Q. Role of Blood-Brain Barrier in Alzheimer's Disease. *J Alzheimers Dis.* 2018;63(4):1223-1234. doi:10.3233/JAD-180098

229. Bernardino PN, Hobson BA, Huddleston SL, et al. Time- and region-dependent blood-brain barrier impairment in a rat model of organophosphate-induced status epilepticus. *Neurobiol Dis.* Oct 15 2023;187:106316. doi:10.1016/j.nbd.2023.106316

230. Park JH, Choi JY, Lee HK, Jo C, Koh YH. Notch1-mediated inflammation is associated with endothelial dysfunction in human brain microvascular endothelial cells upon particulate matter exposure. *Arch Toxicol.* Feb 2021;95(2):529-540. doi:10.1007/s00204-020-02942-9

231. Adivi A, Lucero J, Simpson N, McDonald JD, Lund AK. Exposure to traffic-generated air pollution promotes alterations in the integrity of the brain microvasculature and inflammation in female ApoE(-/-) mice. *Toxicol Lett.* Mar 15 2021;339:39-50. doi:10.1016/j.toxlet.2020.12.016

232. Roque PJ, Dao K, Costa LG. Microglia mediate diesel exhaust particle-induced cerebellar neuronal toxicity through neuroinflammatory mechanisms. *Neurotoxicology.* Sep 2016;56:204-214. doi:10.1016/j.neuro.2016.08.006

233. Han B, Li X, Ai RS, et al. Atmospheric particulate matter aggravates cns demyelination through involvement of TLR-4/NF-kB signaling and microglial activation. *Elife.* Feb 24 2022;11doi:10.7554/eLife.72247

234. Pradhan SH, Gibb M, Kramer AT, Sayes CM. Peripheral (lung-to-brain) exposure to diesel particulate matter induces oxidative stress and

increased markers for systemic inflammation. *Environ Res.* Aug 15 2023;231(Pt 3):116267. doi:10.1016/j.envres.2023.116267

235.Ljubimova JY, Braubach O, Patil R, et al. Coarse particulate matter (PM(2.5-10)) in Los Angeles Basin air induces expression of inflammation and cancer biomarkers in rat brains. *Sci Rep.* Apr 9 2018;8(1):5708. doi:10.1038/s41598-018-23885-3

236.Wallin C, Sholts SB, Osterlund N, et al. Alzheimer's disease and cigarette smoke components: effects of nicotine, PAHs, and Cd(II), Cr(III), Pb(II), Pb(IV) ions on amyloid-beta peptide aggregation. *Sci Rep.* Oct 31 2017;7(1):14423. doi:10.1038/s41598-017-13759-5

237.Best EA, Juarez-Colunga E, James K, LeBlanc WG, Serdar B. Biomarkers of Exposure to Polycyclic Aromatic Hydrocarbons and Cognitive Function among Elderly in the United States (National Health and Nutrition Examination Survey: 2001-2002). *PLoS One.* 2016;11(2):e0147632. doi:10.1371/journal.pone.0147632

238.Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature.* Jan 26 2017;541(7638):481-487. doi:10.1038/nature21029

239.Goshi N, Morgan RK, Lein PJ, Seker E. A primary neural cell culture model to study neuron, astrocyte, and microglia interactions in neuroinflammation. *J Neuroinflammation.* May 11 2020;17(1):155. doi:10.1186/s12974-020-01819-z

240.Monoson A, Schott E, Ard K, et al. Air pollution and respiratory infections: the past, present, and future. *Toxicol Sci.* Mar 20 2023;192(1):3-14. doi:10.1093/toxsci/kfad003

241.Carraro S, Ferraro VA, Zanconato S. Impact of air pollution exposure on lung function and exhaled breath biomarkers in children and adolescents. *J Breath Res.* Aug 19 2022;16(4) doi:10.1088/1752-7163/ac8895

242.Wang M, Aaron CP, Madrigano J, et al. Association Between Long-term Exposure to Ambient Air Pollution and Change in Quantitatively Assessed Emphysema and Lung Function. *JAMA.* Aug 13 2019;322(6):546-556. doi:10.1001/jama.2019.10255

243.Melbourne CA, Mesut Erzurumluoglu A, Shrine N, et al. Genome-wide gene-air pollution interaction analysis of lung function in 300,000 individuals. *Environ Int.* Jan 15 2022;159:107041. doi:10.1016/j.envint.2021.107041

244.Laratta CR, Kendzerska T, Carlsten C, et al. Air Pollution and Systemic Inflammation in Patients With Suspected OSA Living in an Urban Residential Area. *Chest.* Oct 2020;158(4):1713-1722. doi:10.1016/j.chest.2020.05.596

245.Lucking AJ, Lundback M, Mills NL, et al. Diesel exhaust inhalation increases thrombus formation in man. *Eur Heart J.* Dec 2008;29(24):3043-51. doi:10.1093/eurheartj/ehn464

246.Mills NL, Tornqvist H, Robinson SD, et al. Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation.* Dec 20 2005;112(25):3930-6. doi:10.1161/CIRCULATIONAHA.105.588962

247.Peretz A, Peck EC, Bammler TK, et al. Diesel exhaust inhalation and assessment of peripheral blood mononuclear cell gene transcription effects: an exploratory study of healthy human volunteers. *Inhal Toxicol.* Nov 2007;19(14):1107-19. doi:10.1080/08958370701665384

248.Zhang Z, Hoek G, Chang LY, et al. Particulate matter air pollution, physical activity and systemic inflammation in Taiwanese adults. *Int J Hyg Environ Health.* Jan 2018;221(1):41-47. doi:10.1016/j.ijheh.2017.10.001

249.Thome AD, Faridar A, Beers DR, et al. Functional alterations of myeloid cells during the course of Alzheimer's disease. *Mol Neurodegener.* Nov 13 2018;13(1):61. doi:10.1186/s13024-018-0293-1

250.Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat Rev Neurosci.* Mar 2019;20(3):148-160. doi:10.1038/s41583-019-0132-6

251.Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. *Lancet*

Neurol. Apr 2015;14(4):388-405. doi:10.1016/S1474-4422(15)70016-5

252. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science.* Aug 19 2016;353(6301):777-83. doi:10.1126/science.aag2590

253. Xie J, Van Hoecke L, Vandenbroucke RE. The Impact of Systemic Inflammation on Alzheimer's Disease Pathology. *Front Immunol.* 2021;12:796867. doi:10.3389/fimmu.2021.796867

254. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimers Dement.* Jun 2016;12(6):719-32. doi:10.1016/j.jalz.2016.02.010

255. Lutsey PL, Chen N, Mirabelli MC, et al. Impaired Lung Function, Lung Disease, and Risk of Incident Dementia. *Am J Respir Crit Care Med.* Jun 1 2019;199(11):1385-1396. doi:10.1164/rccm.201807-1220OC

256. Grande G, Li Y, Trevisan C, et al. Lung function in relation to brain aging and cognitive transitions in older adults: A population-based cohort study. *Alzheimers Dement.* Jul 5 2024;doi:10.1002/alz.14079

257. Russ TC, Kivimaki M, Batty GD. Respiratory Disease and Lower Pulmonary Function as Risk Factors for Dementia: A Systematic Review With Meta-analysis. *Chest.* Jun 2020;157(6):1538-1558. doi:10.1016/j.chest.2019.12.012

258. Gilsanz P, Mayeda ER, Flatt J, Glymour MM, Quesenberry CP, Jr., Whitmer RA. Early Midlife Pulmonary Function and Dementia Risk. *Alzheimer Dis Assoc Disord.* Oct-Dec 2018;32(4):270-275. doi:10.1097/WAD.0000000000000253

259. Mumaw CL, Levesque S, McGraw C, et al. Microglial priming through the lung-brain axis: the role of air pollution-induced circulating factors. *FASEB J.* May 2016;30(5):1880-91. doi:10.1096/fj.201500047

260. Erickson MA, Jude J, Zhao H, et al. Serum amyloid A: an ozone-induced circulating factor with potentially important functions in the lung-brain axis. *FASEB J.* Sep 2017;31(9):3950-3965. doi:10.1096/fj.201600857RRR

261. Mao Y, Bajinka O, Tang Z, Qiu X, Tan Y. Lung-brain axis: Metabolomics and pathological changes in lungs and brain of respiratory syncytial virus-infected mice. *J Med Virol.* Dec 2022;94(12):5885-5893. doi:10.1002/jmv.28061

262. Hosang L, Canals RC, van der Flier FJ, et al. The lung microbiome regulates brain autoimmunity. *Nature.* Mar 2022;603(7899):138-144. doi:10.1038/s41586-022-04427-4

263. Millan-Zambrano G, Burton A, Bannister AJ, Schneider R. Histone post-translational modifications - cause and consequence of genome function. *Nat Rev Genet.* Sep 2022;23(9):563-580. doi:10.1038/s41576-022-00468-7

264. Sood AJ, Viner C, Hoffman MM. DNAmod: the DNA modification database. *J Cheminform.* Apr 23 2019;11(1):30. doi:10.1186/s13321-019-0349-4

265. Zhao LY, Song J, Liu Y, Song CX, Yi C. Mapping the epigenetic modifications of DNA and RNA. *Protein Cell.* Nov 2020;11(11):792-808. doi:10.1007/s13238-020-00733-7

266. Creyghton MP, Cheng AW, Welstead GG, et al. Histone H3K27ac separates active from poised enhancers and predicts developmental state. *Proc Natl Acad Sci U S A.* Dec 14 2010;107(50):21931-6. doi:10.1073/pnas.1016071107

267. Martinez-Feduchi P, Jin P, Yao B. Epigenetic modifications of DNA and RNA in Alzheimer's disease. *Front Mol Neurosci.* 2024;17:1398026. doi:10.3389/fnmol.2024.1398026

268. Cavalli G, Heard E. Advances in epigenetics link genetics to the environment and disease. *Nature.* Jul 2019;571(7766):489-499. doi:10.1038/s41586-019-1411-0

269. Greenberg MVC, Bourc'his D. The diverse roles of DNA methylation in mammalian development and disease. *Nat Rev Mol Cell Biol.* Oct 2019;20(10):590-607. doi:10.1038/s41580-019-0159-6

270. Yang Y, Hsu PJ, Chen YS, Yang YG. Dynamic transcriptomic m(6)A decoration: writers, erasers, readers and functions in RNA metabolism. *Cell Res.* Jun 2018;28(6):616-624. doi:10.1038/s41422-018-0040-8

271. Delaunay S, Helm M, Frye M. RNA modifications in physiology and disease: towards clinical applications. *Nat Rev Genet*. Feb 2024;25 (2):104-122. doi:10.1038/s41576-023-00645-2

272. Dan J, Chen, T. Chapter 3 - Writers, erasers, and readers of DNA and histone methylation marks. In: Gray SG, ed. *In Translational Epigenetics, Epigenetic Cancer Therapy*. Second Edition ed. 2023:39-63:chap 3.

273. Cacciottolo M, Wang X, Driscoll I, et al. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. *Transl Psychiatry*. Jan 31 2017;7(1):e1022. doi:10.1038/tp.2016.280

274. Zhang L, Wang H, Abel GM, Storm DR, Xia Z. The Effects of Gene-Environment Interactions Between Cadmium Exposure and Apolipoprotein E4 on Memory in a Mouse Model of Alzheimer's Disease. *Toxicological Sciences*. 2020 2020;173(1): 189-201. doi:10.1093/toxsci/kfz218

275. Panitch R, Sahelijo N, Hu J, et al. APOE genotype-specific methylation patterns are linked to Alzheimer disease pathology and estrogen response. *Transl Psychiatry*. Feb 29 2024;14(1):129. doi:10.1038/s41398-024-02834-x

276. Cochran JN, Geier EG, Bonham LW, et al. Non-coding and Loss-of-Function Coding Variants in TET2 are Associated with Multiple Neurodegenerative Diseases. *Am J Hum Genet*. May 7 2020;106(5) :632-645. doi:10.1016/j.ajhg.2020.03.010

277. Armstrong MJ, Jin Y, Vattathil SM, et al. Role of TET1-mediated epigenetic modulation in Alzheimer's disease. *Neurobiol Dis*. Sep 2023;185 :106257. doi:10.1016/j.nbd.2023.106257

278. Park H, Shin J, Kim Y, Saito T, Saido TC, Kim J. CRISPR/dCas9-Dnmt3a-mediated targeted DNA methylation of APP rescues brain pathology in a mouse model of Alzheimer's disease. *Transl Neurodegener*. Sep 15 2022;11(1):41. doi:10.1186 /s40035-022-00314-0

279. Santana DA, Smith MAC, Chen ES. Histone Modifications in Alzheimer's Disease. *Genes (Basel)*. Jan 29 2023;14(2)doi:10.3390/genes14020347

280. De Jager PL, Srivastava G, Lunnon K, et al. Alzheimer's disease: early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci. *Nat Neurosci*. Sep 2014;17(9):1156-63. doi: 10.1038/nn.3786

281. Zheng Y, Sanchez-Guerra M, Zhang Z, et al. Traffic-derived particulate matter exposure and histone H3 modification: A repeated measures study. *Environ Res*. Feb 2017;153:112-119. doi:10. 1016/j.envres.2016.11.015

282. Ding R, Jin Y, Liu X, et al. Dose- and time-effect responses of DNA methylation and histone H3K9 acetylation changes induced by traffic-related air pollution. *Sci Rep*. Mar 3 2017;7:43737. doi:10.1038/srep43737

283. Jiang X, Liu B, Nie Z, et al. The role of m6A modification in the biological functions and diseases. *Signal Transduct Target Ther*. Feb 21 2021;6(1):74. doi:10.1038/s41392-020-00450-x

284. Wang S, Lv W, Li T, et al. Dynamic regulation and functions of mRNA m6A modification. *Cancer Cell Int*. Jan 29 2022;22(1):48. doi:10.1186/s12935-022-02452-x

285. Zhu X, Fu H, Sun J, Xu Q. Interaction between N6-methyladenosine (m6A) modification and environmental chemical-induced diseases in various organ systems. *Chem Biol Interact*. Mar 1 2023;373:110376. doi:10.1016/j.cbi.2023.110376

286. Li Z, Su Q, Xu R, et al. Effect of acute PM(2.5) exposure on PTGS2 and RNA m6A modification. *Environ Pollut*. Oct 15 2023;335:122264. doi:10.10 16/j.envpol.2023.122264

287. Wu T, Liu B, Wei Y, Li Z. TGF-beta Regulates m(6)A RNA Methylation after PM(2.5) Exposure. *Toxics*. Dec 16 2023;11(12)doi:10.3390/toxics11121026

288. Huang H, Camats-Perna J, Medeiros R, Anggono V, Widagdo J. Altered Expression of the m6A Methyltransferase METTL3 in Alzheimer's Disease. *eNeuro*. Sep/Oct 2020;7(5)doi:10.1523/ENEURO.0125-20.2020

289.Zhao F, Xu Y, Gao S, et al. METTL3-dependent RNA m(6)A dysregulation contributes to neurodegeneration in Alzheimer's disease through aberrant cell cycle events. *Mol Neurodegener.* Sep 30 2021;16(1):70. doi:10.1186/s13024-021-00484-x

290.Shafik AM, Zhang F, Guo Z, et al. N6-methyladenosine dynamics in neurodevelopment and aging, and its potential role in Alzheimer's disease. *Genome Biol.* Jan 5 2021;22(1):17. doi:10.1186/s13059-020-02249-z

291.Miguel V, Lamas S, Espinosa-Diez C. Role of non-coding-RNAs in response to environmental stressors and consequences on human health. *Redox biology.* 2020/10// 2020;37:101580. doi:10.1016/j.redox.2020.101580

292.Diao Q, Qin X, Hu N, et al. Long non-coding RNAs mediate the association between short-term PM2.5 exposure and circulating biomarkers of systemic inflammation. *Environmental Pollution.* 2023/10/15/ 2023;335:122299. doi:10.1016/j.envpol.2023.122299

293.Aghaei-Zarch SM, Alipourfard I, Rasoulzadeh H, et al. Non-coding RNAs: An emerging player in particulate matter 2.5-mediated toxicity. *Int J Biol Macromol.* 2023/04/30/ 2023;235:123790. doi:10.1016/j.ijbiomac.2023.123790

294.Zheng R, Gao F, Xiao Y, et al. PM2.5-derived exosomal long noncoding RNA PAET participates in childhood asthma by enhancing DNA damage via m6A-dependent OXPHOS regulation. *Environment International.* 2024 2024;183:108386. doi:10.1016/j.envint.2023.108386

295.Wang L, Rowe RG, Jaimes A, et al. Small-Molecule Inhibitors Disrupt let-7 Oligouridylation and Release the Selective Blockade of let-7 Processing by LIN28. *Cell Rep.* Jun 5 2018;23(10):3091-3101. doi:10.1016/j.celrep.2018.04.116

296.Lee JM, Lee JH, Kim YJ. Blockade on Lin28a Prevents Cognitive Impairment and Disruption of the Blood-Brain Barrier Induced by Chronic Cerebral Hypoperfusion. *Biomedicines.* Apr 5 2022;10(4)doi:10.3390/biomedicines10040852

297.Motta V, Angelici L, Nordio F, et al. Integrative Analysis of miRNA and inflammatory gene expression after acute particulate matter exposure. *Toxicol Sci.* Apr 2013;132(2):307-16. doi:10.1093/toxsci/kft013

298.Luo F, Wu Y, Li Y, et al. PM2.5 regulates the progression of lung adenocarcinoma through the axis of HCG18, miR-195 and ATG14. *Clin Exp Pharmacol Physiol.* 2024/06// 2024;51(6):e13861. doi:10.1111/1440-1681.13861

299.Cao J, Huang M, Guo L, et al. MicroRNA-195 rescues ApoE4-induced cognitive deficits and lysosomal defects in Alzheimer's disease pathogenesis. *Molecular Psychiatry.* 2021/09// 2021;26(9):4687-4701. doi:10.1038/s41380-020-0824-3

300.Hoogmartens J, Cacace R, Van Broeckhoven C. Insight into the genetic etiology of Alzheimer's disease: A comprehensive review of the role of rare variants. *Alzheimers Dement (Amst).* 2021;13(1):e12155. doi:10.1002/dad2.12155

301.Giau VV, Bagyinszky E, Yang YS, Youn YC, An SSA, Kim SY. Genetic analyses of early-onset Alzheimer's disease using next generation sequencing. *Sci Rep.* Jun 10 2019;9(1):8368. doi:10.1038/s41598-019-44848-2

302.Cacace R, Sleegers K, Van Broeckhoven C. Molecular genetics of early-onset Alzheimer's disease revisited. *Alzheimers Dement.* Jun 2016;12(6):733-48. doi:10.1016/j.jalz.2016.01.012

303.Genin E, Hannequin D, Wallon D, et al. APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry.* Sep 2011;16(9):903-7. doi:10.1038/mp.2011.52

304.Yaghmoor F, Noorsaeed A, Alsaggaf S, et al. The Role of TREM2 in Alzheimer's Disease and Other Neurological Disorders. *J Alzheimers Dis Parkinsonism.* Nov 2014;4(5)doi:10.4172/2161-0460.1000160

305.Kiianitsa K, Lukes ME, Hayes BJ, et al. TREM2 variants that cause early dementia and increase Alzheimer's disease risk affect gene splicing. *Brain.* Jul 5 2024;147(7):2368-2383. doi:10.1093/brain/awae014

306. Barber IS, Braae A, Clement N, et al. Mutation analysis of sporadic early-onset Alzheimer's disease using the NeuroX array. *Neurobiol Aging*. Jan 2017;49:215 e1-215 e8. doi:10.1016/j.neurobiolaging.2016.09.008

307. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. Nat Genet. Mar 2019;51(3):414-430. doi:10.1038/s41588-019-0358-2

308. Konig T, Wurm R, Parvizi T, et al. C9orf72 repeat length might influence clinical sub-phenotypes in dementia patients. *Neurobiol Dis*. Dec 2022;175:105927. doi:10.1016/j.nbd.2022.105927

309. Guerreiro RJ, Lohmann E, Kinsella E, et al. Exome sequencing reveals an unexpected genetic cause of disease: NOTCH3 mutation in a Turkish family with Alzheimer's disease. *Neurobiol Aging*. May 2012;33(5):1008 e17-23. doi:10.1016/j.neurobiolaging.2011.10.009

310. Armstrong MJ, Jin Y, Allen EG, Jin P. Diverse and dynamic DNA modifications in brain and diseases. *Hum Mol Genet*. Nov 21 2019;28(R2):R241-R253. doi:10.1093/hmg/ddz179

311. Wightman DP, Jansen IE, Savage JE, et al. A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. *Nat Genet*. Sep 2021;53(9):1276-1282. doi:10.1038/s41588-021-00921-z

312. Giri M, Zhang M, Lu Y. Genes associated with Alzheimer's disease: an overview and current status. *Clin Interv Aging*. 2016;11:665-81. doi:10.2147/CIA.S105769

313. Bellenguez C, Kucukali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet*. Apr 2022;54(4):412-436. doi:10.1038/s41588-022-01024-z

314. (NIAGADS) NIoAGoAsDDSS. Top Variants List from the Alzheimer's Disease Sequencing Project Genome Variant Call.
https://adsp.niagads.org/gvc-top-hits-list/

315. Wu J, Grande G, Stafoggia M, et al. Air pollution as a risk factor for Cognitive Impairment no Dementia (CIND) and its progression to dementia: A longitudinal study. *Environ Int*. Feb 2022;160:107067. doi:10.1016/j.envint.2021.107067

316. Ronaldson A, Stewart R, Mueller C, et al. Associations between air pollution and mental health service use in dementia: a retrospective cohort study. *BMJ Ment Health*. Jul 2023;26(1) doi:10.1136/bmjment-2023-300762

317. Hu J, Zhang H, Chen S, et al. Identifying PM2.5 and PM0.1 sources for epidemiological studies in California. *Environ Sci Technol*. May 6 2014;48(9):4980-90. doi:10.1021/es404810z

318. Calderon-Garciduenas L, Reynoso-Robles R, Gonzalez-Maciel A. Combustion and friction-derived nanoparticles and industrial-sourced nanoparticles: The culprit of Alzheimer and Parkinson's diseases. *Environ Res*. Sep 2019;176:108574. doi:10.1016/j.envres.2019.108574

319. Lu D, Luo Q, Chen R, et al. Chemical multi-fingerprinting of exogenous ultrafine particles in human serum and pleural effusion. *Nat Commun*. May 22 2020;11(1):2567. doi:10.1038/s41467-020-16427-x

320. Kreyling WG, Moller W, Holzwarth U, et al. Age-Dependent Rat Lung Deposition Patterns of Inhaled 20 Nanometer Gold Nanoparticles and their Quantitative Biokinetics in Adult Rats. *ACS Nano*. Aug 28 2018;12(8):7771-7790. doi:10.1021/acsnano.8b01826

321. Lopez-Granero C, Polyanskaya L, Ruiz-Sobremazas D, Barrasa A, Aschner M, Alique M. Particulate Matter in Human Elderly: Higher Susceptibility to Cognitive Decline and Age-Related Diseases. *Biomolecules*. Dec 26 2023;14(1)doi:10.3390/biom14010035

322. Costa LG, Cole TB, Dao K, Chang YC, Coburn J, Garrick JM. Effects of air pollution on the nervous system and its possible role in neurodevelopmental and neurodegenerative disorders. *Pharmacol Ther*. Jun 2020;210:107523. doi:10.1016/j.pharmthera.2020.107523

323.Russ TC, Reis S, van Tongeren M. Air pollution and brain health: defining the research agenda. *Curr Opin Psychiatry.* Mar 2019;32(2):97-104. doi: 10.1097/YCO.0000000000000480

324.Cho J, Sohn J, Noh J, et al. Association between exposure to polycyclic aromatic hydrocarbons and brain cortical thinning: The Environmental Pollution-Induced Neurological EFfects (EPINEF) study. *Sci Total Environ.* Oct 1 2020;737:140097. doi:10.1016/j.scitotenv.2020.140097

325.Kaumbekova S, Torkmahalleh MA, Shah D. Ambient Benzo[a]pyrene's Effect on Kinetic Modulation of Amyloid Beta Peptide Aggregation: A Tentative Association between Ultrafine Particulate Matter and Alzheimer's Disease. *Toxics.* Dec 14 2022;10(12)doi:10.3390/toxics10120786

326. Environment. EPARot. Sulfur Dioxide Emissions. https://cfpub.epa.gov/roe/indicator.cfm?i=22

327.Tapia V, Carbajal L, Vasquez V, et al. [Traffic regulation and environmental pollution by particulate material (2.5 and 10), sulfur dioxide, and nitrogen dioxide in Metropolitan Lima, Peru]. *Rev Peru Med Exp Salud Publica.* Apr-Jun 2018;35(2):190-197. Reordenamiento vehicular y contaminacion ambiental por material particulado (2,5 y 10), dioxido de azufre y dioxido de nitrogeno en Lima Metropolitana, Peru. doi:10.17843/rpmes p.2018.352.3250.

328.Gaffney JS, Marley NA. Atmospheric chemistry and air pollution. *ScientificWorldJournal.* Apr 7 2003;3:199-234. doi:10.1100/tsw.2003.18