Proceedings of the Global Public Health Conference, Vol. 8, Issue 1, 2025, pp.53-70

ISSN 2613-8417 online
DOI: https://doi.org/10.17501/26138417.2025.8105

CHRONIC EXPOSURE TO AMBIENT AIR POLLUTION AND ALZHEIMER'S DISEASE: A NARRATIVE REVIEW

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Abstract: Ambient air pollution is a global threat in the 21st century, and its relationship to human health has been the focus of increasing research. The effects on development of Alzheimer's disease and cognitive impairment, however, have not been extensively researched. Information is sparse on whether there is an association and what exactly the mechanism of insult might be. Meanwhile, global life expectancy and the incidence of Alzheimer's disease as a cause of elderly dementia are on the rise. This study aims to explore the association between Alzheimer's disease and chronic exposure to ambient air pollution. PubMed and Embase were queried with the following string: Air AND (pollution OR PM2.5 OR PM10 OR NO2 OR SO2 OR carbon monoxide OR ozone) AND (Alzheimer OR dementia OR cognition OR cognitive decline) for papers published between 2020 and 2024. 36 articles meeting review criteria were found, and 8 articles were selected for contextual information. The simple answer was yes; ambient air pollution, most often PM2.5, appears to increase the risk for dementia and cognitive decline. Insights into mechanisms were also found, including direct deposition of particles and cortical atrophy. There is even some evidence that the damage is attenuable. However, the study has limitations as there has been no statistical analysis of the studies presented, and the search criteria were not created in accordance with any standard. As countries tend toward clean air, further research into the prevention of air pollution related cognitive impairment is warranted. The greatest gap in research is in prevention, though one study herein suggests a strong policy enforced by governments may help prevent excess cases of Alzheimer's disease due to air pollution.

Keyword: environmental health, cognitive decline, air pollution, dementia, Alzheimer's disease

Introduction

Air pollution may be the greatest common foe of humanity in the 21st century. Massive organizations such as the World Health Organization (WHO), Health Effects Institute (HEI), and American Lung Association (ALA) have spent significant efforts fighting it. The main components of ambient, outdoor air pollution are particulate matter (PM) less than 2.5 or 10 micrometers in diameter ($PM_{2.5}$, PM_{10} respectively), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO) (WHO, 2021). PM is a catch-all category, with PM_{10} being made up of 50-80% $PM_{2.5}$, and $PM_{2.5}$ containing a heterogeneous mixture of chemicals (WHO, 2021; WHO, 2024). For the most part, $PM_{2.5}$ is produced by fossil fuel, coal and wood burning and is made up by black carbon, carbon monoxide, sulfates, nitrates, metals and water (HEI, 2024; WHO 2024) PM_{10} comes from similar sources and, aside from $PM_{2.5}$, is usually composed of coarse ash, smoke, dust or pollen (ALA, 2024). Nitrogen and sulfur oxides (NO_x, SO_x, including the dioxides) are produced most directly by the burning of gasoline or diesel by vehicles (ALA, 2024) and their reaction with other ambient volatile chemicals and sunlight produces ground level ozone (HEI, 2024). These chemicals' concentration in the air contribute to the air quality index (AQI), a rough but practically useful measurement (US EPA, n.d.). According to the United States Environmental Protection Agency (US EPA), the AQI is determined by the pollutant in

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its highest value bracket; in other words, a high AQI only certainly reflects a high concentration of one pollutant, but a low AQI excludes high concentrations of any pollutant (US EPA, n.d.). But there is a disconnect between the reporting of air quality, specifically the moderate category, and the true disease burden of pollutants. For example, 24-hour $PM_{2.5}$ concentrations of 9.1-35.4 μg m^{-3} is a "moderate" level of air pollution according to the EPA in 2024 (US EPA, n.d.), but the WHO target goal for clean air is 24-hour $PM_{2.5}$ under 15 μg m^{-3} with this target being exceeded under four days per year (HEI, 2024). Thus if $PM_{2.5}$ is the main pollutant in an area, four days of moderate level AQI in a year can reflect meaningfully unhealthy levels of pollution (WHO, 2021). The air quality guideline (AQG) designated by the WHO also designates an annual ambient $PM_{2.5}$ (below 5 μg m^{-3}) target; these targets are based on comprehensive systematic reviews and meta-analyses which found high quality evidence that air above these targets is significantly hazardous to human health (WHO, 2021). This clarifies that an unassuming AQI does not necessarily mean healthy air, and that AQG cutoffs are more specific measures per pollutant. In 2019, the WHO reported that 99% of humans live in areas with air pollution exposures above AQG levels, although 81% are meeting the more lenient interim target levels (WHO, 2021). The youngest and oldest of society are most greatly impacted by these pollutants, especially in urban areas (ALA, 2024; HEI, 2024). While the numbers seem grim, improvements are being made across the globe. Household burning of solid fuels, the main source of indoor air pollution and a large contributor to outdoor air pollution, has decreased globally between 2010 and 2020, as has the total amount of $PM_{2.5}$ in the atmosphere (HEI, 2024). Even so, an estimated 47% of the global population and 95% in some African countries are reliant on solid fuel for cooking and $PM_{2.5}$ levels remain high in Asia, Africa, and the Middle East (HEI, 2024). Great strides have been taken to reduce the amount of pollution humanity is exposed to through policy and guidelines, but there is yet room to clean the air.

Dementia is a growing problem in the world, and Alzheimer's disease (AD) is the most common cause of dementia (Fan *et al.* 2020; Zhang *et al.* 2024). It is a disease most recognizably characterized by progressive memory loss and cognitive impairment in elderly patients with psychotic symptoms, behavioral changes and mood dysregulation developing late in the course of the disease (Zhang *et al.* 2024). Other symptoms can include impairments in visual-spatial, language, motor, and executive functioning (Zhang *et al.* 2024). The earliest stages of AD are nonspecific and can include a depressed mood, anxiety and sleep disturbances that can easily be interpreted as elderly depression (Zhang *et al.* 2024). A finding more concerning for AD is a mild cognitive impairment, which, despite its name, is a pathological process that is not age appropriate and heralds the development of dementia (Monfared *et al.* 2023; Zhang *et al.* 2024). The disease is relentless in its course but with an insidious development, and late stage diagnosis often leads to poor prognosis (Zhang *et al.* 2024).

The pathogenesis of AD is complex with numerous proposed mechanisms and new mechanisms being elaborated constantly (Fan *et al.* 2020; Zhang *et al.* 2024). The classic theory revolves around a pathologic variant of amyloid beta, amyloid beta-42 ($A\beta_{42}$) formed by alternate hydrolysis of a cell membrane protein, amyloid precursor protein (APP) (Fan *et al.* 2020; Zhang *et al.* 2024). Physiologically, APP is cleaved by α-secretase and then by γ-secretase, which produces non-cytotoxic soluble fragments (Fan *et al.* 2020). Pathologically, APP is cleaved by β-secretase and then by γ-secretase, which produces $A\beta_{42}$, which is prone to formation of insoluble aggregates and soluble oligomers (Fan *et al.* 2020). The soluble oligomers are the most cytotoxic, but the insoluble aggregates form the hallmark senile plaques of AD (Fan *et al.* 2020; Zhang *et al.* 2024). Aβ42 also accelerates hyperphosphorylation of τ protein, an axonal microtubule protein and another major player in the development of AD (Fan *et al.* 2020). Hyperphosphorylated τ proteins detach from microtubules, form cytotoxic neurofibrillary tangles (NFTs) and have a strong correlation with the development of clinical symptoms in AD (Fan *et al.* 2020; Zhang *et al.* 2024). Both of these pathologic proteins can spread in a prion-like manner, corrupting their physiologic counterparts and forming further aggregates (Fan *et al.* 2020). They have long been held as the main contributors to widespread neurodegeneration, especially pronounced in cholinergic neurons of the nucleus basalis of Meynert (NBM) (Zhang *et al.* 2024). The pathogenesis of AD is complex and there are other hypotheses, all likely contributory to the final neurodegenerative picture. Notably in the context of air pollution are the neuroinflammatory, oxidative stress and metal ion hypotheses (Zhang *et al.* 2024). Some implicated cell signaling pathways include apolipoprotein E (APOE) mediated cholesterol metabolism, mitochondrial dysfunction and N-methyl-D-aspartate receptor (NMDAR) mediated dysfunction in calcium signaling (Zhang *et al.* 2024).

Because of insidious onset, guidelines have come to recommend clinicians screen all patients with concern for MCI using brief cognitive tests such as the mini-Mental Status Examination (MMSE), but laboratory tests and imaging are not generally recommended for screening (Monfared *et al.* 2023). Most organizations agree diagnostic testing should aim to rule out other, possibly reversible causes of cognitive impairment including metabolic disturbances, psychiatric disorders, and other neurological disorders (Monfared *et al.* 2023). Testing for AD biomarkers is controversial and the general recommendation is to not use laboratory tests in routine diagnosis (Monfared *et al.* 2023). Some organizations recommend analyzing the cerebrospinal fluid (CSF) of patients with dementia for AD biomarkers such as $A\beta_{42}$, phosphorylated and total τ protein, but none of these values can predict the progression of the disease (Monfared *et al.* 2023). They are, however, useful in distinguishing AD from other causes of dementia (Zhang *et al.* 2024). Recommendations for use of magnetic resonance imaging (MRI) and positron emission tomography (PET) in the diagnosis are similarly mixed (Monfared *et al.* 2023); 18-fluorodeoxyglucose (18-FDG) PET can evaluate AD related changes in glucose metabolism

and structural MRI (sMRI) can evaluate for hippocampal atrophy, but neither of these tests is specific enough to rule out other causes of dementia (Zhang *et al.* 2024).

The mainstays for treatment for AD are acetylcholinesterase (AchE) inhibitors (donepezil, galantamine, rivastigmine, etc.) and the NMDA receptor antagonist memantine (Monfared *et al.* 2023), but these medications do not alter the course of the disease (Zhang *et al.* 2024). Treatment is not recommended for MCI in the early stages of disease (Monfared *et al.* 2023). Several monoclonal antibodies against $A\beta_{42}$ including such as aducanumab, lecanemab, and donanemab have been shown to be effective in decreasing $A\beta_{42}$ plaque burden, but their long term clinical efficacy is unclear (Zhang *et al.* 2024). There are many drugs being evaluated for use in AD, especially in the early stages where disease modification may be possible, but concrete treatment thus far remains symptomatic (Monfared *et al.* 2023; Zhang *et al.* 2024).

Materials and Methods

We searched Pubmed (MEDLINE) and Embase with the following basic string: Air AND (pollution OR $PM_{2.5}$ OR PM_{10} OR NO_2 OR SO_2 OR carbon monoxide OR ozone) AND (Alzheimer OR dementia OR cognition OR cognitive decline), with the filters: Clinical Trial, Controlled Clinical Trial, Observational Study, Randomized Controlled Trial, in the last 5 years. A total of 128 articles were collected excluding duplicates. Articles were excluded by title alone if it did not focus on air pollution. Literature reviews, systemic reviews, and meta-analyses were excluded. Articles focusing on communicable diseases were excluded. Studies with total participants under 30 were excluded. Studies focused on indoor air pollutants, household air pollution and acute exposure (biomass burning stoves, inflammatory markers before and after exposure to pollutants) were removed. Articles about water or soil pollution but not air pollution were removed. Crossover studies focusing on acute exposure were removed. Studies focused on hospital and healthcare expenditures were excluded. Industry and occupational specific articles were removed. Several studies that should not have passed the search filters (surgical topics) were excluded. Final result: 36 studies for review and several selected studies for background info.

Results and Discussion

Evidence of the Connection

We will focus on presenting the chief findings with brief explanations and the statistical results in the form of odds ratio (OR), hazard ratio (HR), risk ratio (RR), their adjusted forms (aOR, aHR, aRR) and

correlation coefficient β. All confidence intervals are 95% unless otherwise stated, and all p-values are below 0.05% unless otherwise stated.

East Asia: Prospective Studies

Several prospective studies from China and Taiwan have presented associations between air pollution and cognitive impairment in adults over 65 years old. The first study, from Taiwan, found that chronic exposure to ambient $PM_{2.5}$ over 29.98 μg m^{-3} was associated with an increased risk of global cognitive impairment (Chen *et al.* 2020). Notably the level of $PM_{2.5}$ found to be associated with cognitive impairment is within the AQI category of "moderate" (US EPA, n.d.). The second study comes from China and found the risk of cognitive impairment increased with exposure to $PM_{2.5}$, and SO_2 (He *et al.* 2020) This study did not find similar relationships with NO_2, CO, O_3, or the AQI (He *et al.* 2020). Cognitive status was measured using the Chinese MMSE (He *et al.* 2020). The next study reported people living in areas with the highest quintile of chronic $PM_{2.5}$ exposure (62-106 μg m^{-3}) compared to the lowest (9-38 μg $m^{-3)}$ were at higher risk for cognitive impairment, defined as MMSE score below 18 (Zhu *et al.* 2022). These researchers also found a roughly 10% increase in risk of cognitive impairment per 10 μg m^{-3} increase in $PM_{2.5}$, and that the hazard was especially pronounced in people with low plant based dietary intake (Zhu *et al.* 2022).

Table 1: Prospective Studies from East Asia

Author, year	Key findings	Pollutant(s)	Quantitative measures
Chen *et al.* 2020	Cognitive impairment	$PM_{2.5}$	aOR 4.56 (1.51, 13.82)
He *et al.* 2020	Cognitive impairment	$PM_{2.5}$	aOR 1.04 (1.01, 1.08)
		PM_{10}	aOR 1.03 (1.001, 1.06)
		SO_2	aOR 1.04 (1.01, 1.08)
Zhu *et al.* 2022	Cognitive impairment	$PM_{2.5}$	HR 1.46 (1.20, 1.77)

East Asia: Retrospective Studies

The first study comes from Hong Kong and reported increased odds of dementia mortality related to increasing O3 exposure and regional air pollution (Ho et al. 2020). Regional air pollution in this study is the term they used to describe PM2.5 (Ho et al. 2020). They also note findings suggesting chronic PM10 and NOx exposure had a stronger link to all-cause mortality than development of dementia, and that social isolation had a stronger link to dementia than any air pollutant (Ho et al. 2020). A Taiwanese

study found an increasing risk for AD with increased baseline O3 concentration per 9.63 ppb (Jung et al. 2020). Furthermore, they found an increased risk of AD per increase of 10.91 ppb in O3 and 4.34 μg m-3 in PM2.5 over the course of the study (Jung et al. 2020). Another Taiwanese study found increases in the concentration of PM2.5 increased the risk of dementia by approximately 11% per interquartile range (IQR) increase when considering SO2 in the regression model (Yan et al. 2022). This meant the combination of SO2 and PM2.5 was the strongest predictor of dementia development in this study group (Yan et al. 2022). Lastly, a study of stroke patients from Taiwan, found that PM2.5 increased the odds of subsequent development of dementia, as did NOx after a stepwise logistic regression model controlling for age, gender, other comorbidities, PM2.5 and NOx (Lee et al. 2023).

Table 2: Retrospective Cohort Studies from East Asia

Author, year	Key findings	Pollutant(s)	Quantitative measures
Ho *et al.* 2020	Dementia	$PM_{2.5}$	OR 1.24 (1.13, 1.37)
		O_3	OR 1.03 (1.01, 1.05)
Jung *et al.* 2020	AD	$PM_{2.5}$	RR 2.38 (2.21, 2.56)
		O_3	aHR 3.12 (2.92, 3.33)
Yan *et al.* 2022	Dementia	$PM_{2.5} + SO_2$	HR 1.11 (1.10, 1.12)
Lee *et al.* 2023	Dementia post stroke	$PM_{2.5}$	aOR 1.05 (1.04, 1.06)
		NO_x	aOR 1.041 (1.02, 1.06)

East Asia: Quasi-Experimental Study

The last East Asian study comes from China and was labeled "quasi-experimental" by the authors. Patients were separated into control (Chinese provinces) and intervention (provinces in which the Chinese Government set a target of reducing PM concentrations by more than 5% annually from 2014 onward) groups (Yao *et al.* 2022). The intervention group had a significantly smaller decline in MMSE scores from 2014 to 2018 compared with the control group: the mean between-group difference was 2.45 points on the MMSE (95% CI 1.32–3.57) (Yao *et al.* 2022). There was a MMSE score decrease of 0.83 points (95% CI 0.24–1.42) per IQR increase in $PM_{2.5}$; similarly, IQR increases in SO2 were also associated with a significant MMSE score decline of 0.80 points (95% CI 0.32–1.29). What is remarkable about this study is that it shows an example of a government's actions against air pollution directly benefiting its people (Yao *et al.* 2022).

The World: Prospective Studies

All three prospective studies reported HRs. The first study comes from the US and focused on a Hispanic population (Paul *et al.* 2020). They found that higher ambient NO_x exposure was associated with increased incident dementia between the highest and lowest tertiles of NO_x concentration (Paul *et al.* 2020). Notably, higher NO_x concentrations also increased the risk for type II diabetes mellitus

(T2DM), and they estimated that 20% of the observed hazard for dementia in this group is due to T2DM caused by pollution, not directly (Paul *et al.* 2020). The next two studies used the United Kingdom (UK) Biobank for information. One group found individuals living in areas with ambient $PM_{2.5}$ levels over 10 μg m^{-3} are at higher risk of developing dementia, as are those exposed to ambient NOx levels over 50 μg m^{-3} (Yuan *et al.* 2023). The next found that the risk for development of dementia following a stroke increased in proportion to increasing air pollution (Wang *et al.* 2024).

Table 3: Prospective Studies from the World

Author, year	Key findings	Pollutant(s)	Quantitative measures
Paul *et al.* 2020	Dementia	NO_x	HR 1.55 (1.04, 2.55)
Yuan *et al.* 2023	Dementia	$PM_{2.5}$	HR 1.10 (1.05, 1.28)
		NO_x	HR 1.14 (1.02, 1.26)
Wang *et al.* 2024	Dementia	$PM_{2.5}$	HR 1.38 (1.15, 1.65)

The World: Retrospective Studies

A cohort of Hispanic adults from San Diego, California was found to have worsening verbal fluency for every 10 μg m-3 increase in PM2.5 (Ilango et al. 2020). They also found for every 10 ppb increase in O3, verbal fluency and executive function both worsened (Ilango et al. 2020). They did not, however, discover a correlation between pollution and cognitive decline (Ilango et al. 2020). Another study from the US, this time a sample with a wide geographic and ethnic distribution, found a correlation between incidence of dementia and O3 levels, but not with PM (Cleary et al. 2020). Specifically, they found that for individuals with baseline MMSE > 26, the correlation of increased O3 with cognitive decline was statistically significant (Cleary et al. 2020). The next US study added education to the question and found PM2.5 was unrelated to incident cognitive impairment among those with 13 or more years of education (Ailshire and Walsemann, 2020). The probability of impairment increased, however, with greater concentrations of PM2.5 in individuals with 8 or less years of education (Ailshire and Walsemann, 2020).

One interesting study from the UK followed the Lothian birth cohort of 1936 (Russ et al. 2020). They found higher air pollution was associated with detriment to intelligence quotient (IQ) scores from age 11-70 years, but not from age 70-79 years (Russ et al. 2020). This study used historical data and estimates of air pollution at the time, it is difficult to say whether this finding is generalizable or reliable (Russ et al. 2020). A retrospective cohort study from Sweden showed increased odds of accelerated cognitive decline per IQR increase in PM2.5 concentrations up until the mean value of 8.6 μg m-3 for individuals older than 80 (Grande et al. 2020). There was no further increase in risk with increases of PM2.5 past the mean (Grande et al. 2020). Another study from Sweden focused on APOE ϵ4 carriers vs. noncarriers and how this genetic predisposition to AD might alter air pollution effect on

development of dementia in these groups (Oudin et al. 2020). They found air pollution was associated with increased dementia incidence, but there was no evidence for a modifying effect by APOE ε4 (Oudin et al. 2020).

A US study following adults 75 and older from the Ginkgo Memory study cohort found an increased risk of dementia associated with increasing concentrations of PM2.5, PM10, and NO2 (Ilango et al. 2023). The last US study actually separated and specified certain elements of PM2.5, including elemental (black) carbon (EC), variable NOx, silicon (Si) and more. IQR increases in EC (0.8 μg m-3) and Si (23.1 ng m-3) was associated with lower Cognitive Abilities Screening Instrument (CASI) scores in global cognitive function (Wang et al. 2023). For each IQR increase in Si, the odds of low cognitive function (LCF) across domains was also higher (Wang et al. 2023). NOx was associated with slower processing speed, assessed by digit symbol coding (DSC), and worse working memory, assessed by total digit span (DS) (Wang et al. 2023).

Table 4: Retrospective Studies from the World

Author, year	Key findings	Pollutant(s)	Quantitative measures
Ilango *et al.* 2020	Verbal fluency	$PM_{2.5}$	β: -0.21 (-0.68, 0.25)
	Verbal fluency Executive function	O_3	β: -0.19 (-0.34, -0.03)
		O_3	β: -0.01 (-0.01, 0.09)
Cleary *et al.* 2020	Dementia	O_3	β: –2.44 (No CI)
Ailshire and Walsemann, 2020	Dementia	$PM_{2.5}$	37% (No CI)
Russ *et al.* 2020	Decreased IQ	$PM_{2.5}$	β: –0.006 (SE 0.002)
Grande *et al.* 2020	Cognitive decline	$PM_{2.5}$	OR 1.81 (1.2, 3.2)
Oudin *et al.* 2020	Dementia	NO_x	HR 1.72 (0.94, 3.15)
Ilango *et al.* 2023	Dementia	$PM_{2.5}$	HR 1.55 (1.01, 2.18)
		PM_{10}	HR 1.31 (1.07, 1.60)

		NO_x	HR 1.18 (1.02, 1.37)
Wang *et al.* 2023	CASI score	EC	-1.27 (-0.09, -2.45)
	CASI score	Si	-0.88 (-0.21, -1.54)
	LCF	Si	OR 1.29 (1.04, 1.60)
	DSC score	NO_x	-2.01 (-3.50, -0.52)
	DS score	NO_x	-0.4 (-0.78, -0.01)

One Cross Sectional Study from Mexico

At last, a cross-sectional study in Mexico assessed the MoCA scores of metropolitan Mexico City (MMC) residents of all ages (Calderón-Garcidueñas et al. 2022a). They found residents over 31 years from the heavily polluted MMC had MoCA scores of 20.4 ± 3.4, and low pollution controls had 25.2 ± 2.4 (Calderón-Garcidueñas et al. 2022a). This study is one of the many great contributions by a certain group of researchers who have become central to this review (Calderón-Garcidueñas et al. 2022a).

Mechanisms

Mexico

A group of researchers in Mexico has carried out multiple studies detailing neurological findings in children and adults in MMC, Mexico. MMC is a densely populated area with some of the worst automobile and industrial emissions in the world (Calderón-Garcidueñas et al. 2020b). The first study of interest from MMC compared the Wechsler Intelligence Scale for Children (WISC-R) scores and University of Pennsylvania Smell Identification Test (UPSIT) for 22 children who were APOE ϵ4 carriers with a group of 28 children who were not (Calderón-Garcidueñas et al. 2020b). The children were aged roughly eight to eighteen (Calderón-Garcidueñas et al. 2020b). They found that the APOE ϵ4 children had significantly decreased scores of intelligence quotient (IQ), attention and short term memory compared to children with the ϵ3 allele and suggested that APOE ϵ4 positivity predisposes children to more harm from air pollution (Calderón-Garcidueñas et al. 2020b). However, this study has a small sample size and there is no clean air control (Calderón-Garcidueñas et al. 2020b). There were also alterations in various metabolic ratios, notably decreased N-acetylaspartate (NAA)/creatine (Cr) ratio which was the focus of their next study (Calderón-Garcidueñas et al. 2020b).

The next study followed APOE ϵ4 positive children and their parents from a low pollution city and from MMC (Calderón-Garcidueñas et al. 2020c). It was found that subjects in the more polluted area had a significantly lower hippocampal NAA/Cr ratio, correlating to greater τ burden and severity of dementia, which may make it a marker of early subclinical neurodegeneration in asymptomatic adults and children

as detailed in this study (Calderón-Garcidueñas et al. 2020c). They attribute this specifically to high levels of O3 and PM, which are higher in MMC than in Mexico (Calderón-Garcidueñas et al. 2020c; HEI, 2024). Their next study focused on various cerebrospinal fluid (CSF) biomarkers of neurodegeneration in young MMC patients compared to clean air controls (Calderón-Garcidueñas et al. 2020a). Of interest, they found decreased concentrations of Aβ42, as is seen in AD, in MMC residents compared to clean air controls (Calderón-Garcidueñas et al. 2020a). They found an increased burden of non-phosphorylated τ protein in the CSF of MMC children as well, compared to clean air children (Calderón-Garcidueñas et al. 2020d). This is a known marker of axonal damage seen in AD patients during cognitive decline (Calderón-Garcidueñas et al. 2020d). Another study of theirs found increased deposition of combustion derived nanoparticles (essentially PM) in the brains via transmission electron microscopy which they believe may cause oxidative stress and contribute to development of AD (González-Maciel et al. 2020). The team's research continued, and they found multiple areas of decreased cortical thickness, decreased caudate and cerebellar volumes in adult MMC residents, average age 33, compared to clean air controls (Calderón-Garcidueñas et al. 2022c). The strongest associations with poor cognitive assessment on the Montreal Cognitive Assessment tool (MoCA) were caudate and left orbital gyrus atrophy (Calderón-Garcidueñas et al. 2022c). Another of their studies found an increase in transactive response DNA-binding protein 43 (TDP-43) in the CSF of MMC adults and children, a finding seen in various neurodegenerative disorders (NDDs) including AD (Calderón-Garcidueñas et al. 2022d). These patients also had AD like cognitive defects (Calderón-Garcidueñas et al. 2022d). In another study of MMC adults and children, they found deposition of nanoparticles, including heavy metals along with alpha synuclein and phosphorylated τ protein in the locus coeruleus and substantia nigra pars compacta (Calderón-Garcidueñas et al. 2022b). Finally they found neurofibrillary tangles and heavy metal deposition in the brain matter of MMC children in forensic cases aged 10-20, especially Fe, Ti, and Ca (Calderón-Garcidueñas et al. 2023). Taken as a whole, this group's research is invaluable in painting a mechanism for the development of AD, as well as other NDDs, due to air pollution.

The World

Other researchers around the world have also found interesting phenomena which may explain how cognitive decline and AD arise due to air pollutants.

A retrospective cohort study of elderly women without dementia found inverse associations between PM2.5 exposure and white matter volumes in the brain as a whole and more specifically in the frontal, parietal, and temporal lobes (Chen et al. 2020). They found that higher levels of long chain omega-3 polyunsaturated fatty acid levels in red blood cells seemed to protect against this air pollution related cortical volume loss (Chen et al. 2020). Another retrospective cohort study in older women observed the relationship between air pollution, Mediterranean- Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet, and white matter volume loss (Chen et al. 2021). Per 3.22 μg m-3 increase in ambient PM2.5, total white matter volume loss was 4.16 cm3 (95% CI: -6.99, -1.33) and temporal lobe loss was 1.46 cm3 (95% CI: -2.16, -0.76) (Chen et al. 2021).

Several cross-sectional studies were found studying humans. The first measured CSF levels of biomarkers of vascular damage in people with and without MCI/AD who were exposed to pollution (Shaffer et al. 2020). In cognitively normal individuals, a 5 μg m-3 increase in average ambient PM2.5 was associated with elevated vascular cell adhesion molecule 1 (VCAM-1) levels. (51.8 (6.5, 97.1) ng L-3) (Shaffer et al. 2020). The same increase in PM2.5 was also associated with elevated e-selectin (53.3 (11.0, 95.5) pg L-3) (Shaffer et al. 2020). A study in Spain found exposure to increasing levels of NO2 was associated with reduced gray matter volume in the precuneus, while exposure to increasing levels of PM2.5 was actually associated increased white matter volume in certain areas of the brain. (Falcón et al. 2021). Another study aimed to associate de novo mutations in neuropsychiatric disorders with air pollutants, but did not find an association between ambient air pollution and de novo mutations in AD (Baker et al. 2023).

One randomized controlled trial studied the interaction between high intensity interval training's benefit on cognitive health and PM2.5 exposure's detriment to it (Liu et al. 2023). The study found the cognitive benefits of HIIT were attenuated or even reversed under high PM2.5 exposure (Liu et al. 2023).

The last study was a chemical simulation study from Kazakhstan, which found strong hydrophobic interactions between four Aβ42 peptides in solution with 5 mM benzo[a]pyrene, a common constituent of PM2.5 (Liu et al. 2023). In the simulation, this resulted in increased interpeptide electrostatic interactions, accelerated formation of the peptide tetramer by 30%, and stabilized C-terminus in Aβ42 peptides. These chemical changes are known to occur in natural AD (Kaumbekova et al. 2022)

Conclusion

There are several different conclusions that we hope the reader can draw from the research presented.

Foremost, the study of the relationship between air pollution and AD is underdeveloped. To be more precise, the pool of recent research is small. 16 of the sources presented come from Volume 8 of Advances in Alzheimer's Research. 10 of the articles investigating the mechanism of air pollution's impact on AD come from a single team of researchers. There should be impetus for other environmentalists and neuroscientists to join in this research, especially in the developing world. The search query and exclusion criteria we specified did not produce any articles written in Africa, the Middle East, or South Asia, which are the areas of the world with the highest levels of air pollution (HEI, 2024). This demonstrates a disconnect between the regions most affected by air pollution (Health Effects Institute, 2024; WHO 2024) and the study of dementia as a result. There is, however, a significant amount of research from those regions regarding cardiovascular and respiratory diseases as a result of air pollution. In any case, it seems research into the effects of air pollution on cardiopulmonary health is far more common than that investigating neurological disease.

From our review, it seems there is an observable connection between air pollution, accelerated cognitive impairment, and increased incidence of AD. There are several limitations to this conclusion. This is a narrative review and though defined search criteria was used, there has been no quantitative analysis of the data presented. The defined search criteria were also arbitrarily defined, not by any systematic

guidelines. There is an inherent risk of bias with this methodology, and the papers themselves were not evaluated for bias or quality.

Many of these studies were conducted by one group of researchers whose work built upon itself, and whose work is limited to one city (MMC). Several of the mechanistic studies measured cortical volume, which is nonspecific and does not necessarily indicate cognitive function (Chen et al. 2020; Chen et al. 2021; Falcón et al 2021; Calderón-Garcidueñas et al. 2022c). The biomarkers measured in several studies are not diagnostic of AD, nor can they specify a causal relationship between measured air pollutants and cognitive impairment (Calderón-Garcidueñas et al. 2020a, 2020c, 2020d; Shaffer et al. 2020; Calderón-Garcidueñas et al. 2022b, 2022d, Calderón-Garcidueñas et al. 2023). Conversely, some of these studies did find PM, heavy metals and other nanoparticles directly deposited in CNS which the researchers claim suggests a possible causative role (Calderón-Garcidueñas et al. 2020c, Calderón-Garcidueñas et al. 2022b, Calderón-Garcidueñas et al. 2023). It should be noted that most of the mechanistic studies were quite different from one another in what exact parameter they were measuring. There is a need for more consistent and replicable research into the chemical and physiological changes that have been observed. Ultimately, it can be said the epidemiological studies presented here do demonstrate a probable correlation between increasing air pollution and AD, but the mechanism is unclear.

Interestingly, it seems some of the more well-known effects of air pollution (cardiovascular, pulmonary, metabolic) may contribute more directly to AD in those exposed to pollutants than direct neurotoxicity of the pollutants themselves. This relationship is deserving of further investigation, as is the true in vivo mechanism of purported neurotoxicity by the constituents of air pollution. If one could measure the average concentration of PM2.5 constituents in a person's CSF or CNS parenchyma and then expose animal CNS tissues to the same or increasing concentrations of specific as well as mixed pollutants, then one might be able to narrow down a specific cytotoxic action. One could also test which PM chemicals easily cross the blood brain barrier. The fact that researchers found increased levels of heavy metals in MMC brains (Calderón-Garcidueñas et al. 2020c, Calderón-Garcidueñas et al. 2022b, Calderón-Garcidueñas et al. 2023) lends credit to the oxidative hypothesis of AD, maybe pollution contributes through this mechanism (Fan et al. 2020). Neuroinflammation and APOE dysfunction could also be caused by glial hyperresponsiveness to the presence of inappropriate PM2.5 constituents in polluted brain matter (Fan et al. 2020).

To close, there is hope shown by the study of Yao et al. 2022. They demonstrated that one government's order, that a certain province must reduce emissions by a specified amount at any cost, significantly altered the cognitive outcomes of that group compared to control (Yao et al. 2022). This means that while the global enemy of air pollution may seem insurmountable, it is possible if a nation decides to prioritize health over industry.

Acknowledgements

Acknowledgements to my mentor Dr. Chitra Pai for her wisdom and guidance. Acknowledgements to the teams led by Dr. Calderón-Garcidueñas, who contributed so much of the content of this review.

Declaration of Interest Statement

The authors declare that they have no conflict of interests.

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