ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Review

Investigating the Potential Impact of Air Pollution on Alzheimer's Disease and the Utility of Multidimensional Imaging for Early Detection

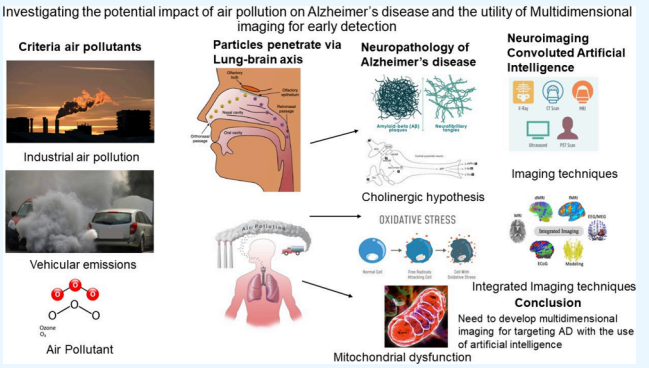
Ankul Singh S, Mohd Nazam Ansari, Gehan M. Elossaily, Chitra Vellapandian,* and Bhupendra Prajapati*

Cite This: *ACS Omega* 2024, 9, 8615−8631

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Pollution is ubiquitous, and much of it is anthropogenic in nature, which is a severe risk factor not only for respiratory infections or asthma sufferers but also for Alzheimer's disease, which has received a lot of attention recently. This Review aims to investigate the primary environmental risk factors and their profound impact on Alzheimer's disease. It underscores the pivotal role of multidimensional imaging in early disease identification and prevention. Conducting a comprehensive review, we delved into a plethora of literature sources available through esteemed databases, including Science Direct, Google Scholar, Scopus, Cochrane, and PubMed. Our search strategy incorporated keywords such as "Alzheimer Disease", "Alzheimer's", "Dementia", "Oxidative Stress", and "Phytotherapy" in conjunction with "Criteria Pollutants", "Imaging", "Pathology", and "Particulate Matter". Alzheimer's disease is not only a result of complex biological factors but is exacerbated by the infiltration of airborne particles and gases that surreptitiously breach the nasal defenses to traverse the brain, akin to a Trojan horse. Various imaging modalities and noninvasive techniques have been harnessed to identify disease progression in its incipient stages. However, each imaging approach possesses inherent limitations, prompting exploration of a unified technique under a single umbrella. Multidimensional imaging stands as the linchpin for detecting and forestalling the relentless march of Alzheimer's disease. Given the intricate etiology of the condition, identifying a prospective candidate for Alzheimer's disease may take decades, rendering the development of a multimodal imaging technique an imperative. This research underscores the pressing need to recognize the chronic ramifications of invisible particulate matter and to advance our understanding of the insidious environmental factors that contribute to Alzheimer's disease.



INTRODUCTION

Air pollution has been a matter of concern for decades. The environment is not as clean as it used to be in ancient times. Various diseases like ischemeic heart disease, chronic obstructive pulmonary disease, lung cancer, and acute lower respiratory infections in children are linked with air pollution, and Alzheimer's disease is also one among them.[1] Air pollution is a complicated mixture comprising carbon monoxide, particulate matter, lead, nitrogen dioxide, ozone, sulfur dioxide, and so on. Most significantly, the fine particulate matter with ≥2.5 μm diameter (PM2.5) is now considered as one of the most harmful factors affecting health.[2] According to a World Health Organization (WHO) analysis, in 2016 around 4.2 million people suffered from air pollution contributing to short lifespan, mostly due to PM2.5.[3] According to the air quality database, 98.0% cities in both low- and middle-income countries do not comply with air quality standards imposed by WHO. Yet, the percentage of those in high-income countries has declined to 56.0%.[4] Hazardous pollutants including benzene, formaldehyde, polycyclic aromatic hydrocarbons, toluene, tri- and tetrachloroethylene, volatile organic compounds, and metals such as arsenic, cadmium, cobalt, iron, lead, manganese, and mercury should also be monitored promptly owing to their effects.[5]

In contrast to other PM, ultrafine particulate matter can directly permeate without the assistance of other metals, enter the brain via the olfactory nerves, and enter the central nervous system (CNS) through systemic uptake, eventually causing

Received: August 28, 2023
Revised: December 25, 2023
Accepted: January 30, 2024
Published: February 15, 2024

inflammation and damage from oxidative stress.[6−8] The main exposure to air pollution for the urban population is mainly due to traffic-related dust on roads, and exposure is found to be highest near busy roads.[9] Human daily activities affect the air quality and lead to damage of surroundings and imbalances in the ecosystem.[10] According to the Global Burden of Diseases, the contaminated air itself accounts for roughly 80.0% of deaths, with rates in Southeast Asian and Western-Pacific nations being the highest.[11] The highest risk of PM exposure is also found in 18 out of 122 Indian cities for household particulate matter, which were found not to comply with WHO guidelines.[12]

Alzheimer's disease (AD) causes a decline in cognitive function in children, while neuropathological AD is seen in infants whose incidence and prevalence increase with age.[13−16] The risk of Alzheimer's is due to several genetic factors such as age, apolipoprotein E (APOE) 34 alleles, metabolism, and nongenetic factors such as education, environmental factors, oxidative stress, lifestyle modifications, and sex.[17−21] The importance in identifying the epidemiology and discovery of Alzheimer's lies in specific changes of pathology like senile plaques and neurofibrillary tangles.[22] Air pollution affecting CNS-related Alzheimer's is reported from various clinical, epidemiological, experimental, and observational studies.[23] Alzheimer's risk is early life exposure, which is suggested by the Latent Early-Life Associated Regulation Model, besides the two-hit theory, which includes both environmental and genetic risk factors[24,25]

Nevertheless, attention is kept toward environmental risk factors besides neurotoxins and their interaction with APOE alleles,[26,27] preferably in females compared to men due to the potentially increased Alzheimer's risk for E4 alleles; moreover, women also incur cardiopulmonary and neurological consequences from PM exposure.[28] However, it was also noteworthy that good air quality was observed during lockdown periods, and AQI data statistics after lockdown showed unhealthy air quality levels for the public to breathe, which is due to traffic related air pollution exposure.[29] Multiplexing in AD diagnosis involves simultaneously detecting multiple biomarkers to achieve early and precise identification of the disease, improving diagnostic accuracy and allowing for timely intervention. By analyzing a combination of biomarkers, patterns or signatures specific to the disease can be identified. These patterns can enhance the accuracy of diagnosis, as they consider multiple factors rather than relying on a single biomarker.[30] Multiplexing can reduce the risk of false positives and false negatives. By cross-referencing multiple biomarkers, the diagnostic criteria become more robust, decreasing the likelihood of misdiagnosis.[31] The aim of the current Review is to identify the major risk factors involved in the environment and its impact in Alzheimer's disease. It also focuses on the need to identify multidimensional imaging for early detection and prevention of disease progression.

CRITERIA AIR POLLUTANTS AND ALZHEIMER'S RISK MECHANISM: UNDERSTANDING THE LINK

The environmental pollution poses several risks to both health and the environment. Various criteria air pollutants, their risk levels, and their mechanism are explained clearly in Table 1 Greater exposure to PM2.5, PM10, and NO_2 to various degrees has been highly related with declines in cognitive function, executive function, memory, and language,[32] while a sufficient mechanism needs to be addressed. PM is mutagenic and can cause oxidative damage, activate inflammatory signal cascades, and trigger cell death.[33−35] PM2.5 is known to induce cytokine-dependent autophagy pathways, toll-like receptors, the Janus kinase-signal transducer pathway, and the cyclooxygenase 2 pathway.[36] It is also evidenced that, owing to the differences in men's and women's neural structures, women may be more at risk than men for decreased cognition linked to increased exposure to PM10 and PM2.5.[37] Generally, PM2.5 is associated with amyloid-β (Aβ) and α-synuclein aggregation[38,39] due to neuroinflammatory signals and oxidative stress including iNos and TNF- α,[40] which ultimately disrupts lipid peroxidase and GFAP levels leading to the destruction of hippocampal cells (Figure 2). Oxidative stress also leads to peripheral systemic inflammation-related neuronal injury via olfactory neurons, including oxidative stress-associated neurotoxicity and metabolic dysfunction.[41]

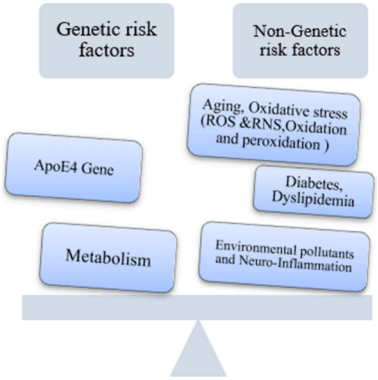


Figure 1. Exploring Alzheimer's disease risk factors: a blend of genetics and environment.

Environmental exposure and traffic-related exposure in children and the adult population have been found to modify DNA methylation essential for maintaining genomic integrity and regulating gene function.[42−45] Air pollutants target both the respiratory tract and brain through the olfactory axis, leading to microglial activation and the action of cytotoxic molecules in neuroinflammation and cell death.[46] In fact, studies on animals using diesel exhaust with high levels of ultrafine particles have demonstrated that oxidative stress, protein misfolding, and plaques all contribute to the link between black carbon (pollutant and PM) and Alzheimer's disease.[47−49] It is believed that the gas, particles, or material desorbed from the particle surface act to trigger inflammatory reactions, microglial activation, the generation of reactive oxygen species, and enhanced production and deposition of Aβ peptides when inhaled through the respiratory tract.[50] Air pollution has the potential to significantly affect the dementia risk globally for every 2 $\mu g/m^3$ increase in the average annual PM2.5 concentration.[51] Additionally, studies have demonstrated that the important Alzheimer's risk gene APOE4 interacts with airborne particles to hasten environmental risk caused by persistent PM2 and brain aging. Older women with two copies of the APOE4 gene had a 2−3× higher exposure compared to older women without the gene.[52] Therefore, after subacute ultrafine particle exposure, overexpression of Abcb1, which is crucial for brain protection by removing xenobiotics and harmful metabolites, is required.[53] As a crucial mediator, cerebralspinal fluid (CSF) sTREM2 established a clear connection between PM2.5 exposure and microglial dysfunc-

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631

Table 1. Summarizing Risk Factors and Possible Mechanisms of Criteria Air Pollutants

criteria pollutant	risk levels ($\mu g/m^3$)	Alzheimer's disease risk	mechanism	references
ozone (O_3)	23.368	211.0% risk in elderly	ozone is a powerful oxidizing molecule and soluble in water. it transfers from the respiratory system to the brain via the bloodstream. meanwhile, ozone inhalation creates reactive oxygen species (ROS) and causes oxidative stress, neuronal dysfunction, inflammation, and apoptosis in the brain. it also activates the amyloidogenic pathway, leading to overproduction of Aβ-42 and mitochondrial dysfunction.	58−60
nitrous oxide (NO_2)	20.527	5.0% risk in elderly	it is an irritating water-soluble gas that enters the brain via the respiratory tract−lung−bloodstream−brain pathway, besides the nose and olfactory pathway. it increases ROS production and causes damage in structure and mitochondrial dysfunction.	61−63
carbon monoxide (CO)	≥57.28	32.3% risk in dementia, 60% due to vehicles	ultrastructural changes in thrombus and kinetic of plasma coagulation by asphyxiant gas which is lower in summer. pleiotropic effect in cellular and mitochondrial levels. increased metabolic rate upon exposure, leading to ROS and oxidative stress.	64, 65
sulfur dioxide (SO_2)	≥57.28	3.0% mortality risk	neuroinflammation and abnormal signal transduction in the neuronal cytoplasm and gene transcription in the nucleus.	66, 67
particulate matter (PM)				
PM0.1 (ultra fine particles)	N/A	22.6% in AD risk for PM2.5	fine and ultrafine PM, the toxic one can get deposited efficiently through the respiratory tract and has a higher rate of translocation to organs like the brain and others or directly through the olfactory nerve. It can cross the bloodstream, leading to oxidative stress and mitochondrial damage.	68, 69
PM2.5 (fine particles)	≥2.82			
PM10 (coarse particles)	N/A			

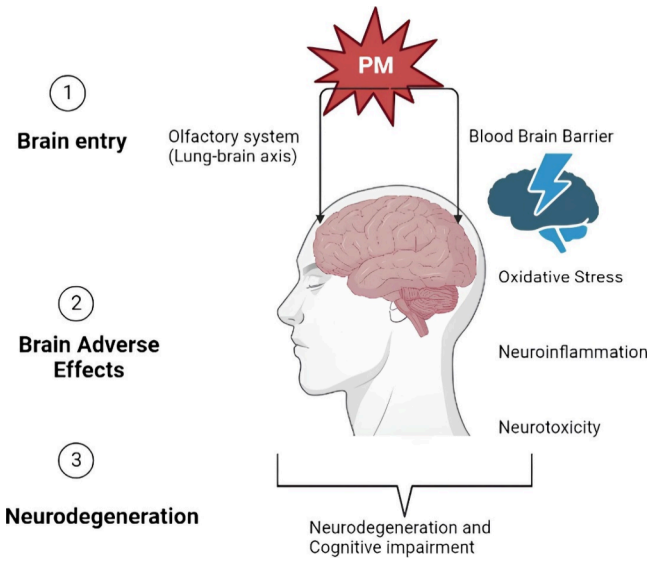


Figure 2. Connecting the dots: mechanisms linking air pollution and neurodegenerative disease.

tion by controlling the effects of PM2.5 exposure on AD amyloid pathology. By focusing on sTREM2, researchers hope to lessen the burden of amyloid buildup, delay the beginning of AD, and halt the spread of the disease.[54]

Significant progress has been made in understanding complex disease mechanisms and exploring multidimensional approaches for imaging and treatment. One study utilized a multimodal approach, using deep learning to combine imaging, electronic health records (EHR), and genomic single nucleotide polymorphism data (stacked denoising autoencoders), to predict Alzheimer's disease stages and successfully classify patients into control, mild cognitive impairment, and Alzheimer's disease groups, surpassing single-modality deep learning models.[55] Researchers have given us insights into a statistical model (two components: one that looks at how biomarkers and cognitive tests change together and another that predicts clinical outcomes) that tracks how biomarkers and cognitive tests change over time in Alzheimer's disease. The part that tracks changes uses equations to follow how an individual's biomarkers and cognitive tests change.[56] When selecting a method for picking out important features, it is essential to choose the one that suits the classification task best. For instance, when comparing Alzheimer's disease to healthy controls, SMML is a better choice than HGM-FS for achieving higher accuracy.[57]

UNRAVELING THE HISTORICAL JOURNEY OF ALZHEIMER'S DISEASE

Alois Alzheimer described the symptoms of pre-senile dementia over a century ago, which led to the disease bearing his name, but until date there is no such disease-modifying agent that has been discovered or preventive medicine that has been brought in for this stealthy disease.[70] The Latin word "dementia" indicates the situation happening outside the mind. Aging was found to be a factor for developing atherosclerosis in the early 20th century and later was linked in the process of developing dementia as a result of the major blood supply to the brain.[71] During the evolution from 19th −20th century, neurosyphilis was considered to be the main form of dementia due to its tremendous prevalence before the antibiotic era.[72] A

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631

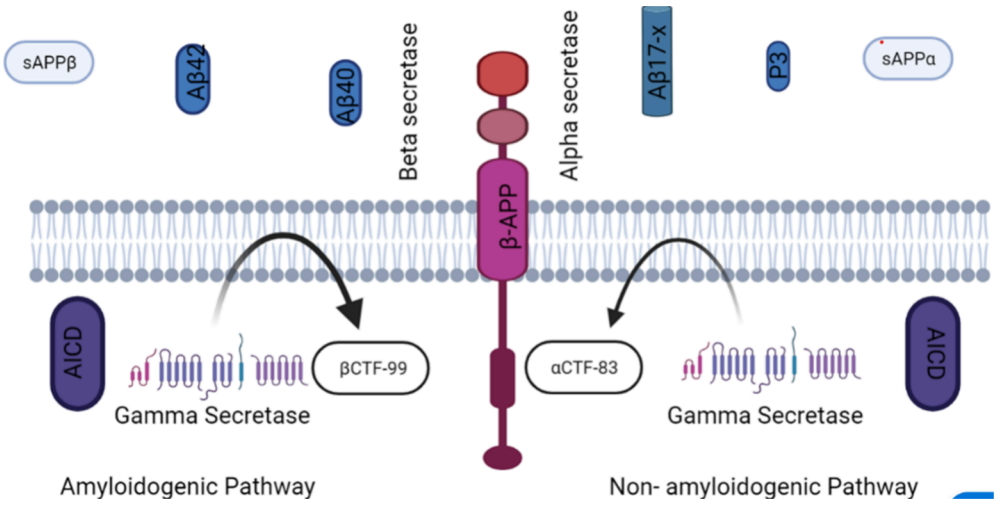


Figure 3. Schematic diagram of the APP processing pathway, where the upper portion represents the N terminal end and the lower portion represents the C terminal end. The amyloidogenic pathway to the left involves BACE1 inhibitors, i.e., β-secretase cleaves APP in the N terminus domain, thereby producing sAPPβ, and the β-CTF-99 fragment later produces amyloid intracellular domain (AICD) by cleavage with γ-secretase (multiunit complex of PS1,2, APHI, and nicatrin) and soluble amyloid-β plaques Aβ40 and Aβ42. The non-amyloidogenic pathway to the right involving α-secretase i.e., ADAM10 (A Disintegrin and Metalloprotease 10) cleaves APP within the Aβ domain, leading to sAPPα and the αCTF-83 fragment, which is further cleaved by γ-secretase leading to P3 and AICD fragments. sAPPβ = soluble fragment amyloid-β peptide.

study states that, "Dementia is a complete forgetting of preceding state, biased judgement, reciprocated act of exaggeration, simultaneous alteration of ideas".[73] It seemed, however, that chronic dementia causation was still misleading and was linked with stress, alcohol, masturbation, and exorbitant study.[74] The modern concept of dementia constitutes the tripod changes, viz., behavioral changes, cognitive changes, and deterioration of daily activities.[75] The proper diagnosis of AD is still 65.0−90.0% accurate despite the advancement in technologies related to the disease, and only autopsy can be preferred as a definitive diagnosis.[76] In such situation there is an urgent need to develop biomarkers for Alzheimer's diagnosis.[77]

NEUROPATHOLOGY OF ALZHEIMER'S DISEASE: UNRAVELING THE BRAIN'S CHANGES

Alzheimer's disease is classified into two types, familial (genetic factors) or sporadic, which accounts for 95.0% of all cases, and its risk gets doubled for every five years after the age of 65 at high risk.[78] The former type is known as early onset Alzheimer's disease (EOAD) at ages above 65, representing only about 2.0% targeting on presenilin 1 and 2 with APP, and the other type is known as late-onset Alzheimer's disease (LOAD) involving the APOE4 allele. The most common cause of dementia is Alzheimer's, which is not understood well and is determined as a protein misfolding disease, i.e., proteopathy owing to abnormal Aβ folded plaques.[79] The monomers of amyloid-β are soluble and comprised of a large α-helical structure in contrast to a short region of β-sheets and polyproline 2 helix in solution.[80,81] However, at high concentrations it undergoes several changes in conformation to form a β-sheet (tertiary structure) that further undergoes aggregation, leading to the formation of amyloid fibrils,[82] and dense extracellular deposition in neurons, leading to senile plaques or neuritic plaques. In a macroscopic level, Alzheimer's disease is caused by atropy of various affected regions comprised of the cingulate gyrus, frontal lobe, parietal lobe, and temporal lobe.[83] Macroscopic views of both Aβ plaques and neurofibrill tau tangles are clearly visible in the brains of Alzheimer's disease patients, where the former are dense deposits of protein that is mostly soluble in nature and cellular material located outside the brain and the latter is twisting of fibers within the neuronal cell, which is also insoluble in nature.[84,85]

Amyloid-β (Aβ) Pathology: Building Blocks of Alzheimer's Brain Changes. Evidence suggests the accumulation of β-plaques and conformation change leading to a β-sheet structure are central in the pathogenesis of Alzheimer's disease.[86] The schematic diagram of the APP processing pathway is illustrated for better understanding (Figure 3). Though dominantly inherited Alzheimer's disease (DIAD) causes memory loss and dementia in less than 1.0% individuals where people are affected in their thirties to fifties rarely, the mutation is most probably in three different genes individually, viz., APP, PSEN1, and PSEN2, which is more evident.[87] The higher aggregation property of Aβ lies in the residue that ends in 42 in contrast to the residue ending in 40, which is less prone to aggregation.[88] Several studies suggest that antagonist effect of Aβ40 on Aβ42 could be a more relevant biomarker in the pathology by having the antagonist effect on Aβ42 and decreasing its capacity to aggregate, thereby leading to an increase in Aβ42 levels or the Aβ42/Aβ40 ratio as the biomarker of pathology.[89] Nonetheless, Aβ-derived fragments that are generated by γ-secretase, which is distinct from amyloid-β, could have been noticed to a lesser extent where membrane tethering of the C99 fragment or βCTF production along with AICD could also contribute to various pathological dysfunctions.[90−92] Recent findings bring us to the point that the η -cleavage site is novel and thus leads to the rise of a subset of various new fragments, viz., A-$\eta\alpha$, A-$\eta\beta$, and η-CTF, with the help of enzyme MT5-MMP, i.e., matrix metalloproteinase on βAPP.[93−95] With enormous amount of information on Aβ40 and Aβ42, C terminal end truncated peptides of Aβ have not received the spotlight and are to be considered in pathology, where Aβ37, Aβ38, and Aβ39 have been identified in plasma and CSF of Alzheimer patients. Aβ38

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631

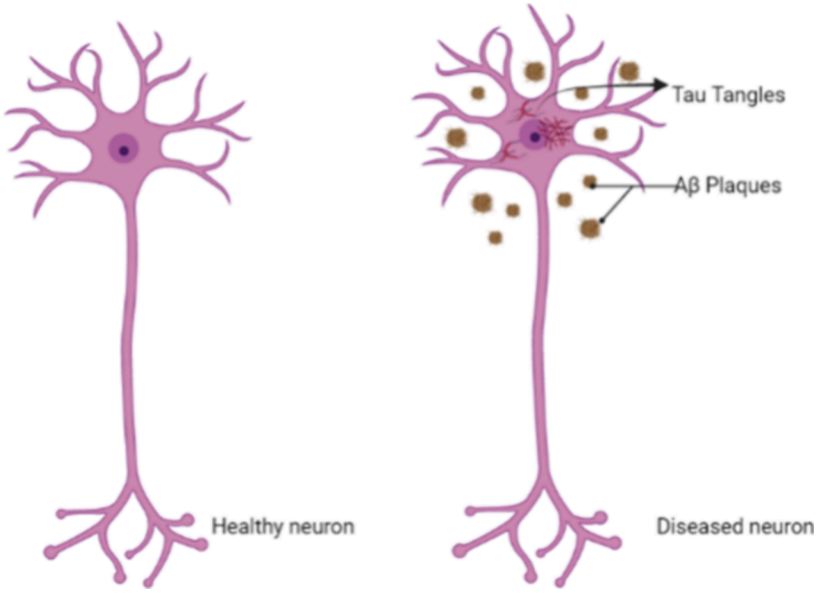


Figure 4. Illustration of tau pathology.

was in fact found to be the second most prominent of Aβ form after Aβ40 in terms of quantity.[96]

APOE Gene and Alzheimer's Disease: Linking the Genetic Connection. The APOE protein (299 amino acids) of the fat-binding family of proteins is mainly involved in the metabolism of fat and is insinuated in Alzheimer's and cardiac disorders. It has three isoforms in humans differing in 1 or 2 amino acids, viz., APOE 2−4 forms, with changes in Cys112, Cys158, Arg112, and Arg158 compositions. The prevalence for each allele is in the order 7.0%, 78.0%, and 15.0%, wherein the APOE3 isoform of the allele is more dominant and involved in the disease in Americans of European descent.[97] However, population studies suggest that the risk of developing Alzheimer's disease is increased in the APOE4 isoform and is also accompanied by early onset of Alzheimer's disease at an earlier age, which most likely accounts for 50.0% of sporadic AD.[98,99] On the contrary, the APOE2 isoform allele decreases the associated risk for developing Alzheimer's disease.[100,101] Nonetheless, there is evidence showing that ApoE knock-down mice demonstrates its role in Aβ clearance from the central nervous system to plasma, which is further inhibited depending on the isoform of allele as ApoE4 > ApoE3 or ApoE2.[102]

Tau Protein: The Crucial Player in Alzheimer's Pathology. Alzheimer's disease is linked with increases in the level of both total tau and phosphorylated tau in both the brains and CSF, where the former includes all isoforms of tau regardless of phosphorylation and the latter includes tau with phosphorylation at 181 or 231 residues.[103] The analogy of tau pathology is the case for both healthy and diseased neurons (Figure 4). Therefore, the focus is to know the mechanism of tau formation due to either increased tau formation or aggregated tau as a result of impaired clearance, which is not fully understood. Knowing about half-life of tau in the CNS and the kinetics alteration profile and quantifying the ability of drugs to modulate tau have not been addressed so far. It is briefly seen that exhausted propyl isomerase protein belonging to the parvulin family expedites the accumulation of abnormal tau proteins.[104,105] Neurofibrillary tau tangles (NFTs) appear first in the transentorhinal region and the entorhinal cortex, are superseded by CA1 of the hippocampal region, and spread through limbic structures like the subiculum of the hippocampal formation and the amygdala. Finally, the whole cortex becomes affected by NFTs, resulting in an impairment of associative, sensory, and motor functions.[106] Furthermore, tau is a major microtubule-associated protein (MAP) since it accounts for approximately 80% of total MAPs.[107] Tau phosphorylation is enhanced prior to its dissociation from microtubules, thereby favoring the aggregation of tau and the formation of paired helical filaments due to impairment of axon transport and synapse function and ultimately to neurotoxicity.[108−110]

Hyperphosphorylation of tau tangles intracellularly occurs due to the imbalance between neuronal kinase (cyclin-dependent kinase 5) and phosphatase activities (glycogen synthase kinase 3β).[111] Though total tau concentration, despite its phosphorylated state, is a nonspecific biomarker in neurodegeneration, it was found that phosphorylated tau at 181 (threonine), pTau199, and pTau231 was found to be a specific hallmark of AD.[112−114] The presence of tau tangles comprising dense fibrils in the perinuclear cytoplasm, Meynert, and locus coeruleus is constituted to be one of the hallmarks of Alzheimer's disease upon degeneration of the brainstem, i.e., noradrenaline producing nucleus in the brain.[115] Various evidence also suggests that deaminated catecholamine-derived metabolites 3,4-dihydroxyphenylactaldehyde (DOPAL) and 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL) are neurotoxic which might also be responsible for cellular and neuronal death by several cytotoxic mechanisms besides free radical generation and apoptosis.[116,117]

The Cholinergic Hypothesis: Extending the Role of Neurotransmitters in Alzheimer's. The acetylcholinetransferrase enzyme breaks down acetylcholine and depletes further, leading to several complications. Many drugs have only ameliorated the symptoms rather than reversing or preventing the disease, indicating that damage of brain tissue is widespread and thus cell replacement therapy is impractical in treatment.[118]

Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease Pathology. The accumulation of Aβ initiates a chain reaction of events, including oxidative stress,

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631

endoplasmic reticulum stress, mitochondrial dysfunction, and neuronal apoptosis, ultimately resulting in cognitive impairment.[119] Research has shown that Aβ can harm the structure and function of mitochondria, causing mitochondrial oxidative stress and activating apoptotic pathways in both Alzheimer's disease cell lines and mouse models; this has been shown to be ameliorated by luteolin.[120−122] Antioxidants, including enzymes like SOD, GPX, CAT, and Trx, play a crucial role in delaying or preventing cellular damage by protecting against oxidative stress and thereby mitigating organelle dysfunction.[123] Higher levels of free radicals and increased macromolecule oxidation, including mitochondrial DNA, are found in Alzheimer's disease, and these free radicals can boost the activity of enzymes responsible for amyloid-β generation.[124] Lately, there has been interest in how quercetin affects various aspects of mitochondria, including biogenesis, respiration, membrane potential, quality control, and ATP production.[125] Research also indicates that PC12 cells exposed to 6-OHDA show signs of mitochondrial problems like reduced mitochondrial content, increased oxidative stress, and a drop in mitochondrial membrane potential that are alleviated when treated with quercetin.[126]

EXPLORING ALZHEIMER'S WITH NEUROIMAGING TECHNIQUES

Clinical diagnosis is done primarily based on the standard cognitive and neuropsychological tests, with additional diagnosis done by biomarkers, genetics, and neuroimaging techniques, though definitive diagnosis can be done only upon post-mortem. Double transgenic mice have higher advantage compared to single transgenic mouse, wherein the former displays more phenotype of AD with large amount of deposited Aβ plaques.[127] Two new models, viz., APPSwDI and APPSw, developed on nitric oxide synthase 2 background found that pathological expression in mice and that in humans were similar in all processes initiating from Aβ deposition and tau tangles along with neuronal death and behavioral deficits.[128] Magnetic resonance imaging techniques are utilized to observe the pathology of the disease, and thus a high-powered MRI machine (7T) is deployed for analyzing the rat brain due to its small size instead of 1.5T or 3T, which are usually used on the human brain with comparable results.[129,130]

Structural MRI: Peering into Alzheimer's Brain Anatomy. The greatest challenge in utilizing MRI on a mouse model lies in its high resolution and its requirement for much less thickness in micrometers. Plaques found in the thalamus region can be imaged faster with a low-resolution sequence in contrast to plaques found in the cortical and hippocampal regions.[129] A tau transgenic model of wild-type mice (rTg4510) was found to have severe atropy in the neuronal cortex region and hippocampal region by looking at its morphometry along with enlarged ventricles, concluding that MRI is a useful tool in identifying pathology and comparing the responses of treatment between humans and mice.[131] The MRI technique utilizes both spatial resolution and superior soft tissue contrast that thus enables MRI volumetry in detecting atropy of the brain region, which represents the final stages of AD where irreversible damage and clinical manifestations have already occurred.

Functional MRI (fMRI): Mapping Brain Activity in Alzheimer's Disease. Functional MRI is used to investigate the functional integrity of the brain network in Alzheimer's disease. It helps with differentiating the disease and the state of progression. Blood oxygenation level-dependent imaging is utilized to visualize signal changes due to changes in blood volume or flow, and positron emission tomography (PET) is used to visualize glucose metabolism of brain cells to measure synaptic activity. The study suggests that other networks might enhance activity as a compensatory mechanism during the failure of hippocampal region.[132] Other magnetic resonance techniques such as arterial spin labeling measures, diffusion tensor imaging of cerebral blood flow, and PET tracers targeted at the cholinergic system, microglial activation, and other tracers in development will contribute to the understanding of the pathology in future. Entorhinal volumes and hippocampal volume are lower by about 20−30% and around 15.0−25.0%, respectively, in patients with mild cognitive individuals.[133]

PET Studies: Illuminating Alzheimer's Disease through Molecular Imaging. Techniques like micro-PET scanners are found to be efficient in imaging an animal's brain. Other Aβ probes, ^{18}F-FDG (fludeoxyglucose) and ^{18}F-FDDNP (2-(1-6-[(2-[*F*]fluoroethyl methylamino]-2-naphthyl ethylidene) malononitrile)) were found to be very significant, with less difference between Tg2576 mice and wild-type mice.[134] The most common and validated marker of amyloid-β aggregation is 11C-Pittsburgh compound B having high affinity for vascular fibrillary deposits of amyloid-β with lower affinity toward amorphous amyloid, soluble Aβ, and intracellular neurofibrillary tangles.[135] Several other amyloid tracers include [^{11}C] AZD2184, [^{11}C] SB-13, [^{18}F] BAY94−9172, and [^{18}F] AmyvidTM, and tau targeting novel tracers including [^{18}F] T807 and [^{18}F] THK523 were published. However, the marginal capture of Aβ plaques by amyloid tracers in transgenic mice during PET studies was overcome by Pittsburgh compound B (PIB), which was synthesized with highly specific radioactivity.[136] Despite various biomarkers available to measure Aβ accumulation, MRI-based atropy can also be a better choice due to its noninvasiveness and lack of ionizing radiation.[137] The thalamus region and hippocampus region reveal atropy in similar rates on Alzheimer's patients.[138]

Biograph MMR: Advancing Alzheimer's Imaging with Cutting-Edge Technology. The beneficial effects of both single-modality magnetic resonance and positron emission tomography techniques in the assessment of Alzheimer's disease are established for a better understanding of the pathology. A comprehensive diagnosis picture of function, brain metabolism, and morphology can be assessed simultaneously, with just one scan itself showing data in virtually seamless spatial alignment and thereby improving the quality of image in brain patterns and in challenging body regions like the abdomen.[139]

DTI and Fiber Tracking: Tracing the Brain's Connectivity in Alzheimer's Disease. Diffusion tensor imaging (DTI) estimates anisotropy, location, and orientation of the white matter tracts of human brain and is efficient in monitoring the disintegration of white matter and the loss of myelin in the transgenic mouse model. It was observed in a comparison of old platelet-derived growth factor promoter-driving amyloid precursor protein (PDAPP) mice with old wild type mice that the relative anisotropy was comparatively lower and showed no significant changes between young PDAPP mice and young wild-type mice; through this, damage in myelin can be sorted out easily, which occurs mainly in late progression after Aβ deposition.[140] Based on the eigenvalues

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631

and eigenvector-combined Gaussian diffusion probability model, fractional anisotropy is measured to show the direction of water diffusion, mean diffusivity to measure magnitude, and axial diffusivity to measure the rate of diffusion along the principal axis, which indicates that whether the rate is fast or slow depends upon orientation. The DTI measurements in axons parallel over a white fiber tract exhibit slow diffusion when compared to perpendicular measurement until axons are twisted. The model also measures radial diffusivity to measur the e rate of diffusion transversely.[141] Though it has various advantages, it has several limitations too in illustrating specific pathological changes, as a decline in fractional anisotropy and increase in mean diffusivity might establish demyelination or axon loss.[142]

Non-Invasive Techniques: Unveiling Alzheimer's Insights with Minimal Intrusiveness. Various neuroimaging tools have been recommended for noninvasive monitoring of Aβ load. Despite numerous advances in PET imaging of Alzheimer's disease, most radio ligands are not suitable for quantification techniques due to their nonspecific binding/unfavorable kinetics, low signal-to-noise ratio, and burden due to radiation.[143]

Diffusion-Weighted MRI: Unraveling Microstructural Changes in an Alzheimer's Brain. Diffusion-weighted MRI is a technique that establishes an exclusive method of quantifying the diffusion of water in the brain, where the microstructure of tissue is reflected where the diffusion in the brain structure is hindered by the membranous structure. Thus, it is an emerging technique for biomarker identification that affects the CNS.[144−147] Diffusion-weighted MRI tracks anisotropic diffusion of water along axons, revealing microstructural white matter fibers connecting cortical and subcortical regions. The major bundles in the brain region can be reconstructed by whole brain tractography.[148]

Tractography (Fiber Tracking): Charting Neural Pathways in Alzheimer's Disease. Nearly in the 40s, superficial white matter tracts below the infragranular layer of the cerebral cortex often myelinate, which could be more vulnerable to Alzheimer's disease.[149] Superficial white matter tracts are comprised of Crown fibers, Meynert U fibers, and merging deep white matter fibrils.[150] Due to the complex structure and variability in different subjects of superficial white matter tracts, there are limited studies involved in Alzheimer's disease. Tractography application with diffusion tensor MRI involves reconstruction of white matter tracts by restricted diffusion of water molecules together with myelinated axons.[151] Tract diffusion is detected as enhanced mean diffusivity for the degree of diffusion, enhanced axial diffusivity with a large eigenvalue, increased radial diffusivity with an average of two small eigenvalues, or a decline in fractional anisotropy showing the diffusion direction. Fibers can be followed across voxels by fiber assignment by continuous tracking involving diffusion tensor principal with eigenvectors in current propagation.[152] Reginold hypothesized that decreased fractional anisotropy and enhanced mean/axial/radial diffusivity could lead to Alzheimer's, where enhanced mean diffusivity represents atrophy in tissue, enhanced axial diffusivity represents Wallerian degeneration, and enhanced radial diffusivity represents disruption of myelin.[153,154]

The novel biomarker in neuronal injury of Alzheimer's disease is assessed by tractography of temporal superficial white matter.[154] Tractography is, however, limited to several complex areas of the brain due to its inability in resolving crossing fibers within a voxel, which can also be overcome by 3D model of orientation distribution function, typically referred as Q- ball imaging and diffusion spectrum imaging (DSI) with higher angular diffusion imaging.[155−157] For diffusion spectrum imaging, multiple b values are required to fill q-space with diffusion weighting, leading to long imaging minutes, i.e., ≥30 min; this is not necessary for Q-ball imaging, which requires only one strong b value, i.e., 3000 s/mm^2, thus making it clinically applicable. Even after having some advantage with diffusion spectrum imaging, it has its own demerit, as it has strong diffusion weighting and is thus unable to provide clinically valuable diffusion parameters owing to the dependent b value.[158]

Limitations: Constraints and Considerations.

1 Relative long image acquisition time to DTI with two nonzero b values and 15 diffusion directions to estimate diffusion and kurtosis tensor. However, 7−10 min of imaging is suggested for reliable results

2 It has 21 independent parameters in contrast to DTI, which has only 6 independent parameters

DKI: Expanding Insights with Advanced Diffusion Imaging Beyond DTI. Diffusion kurtosis imaging estimates kurtosis, i.e., Skewed distribution of diffusion, and is sensitive to the Brownian motion of water, which helps in measuring restricted/hindered movement of water molecules based on their diffusivity in the brain. Due to the highly organized nature of the white matter, the main diffusion orientation will coincide with the orientation of the axons in tissue, thus enabling the characterization of the orientation and integrity of white matter fibers.[159,160] DKI provides an estimate of both the Gaussian diffusion distribution and the deviation of this Gaussian distribution at higher b values. The latter makes diffusion kurtosis a more sensitive technique than DTI for visualizing microstructural changes.[161] Several studies indicated the ability of diffusion kurtosis to provide additional parameters like axial kurtosis, fractional kurtosis anisotropy, mean kurtosis, and radial kurtosis, which are much sensitive in detecting developmental and changes in pathology of neural tissues in comparison with conventional DTI.[162−164]

Several studies state that kurtosis parameters are good probes for barriers and membranes that act by detecting permeability changes.[144,162] Thus, diffusion kurtosis—an extension of DTI—acts as potential noninvasive biomarker with several insights omtp cell physiology during pathology and is useful in the investigation of abnormal tissues where DTI is not very significant; it could also be useful in accurately diagnosing the progression of disease.[165] Diffusional kurtosis imaging can overcome the limitations that have been brought down by diffusion Tensor imaging by kurtosis (dimensionless) estimation of water diffusion based on the probability distribution function.[166] Greater restriction is shown in tissue with an increased kurtosis value, and a decreased kurtosis value indicates neuronal loss.[162] Kurtosis parameters have an additional advantage compared with fractional anisotropy in measuring water diffusion restriction in both isotropic and anisotropic environments, whereas in fractional anisotropy it involves only anisotropic environments.[167]

Magnetic Resonance Spectroscopy: Probing Molecular Clues in Alzheimer's Pathophysiology. Magnetic resonance spectroscopy is helpful for identifying Alzheimer patients before the onset of clinical symptoms as well as for distinguishing Alzheimer's disease from other neurodegener-

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631

ative disorders, making it powerful in the differentiation of neurological disorders. It also performs regional measurement of various metabolites of the brain including choline, creatine, myo-Inositol, and *N*-acetyl aspartate; creatine is used as an internal reference to control for variability in measurement, as it remains unaltered in Alzheimer's disease.[168−170]

Revolutionizing Alzheimer's Disease Diagnosis with NIRF Imaging. Despite previous challenges, the use of near-infrared fluorescence (NIRF) in monitoring Alzheimer's disease (AD) therapy has gained attention. Researchers have explored its potential in this context and found that the fluorescence signal in the group treated with CRANAD-17, a curcumin analogue capable of detecting both soluble and insoluble Aβ species, was notably reduced compared to the control group.[171,172] Hence, there is considerable interest in creating NIRF probes due to their simple production, nonintrusive characteristics, cost-effectiveness, extended shelf life, minimal interference from background fluorescence, and deep tissue penetration, all of which position them as promising options for diagnosing and imaging toxic Aβ aggregates.[173,174]

AIR POLLUTION AND DEMENTIA: UNRAVELING THE CONNECTION

Air pollution exposure with fine PM is thought to provoke the risk of Alzheimer's and dementia in addition to hypertension, oxidative stress, hyperlipidemia, resistance toward insulin, inflammation, and stroke.[175] The fractions of ultrafine PM enter the circulatory system rapidly after entering in the body through an inhalational route and penetrate via the alveolar capillary barrier in lungs, thereby affecting the vascular system directly. The penetration of particles depends on various factors such as the size of the particle, the composition of the chemical, charge, and the susceptibility to generate aggregates.[50] The ability of PM2.5 and nanoparticles to penetrate lung and brain barriers depends on a large surface to volume ratio, which explains how particulate matter can enter neuronal cells and erythrocytes based on their size.[176,177] The average annual mass concentrations of PM2.5 and PM10 in China were found to be 35 and 70 $\mu g/m^3$ previously in 2012 but showed 38.9% and 8.8% deviation for PM2.5 with 21.6% and 6.2% for PM10 in 2015 and 2018, respectively.[178] The three factors govern the deposition behavior such as deposition site, particle size, surface characteristics, and Brownian motion. Thus, these nanoparticles behave like molecules that are deposited in the upper respiratory tract and move toward olfactory mucosa, causing various biological and toxic effects.[179] Uptake of pollutants via a nasal route is due to weakening of the mucosal barrier leading to enhanced neuropathology by inducing systemic inflammation in an inclined way from olfactory mucosa to the olfactory bulb and then toward the frontal cortex.[180] It is clear to see that olfactory impairment, implying exposure linked to breathing, is a prevalent trait in neurodegenerative diseases.[181] It is believed that in USA at least 146 million people live in low air quality standards for each criteria air pollutant, mostly ozone, PM, or both.[182] The elderly are at higher risk of dementia because physiological functions decrease gradually over time as age increases and their ability to expel PM or toxic substances once inhaled decreases.[183,184] Various animal studies and experimental data suggest that PM inhalation leads to enhanced ROS and inflammatory responses in the brain, leading to precipitating (Aβ) peptides, breaching of the BBB, and activation of microglial cells.[185,186] A study also stated that Aβ accumulation occurs more in astrocytes and neuronal cells of people residing in high air pollution areas than people in low air pollution areas.[187,188] The 2018 Lancet commission on pollution emphasizes that the causative factor is building, particularly for fine particulate matter and dementia in the elderly, and much research is required to explore emerging causes.[189] Dermal contact with contaminated soil, dust, or water, though expected to be in a minor concentration, could contribute to an individual's intake of air pollution.[190,191]

PARTICULATE MATTER: TINY PARTICLES, BIG HEALTH CONCERNS

Particulate matter comprises complex physical and chemical substances that exist in the atmosphere as distinct solid particles or suspended liquid. It is emitted into atmosphere directly as a primary source and formed from a precursor as a secondary source, and both originate anthropogenically or from a natural source. The classification of PM is based on size (aerodynamic diameter, μm), and PM is differentiated as ultrafine particles (PM0.1), fine particles (PM2.5), thoracic coarse (PM 2.5−10), and coarse particles (PM10). Pollutant concentration besides air pollution has major negative effects on neurological activity without meeting the accepted air quality index maintained as standard.[192] A wide range of air pollutants, including tobacco smoke, traffic related markers like black carbon, and exposure to wood smoke, are major associative factors in practice for the development of cognitive-like effects due to urban air pollutants.[193] Elevated levels of black carbon led to a decline in cognitive function through both verbal and nonverbal assessments, including memory constructs. Additional, exposure to environmental tobacco smoke had a negative impact on cognition of US adolescents and children aged around 6−16 years.[194] Additionally, PM and metal associated with each other in higher concentrations could be considered a major key factor that is very likely to damage the young brains of urban children.[195] The origin of PM2.5−10 includes sources from unpaved roads, construction and demolition dusts, combustion of wood, burning of municipal solid waste, etc., wherein gas and condensed vapors originate from various sources and activities.[196] The emerging evidence suggests that cognitive disturbances of urban children with chronic exposure to air pollutants could be due to the APOE genotype, i.e., APOE-e4 carriers.[197] It is well-known that monoamines, in particular dopamine, are distributed asymmetrically in the brain, and any alteration of the distribution unilaterally would lead to disturbances in pathogenesis of neurorelated diseases accompanied by various symptoms.[198] Clearly, dietary changes produce significant changes in health outcomes, and the usage of polyunsaturated fatty acid (PUFA) diets modifies the amount of fatty acids present in the frontal cortex region, particularly enhancing PUFA levels. Nevertheless, it is stated that any alterations in PUFA content in diet leads to alterations in cognitive disorders.[199] A detailed information on the target for new drugs is listed in Table 2.

A GLOBAL THREAT: AIR POLLUTION'S FAR-REACHING IMPACT AND THE ROLE OF ARTIFICIAL INTELLIGENCE IN MITIGATION

It was a long-time delusion of humans that air pollution would affect primarily the lungs and cardiovascular system, but it has

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631

Table 2. Potential Drug Targets for the Future

group studying	target	action	clinical trials	status
Alzheimer Preventive Initiative (API) generation study I and II	amyloid-β	prevent clumping of Aβ fragment plaques and produce an antibody against Aβ to clear it from the brain	wnderway CAD106 (active immunotherapy) and CNP520	expected to conclude in 2025 by preventing interference from nerve−nerve communication
N/A	BACE (β-secretases)	interrupt the process of this enzyme and its ability to make Aβ	JNJ-54861911 phase 3	expected to conclude in 2024
N/A	tau protein	prevents collapse and tangle twisting of tau protein where microtubules are destroyed initially and ultimately the neuron itself	AADvac 1 (vaccine) ADAMANT (phase 2)	began March 2016 and expected to complete in June 2019
N/A	inflammation	preventing immune response due to Aβ plaque, tau angles, and microglial cells that act as first-line defense but become overactive and damage nearby cells	sargramostim phase 2 is underway	expected to complete in May 2020
N/A	5HT2A/5HT6 receptor	receptor blocking might increase amount of Ach and maintain normal neuronal communication	primavanserin mimics serotonin shape but has opposite effect to serotonin as it reduces neuronal communication	currently no drug has been approved for this indication
N/A	antiamyloid	drug targeting Aβ	solanezumab	expected in July 2022
Dominantly Inherited Alzheimer Network Trials unit	mutation of genes	prevents mutation of three genes (less than 1% cause) and helps to remove excess Aβ in the brain	ganterumab solanezumab	expected to conclude in March 2021
Autosomal Dominant Alzheimer's disease trial	Aβ	it acts against Aβ to reduce negative cognitive effects of excess Aβ	crenezumab (immune-based therapy)	N/A
API generation study	symptoms	prevent or delay the onset of Alzheimer symptoms	active immune therapy CAD106 and CNP520 (BACE Inhibitor)	expected to conclude in February 2022

recived special focus nowadays due to the detrimental effects in the brain, which is renowned by neuroscientists and toxicologists. If the focus is put on preventing the air pollution from the source itself, we can get significant health effects worldwide, as the tiny particles even move to nose via the olfactory nerve and are carried out straight to the brain, bypassing the blood−brain barrier.[200,201] Ultrafine particles are more like little Trojan horses that stealthily reach the brain directly and damage neurons, dysregulating microglia activation (immune cells of brain) into mistaking intruders for pathogens and killing them by releasing chemicals that later accumulate and trigger neuroinflammation, thus implicating neurodegeneration.[202] Nonetheless, an ingested particle might have indirect effects on neurons through the gut, and a strong connection between the gut microbiome and the brain is well established by researchers; additionally, previous studies suggest that systemic inflammation is caused by the delivery of fine particles to the gut.[203,204] Short-term exposure to air pollution was linked with impaired cognition in aged mice based on movement, navigation, and recognition.[205] Another study reported that nearly 3000 school-going children had declines in cognitive development with more traffic pollution, and the implications were too frightening.[206] Mice exposed to diesel exhaust during prenatal and early postnatal life showed significant lower Reelin protein levels required for the brain development.[207] It is possible that the matter of concern could be due to the content of particulate matter in addition to particulate size, and brain damage at an early age could lead to poor education and lifestyle changes, which prevents people from staying away from those areas in their lifetime.[208] The brain tissue analysis of individuals living in heavily polluted areas showed increase in CD-68, CD-163, and HLA-DR positive cells, suggesting the infiltration of monocytes and enhanced pro-inflammatory markers such as IL-1β and COX-2 in the frontal cortex, substantia niagra, and vagus nerves besides enhanced Aβ42 deposition, blood−brain barrier damage, and endothelial cell activation.[209] Nonetheless, PCB leads to oxidative stress, thus linking endothelial cell inflammation and impaired long chain fatty acid synthesis in the body. Additionally, it is also reported that PCB might affect thyroid hormone function, leading to cognitive impairment.[210] It is thought that the "One Nation-One Fuel Standard" should be made compulsory and enacted soon to breath pure air and eventually escape from diseases that could be averted in this way. Additionally, all public transport and transit vehicles could be converted to run on compressed natural gas (CNG) by providing a steady supply and lower price, thus enabling many private car owners to switch.[6]

Even if the wealth of data produced by noninvasive procedures allows for the development of more precise and reliable biomarkers, it presents difficulties for the computational analysis of the vast amounts of data produced, which can be essential for the early diagnosis of AD. To overcome these difficulties, deep learning and artificial intelligence must be combined.[211] Thus, when analysis of a plethora of information remains difficult and needs accuracy, artificial intelligence (AI) is the choice, as it holds the capacity to uphold various pieces of information and a novel diagnostic AD model can be employed with more sensitivity in diagnosis using daily clinical practice-related information. These AI-based models could help nonspecialists use medical resources more effectively by reducing the number of missed diagnoses.[212,213] Technologies are also employed in identifying the mental state of the patient

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631

by employing the support vector machine technique.[214] Diagnosis thus having its own challenges can be met by deploying artificial intelligence as means of understanding the gaps in the retrieval of information and understanding the core concept of disease based on plasma biomarkers through an artificial neural network.[215,216] Traditional studies using MRI only perform qualitative visual analyses, which frequently miss important prospective discoveries. Contrarily, large data collections offer a potential quantitative foundation to support diagnostics by quantifying the size of the brain structure. As a result, data-centric AI/ML techniques may serve as a catalyst for knowledge discovery, laying the groundwork for the development of new medicines and medications to prevent and treat Alzheimer's disease.[217] These issues may be resolved by the rapidly developing field of using AI in conjunction with neuroimaging to diagnose AD. AI has the capacity to integrate complicated multimodal data and enhance the precision of biomarker-based testing, and it holds great promise for providing reliable and widely available early AD diagnosis.[218,219] STRING and gene ontology techniques are thus employed to evaluate novel gene candidates identified by artificial intelligence in the frontal brain and cerebellum of AD patients.[220] One of the essential techniques to produce input information on the available EEG data and aid in the differentiation of AD, MCI, and HC persons is generative adversarial networks and variational auto-encoder networks.[221] Convolutional neural networks are a crucial component of the AI-based approach used in most advanced deep learning technology that can be used to categorize AD patients based on their MRI images.[222,223]

CONCLUSION

This study suggests that various imaging techniques have evolved, and it is crucial to choose the techniques depending upon the pollutants and its pathway. Various evidence suggests that there is a need to develop multidimensional imaging to check what be suitable for targeting disease before it is too late, as it is practically impossible to reduce air pollution to a greater extent due to political considerations in developing countries who are in the stage of development where, by keeping in mind the health hazards in long-term, they need to choose wisely in order to maintain the pollution or health outcomes. Nonetheless, the field of targeted therapies for genetic diseases will advance with the use of AI and ML, promising methods for discovering disease-associated genes.

AUTHOR INFORMATION

Corresponding Authors

Chitra Vellapandian − *Department of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology (SRMIST), Kattankulathur, Tamil Nadu 603203, India;* orcid.org/0000-0001-7927-0983; Email: chitrav@srmist.edu.in

Bhupendra Prajapati − *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Mehsana, North Gujarat 384012, India;* Email: bhupen27@gmail.com

Authors

Ankul Singh S − *Department of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology (SRMIST), Kattankulathur, Tamil Nadu 603203, India*

Mohd Nazam Ansari − *Department of Pharmacology and Toxicology, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Alkharj 11942, Saudi Arabia;* orcid.org/0000-0001-8580-3002

Gehan M. Elossaily − *Department of Basic Medical Sciences, College of Medicine, AlMaarefa University, Riyadh 13713, Saudi Arabia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c06328

Author Contributions

A.S.S. conceived the experimental method and data analyses. A.S.S. and M.N.A. analyzed the data and prepared the figures. C.V. and B.G.P. surveyed previous literature and compiled it into a table. A.S.S. wrote the original draft of the manuscript. M.N.A. and G.M.E. co-wrote the manuscript and Supporting Information. C.V. and B.G.P. reviewed and edited the manuscript. All authors finalized the manuscript.

Funding

This study is supported via funding from Prince Sattam bin Abdulaziz University, project number PSAU/2024/R/1445.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We express our sincere gratitude to the management of SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Tamil Nadu, India, who extended their contribution and support to this work. B.G.P. would also like to extend heartfelt thanks to the management of Shree S.K. Patel College of Pharmaceutical Education and Research for rendering the support in completion of this work.

REFERENCES

(1) Hu, W.; Fang, L.; Zhang, H.; Ni, R.; Pan, G. Changing Trends in the Air Pollution−Related Disease Burden from 1990 to 2019 and Its Predicted Level in 25 Years. *Environ. Sci. Pollut. Res.* **2023**, *30* (1), 1761−1773.

(2) Choi, J.; Oh, J. Y.; Lee, Y. S.; Min, K. H.; Hur, G. Y.; Lee, S. Y.; Kang, K. H.; Shim, J. J. Harmful Impact of Air Pollution on Severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Particulate Matter Is Hazardous. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2018**, *13*, 1053−1059.

(3) Yang, L.; Li, C.; Tang, X. The Impact of PM2.5 on the Host Defense of Respiratory System. *Front. Cell Dev. Biol.* **2020**, *8*, 91 DOI: 10.3389/fcell.2020.00091.

(4) *Air Quality Database*, update 2016. World Health Organization. https://www.who.int/data/gho/data/themes/air-pollution/who-air-quality-database/2016

(5) Kyle, A. D.; Wright, C. C.; Caldwell, J. C.; Buffler, P. A.; Woodruff, T. J. Evaluating the Health Significance of Hazardous Air Pollutants Using Monitoring Data. *Public Health Rep.* **2001**, *116* (1), 32−44.

(6) Block, M. L.; Calderón-Garcidueñas, L. Air Pollution: Mechanisms of Neuroinflammation and CNS Disease. *Trends Neurosci.* **2009**, *32* (9), 506−516.

(7) González-Maciel, A.; Reynoso-Robles, R.; Torres-Jardón, R.; Mukherjee, P. S.; Calderón-Garcidueñas, L. Combustion-Derived Nanoparticles in Key Brain Target Cells and Organelles in Young Urbanites: Culprit Hidden in Plain Sight in Alzheimer's Disease Development. *J. Alzheimer's Dis.* **2017**, *59* (1), 189−208.

(8) Ye, M.; Yang, J.; Li, J.; Wang, Y.; Chen, W.; Zhu, L.; Wang, T.; Liu, J.; Geng, D.; Yu, Z. Progress in Mechanisms, Pathways and Cohort Studies About the Effects of PM2.5 Exposure on the Central Nervous System. *Rev. Environ. Contam. Toxicol.* **2023**, *261* (1), No. 7.

(9) Wang, X.; Khlystov, A.; Ho, K.-F.; Campbell, D.; Chow, J. C.; Kohl, S. D.; Watson, J. G.; Lee, S.-C. F.; Chen, L.-W. A.; Lu, M.; Ho, S. S. H. Real-World Vehicle Emissions Characterization for the Shing Mun Tunnel in Hong Kong and Fort McHenry Tunnel in the United States. *Res. Rep. Health. Eff. Inst.* **2019**, No. 199, 5−52.
(10) Escamilla, J. A. H.; Flores-Margez, J. P.; Shukla, M. K. Particulate Matter: Capture and Quantification in Natural and Anthropogenic Sources. *J. Environ. Anal. Toxicol.* **2015**, *05* (04), No. 1000281, DOI: 10.4172/2161-0525.1000281.
(11) Cohen, A. J.; Brauer, M.; Burnett, R.; Anderson, H. R.; Frostad, J.; Estep, K.; Balakrishnan, K.; Brunekreef, B.; Dandona, L.; Dandona, R.; Feigin, V.; Freedman, G.; Hubbell, B.; Jobling, A.; Kan, H.; Knibbs, L.; Liu, Y.; Martin, R.; Morawska, L.; Pope, C. A.; Shin, H.; Straif, K.; Shaddick, G.; Thomas, M.; van Dingenen, R.; van Donkelaar, A.; Vos, T.; Murray, C. J. L.; Forouzanfar, M. H. Estimates and 25-Year Trends of the Global Burden of Disease Attributable to Ambient Air Pollution: An Analysis of Data from the Global Burden of Diseases Study 2015. *Lancet* **2017**, *389* (10082), 1907−1918.
(12) Khilnani, G. C.; Tiwari, P. Air Pollution in India and Related Adverse Respiratory Health Effects. *Curr. Opin. Pulm. Med.* **2018**, *24* (2), 108−116.
(13) Raghavendra Rao, M. V.; Kumar, P.; Sireesha, B.; Sripada Pallavi, T.; Krishna Sowmya, M.; Ramanaiah, C. J.; Mahendra, K. V.; Srinivasa, R. D.; Samir, F.; Abraham, N.; Sateesh, B. A. IS ALZHEIMER'S DISEASE ANOTHER BRAIN ON FIRE? (BIG NEWS BIG DEBATE). *Indian J. Clin. Pract.* **2018**, *29* (4), 301−400.
(14) Calderón-Garcidueñas, L.; González-Maciel, A.; Reynoso-Robles, R.; Hammond, J.; Kulesza, R.; Lachmann, I.; Torres-Jardón, R.; Mukherjee, P. S.; Maher, B. A. Quadruple Abnormal Protein Aggregates in Brainstem Pathology and Exogenous Metal-Rich Magnetic Nanoparticles (and Engineered Ti-Rich Nanorods). The Substantia Nigrae Is a Very Early Target in Young Urbanites and the Gastrointestinal Tract a Key Brainstem. *Environ. Res.* **2020**, *191*, No. 110139.
(15) Calderón-Garcidueñas, L.; Torres-Jardón, R.; Kulesza, R. J.; Mansour, Y.; González-González, L. O.; Gónzalez-Maciel, A.; Reynoso-Robles, R.; Mukherjee, P. S. Alzheimer Disease Starts in Childhood in Polluted Metropolitan Mexico City. A Major Health Crisis in Progress. *Environ. Res.* **2020**, *183*, No. 109137.
(16) Calderón-Garcidueñas, L.; Hernández-Luna, J.; Mukherjee, P. S.; Styner, M.; Chávez-Franco, D. A.; Luévano-Castro, S. C.; Crespo-Cortés, C. N.; Stommel, E. W.; Torres-Jardón, R. Hemispheric Cortical, Cerebellar and Caudate Atrophy Associated to Cognitive Impairment in Metropolitan Mexico City Young Adults Exposed to Fine Particulate Matter Air Pollution. *Toxics* **2022**, *10* (4), 156.
(17) Chen, J.-H.; Lin, K.-P.; Chen, Y.-C. Risk Factors for Dementia. *J. Formos. Med. Assoc.* **2009**, *108* (10), 754−764.
(18) Suresh, S.; Begum, R. F.; Singh S, A.; V, C. Anthocyanin as a Therapeutic in Alzheimer's Disease: A Systematic Review of Preclinical Evidences. *Ageing Res. Rev.* **2022**, *76*, No. 101595.
(19) Suresh, S.; Singh S, A.; Vellapandian, C. Bisphenol A Exposure Links to Exacerbation of Memory and Cognitive Impairment: A Systematic Review of the Literature. *Neurosci. Biobehav. Rev.* **2022**, *143*, 104939.
(20) Ankul, S. S.; Chandran, L.; Anuragh, S.; Kaliappan, I.; Rushendran, R.; Vellapandian, C. A Systematic Review of the Neuropathology and Memory Decline Induced by Monosodium Glutamate in the Alzheimer's Disease-like Animal Model. *Front. Pharmacol.* **2023**, *14*, No. 1283440, DOI: 10.3389/fphar.2023.1283440.
(21) Suresh, S.; Singh S, A.; Rushendran, R.; Vellapandian, C.; Prajapati, B. Alzheimer's Disease: The Role of Extrinsic Factors in Its Development, an Investigation of the Environmental Enigma. *Front. Neurol.* **2023**, *14*, No. 1303111, DOI: 10.3389/fneur.2023.1303111.
(22) Perl, D. P. Neuropathology of Alzheimer's Disease. *Mt. Sinai J. Med. A J. Transl. Pers. Med.* **2010**, *77* (1), 32−42.
(23) Genc, S.; Zadeoglulari, Z.; Fuss, S. H.; Genc, K. The Adverse Effects of Air Pollution on the Nervous System. *J. Toxicol.* **2012**, *2012*, 1−23.
(24) Lahiri, D.; Maloney, B.; Riyaz Basha, M.; Wen Ge, Y.; Zawia, N. How and When Environmental Agents and Dietary Factors Affect the Course of Alzheimers Disease: The “LEARn” Model (Latent Early-Life Associated Regulation) May Explain the Triggering of AD. *Curr. Alzheimer Res.* **2007**, *4* (2), 219−228.
(25) Lahiri, D. K.; Maloney, B. The "LEARn" (Latent Early-Life Associated Regulation) Model Integrates Environmental Risk Factors and the Developmental Basis of Alzheimer's Disease, and Proposes Remedial Steps. *Exp. Gerontol.* **2010**, *45* (4), 291−296.
(26) Farrer, L. A. Expanding the Genomic Roadmap of Alzheimer's Disease. *Lancet Neurol.* **2015**, *14* (8), 783−785.
(27) DeKosky, S. T.; Gandy, S. Environmental Exposures and the Risk for Alzheimer Disease. *JAMA Neurol.* **2014**, *71* (3), 273.
(28) Cacciottolo, M.; Wang, X.; Driscoll, I.; Woodward, N.; Saffari, A.; Reyes, J.; Serre, M. L.; Vizuete, W.; Sioutas, C.; Morgan, T. E.; Gatz, M.; Chui, H. C.; Shumaker, S. A.; Resnick, S. M.; Espeland, M. A.; Finch, C. E.; Chen, J. C. Particulate Air Pollutants, APOE Alleles and Their Contributions to Cognitive Impairment in Older Women and to Amyloidogenesis in Experimental Models. *Transl. Psychiatry* **2017**, *7* (1), e1022−e1022.
(29) Ghobakhloo, S.; Khoshakhlagh, A. H.; Mostafaii, G. R.; Chuang, K.-J.; Gruszecka-Kosowska, A.; Hosseinnia, P. Critical Air Pollutant Assessments and Health Effects Attributed to PM2.5 during and after COVID-19 Lockdowns in Iran: Application of AirQ+ Models. *Front. Public Heal.* **2023**, *11*, No. 1120694, DOI: 10.3389/fpubh.2023.1120694.
(30) Alharbi, R. A. Proteomics Approach and Techniques in Identification of Reliable Biomarkers for Diseases. *Saudi J. Biol. Sci.* **2020**, *27* (3), 968−974.
(31) Robinson, R. A. S.; Amin, B.; Guest, P. C. Multiplexing Biomarker Methods, Proteomics and Considerations for Alzheimer's Disease. *Adv. Exp. Med. Biol.* **2017**, *974*, 21−48.
(32) McLachlan, J.; Cox, S. R.; Pearce, J.; Valdés Hernández, M. d. C. Long-Term Exposure to Air Pollution and Cognitive Function in Older Adults: A Systematic Review and Meta-Analysis. *Front. Environ. Heal.* **2023**, *2*, 1205443.
(33) Mirowsky, J. E.; Jin, L.; Thurston, G.; Lighthall, D.; Tyner, T.; Horton, L.; Galdanes, K.; Chillrud, S.; Ross, J.; Pinkerton, K. E.; Chen, L. C.; Lippmann, M.; Gordon, T. In Vitro and in Vivo Toxicity of Urban and Rural Particulate Matter from California. *Atmos. Environ.* **2015**, *103*, 256−262.
(34) Rao, X.; Zhong, J.; Brook, R. D.; Rajagopalan, S. Effect of Particulate Matter Air Pollution on Cardiovascular Oxidative Stress Pathways. *Antioxid. Redox Signal.* **2018**, *28* (9), 797−818.
(35) Xie, W.; You, J.; Zhi, C.; Li, L. The Toxicity of Ambient Fine Particulate Matter (PM2.5) to Vascular Endothelial Cells. *J. Appl. Toxicol.* **2021**, *41* (5), 713−723.
(36) Pryor, J. T.; Cowley, L. O.; Simonds, S. E. The Physiological Effects of Air Pollution: Particulate Matter, Physiology and Disease. *Front. Public Heal.* **2022**, *10*, No. 882569, DOI: 10.3389/fpubh.2022.882569.
(37) Kim, H.; Noh, J.; Noh, Y.; Oh, S. S.; Koh, S.-B.; Kim, C. Gender Difference in the Effects of Outdoor Air Pollution on Cognitive Function Among Elderly in Korea. *Front. Public Heal.* **2019**, *7*, No. 375, DOI: 10.3389/fpubh.2019.00375.
(38) Sahu, B.; Mackos, A. R.; Floden, A. M.; Wold, L. E.; Combs, C. K. Particulate Matter Exposure Exacerbates Amyloid-β Plaque Deposition and Gliosis in APP/PS1Mice. *J. Alzheimer's Dis.* **2021**, *80* (2), 761−774.
(39) Cristaldi, A.; Fiore, M.; Oliveri Conti, G.; Pulvirenti, E.; Favara, C.; Grasso, A.; Copat, C.; Ferrante, M. Possible Association between PM2.5 and Neurodegenerative Diseases: A Systematic Review. *Environ. Res.* **2022**, *208*, No. 112581.
(40) Nirenjen, S.; Narayanan, J.; Tamilanban, T.; Subramaniyan, V.; Chitra, V.; Fuloria, N. K.; Wong, L. S.; Ramachawolran, G.; Sekar, M.; Gupta, G.; Fuloria, S.; Chinni, S. V.; Selvaraj, S. Exploring the

Contribution of Pro-Inflammatory Cytokines to Impaired Wound Healing in Diabetes. *Front. Immunol.* **2023**, *14*, No. 1216321, DOI: 10.3389/fimmu.2023.1216321.
(41) Kim, H.; Kim, W.-H.; Kim, Y.-Y.; Park, H.-Y. Air Pollution and Central Nervous System Disease: A Review of the Impact of Fine Particulate Matter on Neurological Disorders. *Front. Public Heal.* **2020**, *8*, No. 575330, DOI: 10.3389/fpubh.2020.575330.
(42) Martin, E. M.; Fry, R. C. Environmental Influences on the Epigenome: Exposure- Associated DNA Methylation in Human Populations. *Annu. Rev. Public Health* **2018**, *39* (1), 309−333.
(43) Isaevska, E.; Moccia, C.; Asta, F.; Cibella, F.; Gagliardi, L.; Ronfani, L.; Rusconi, F.; Stazi, M. A.; Richiardi, L. Exposure to Ambient Air Pollution in the First 1000 Days of Life and Alterations in the DNA Methylome and Telomere Length in Children: A Systematic Review. *Environ. Res.* **2021**, *193*, No. 110504.
(44) Wu, Y.; Qie, R.; Cheng, M.; Zeng, Y.; Huang, S.; Guo, C.; Zhou, Q.; Li, Q.; Tian, G.; Han, M.; Zhang, Y.; Wu, X.; Li, Y.; Zhao, Y.; Yang, X.; Feng, Y.; Liu, D.; Qin, P.; Hu, D.; Hu, F.; Xu, L.; Zhang, M. Air Pollution and DNA Methylation in Adults: A Systematic Review and Meta-Analysis of Observational Studies. *Environ. Pollut.* **2021**, *284*, No. 117152.
(45) Song, A. Y.; Feinberg, J. I.; Bakulski, K. M.; Croen, L. A.; Fallin, M. D.; Newschaffer, C. J.; Hertz-Picciotto, I.; Schmidt, R. J.; Ladd-Acosta, C.; Volk, H. E. Prenatal Exposure to Ambient Air Pollution and Epigenetic Aging at Birth in Newborns. *Front. Genet.* **2022**, *13*, No. 929416, DOI: 10.3389/fgene.2022.929416.
(46) Manisalidis, I.; Stavropoulou, E.; Stavropoulos, A.; Bezirtzoglou, E. Environmental and Health Impacts of Air Pollution: A Review. *Front. Public Heal.* **2020**, *8*, No. 14, DOI: 10.3389/fpubh.2020.00014.
(47) Hullmann, M.; Albrecht, C.; van Berlo, D.; Gerlofs-Nijland, M. E.; Wahle, T.; Boots, A. W.; Krutmann, J.; Cassee, F. R.; Bayer, T. A.; Schins, R. P. F. Diesel Engine Exhaust Accelerates Plaque Formation in a Mouse Model of Alzheimer's Disease. *Part. Fibre Toxicol.* **2017**, *14* (1), 35.
(48) Shi, L.; Zhu, Q.; Wang, Y.; Hao, H.; Zhang, H.; Schwartz, J.; Amini, H.; van Donkelaar, A.; Martin, R. V.; Steenland, K.; 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.* **2023**, *120* (1), No. e2211282119.
(49) Peters, A. Ambient Air Pollution and Alzheimer's Disease: The Role of the Composition of Fine Particles. *Proc. Natl. Acad. Sci. U.S.A.* **2023**, *120* (3), No. e2220028120.
(50) Peters, R.; Ee, N.; Peters, J.; Booth, A.; Mudway, I.; Anstey, K. J. Air Pollution and Dementia: A Systematic Review. *J. Alzheimer's Dis.* **2019**, *70* (s1), S145−S163.
(51) Sommerlad, A.; Liu, K. Y. Air Pollution and Dementia. *BMJ.* **2023**, p655.
(52) Emrani, S.; Arain, H. A.; DeMarshall, C.; Nuriel, T. APOE4 Is Associated with Cognitive and Pathological Heterogeneity in Patients with Alzheimer's Disease: A Systematic Review. *Alzheimers. Res. Ther.* **2020**, *12* (1), 141.
(53) Puris, E.; Saveleva, L.; Górová, V.; Vartiainen, P.; Kortelainen, M.; Lamberg, H.; Sippula, O.; Malm, T.; Jalava, P. I.; Auriola, S.; Fricker, G.; Kanninen, K. M. Air Pollution Exposure Increases ABCB1 and ASCT1 Transporter Levels in Mouse Cortex. *Environ. Toxicol. Pharmacol.* **2022**, *96*, No. 104003.
(54) Li, M.; Ma, Y.; Fu, Y.; Liu, J.; Hu, H.; Zhao, Y.; Huang, L.; Tan, L. Association between air pollution and CSF sTREM2 in cognitively normal older adults: The CABLE study. *Ann. Clin. Transl. Neurol.* **2022**, *9* (11), 1752−1763.
(55) Venugopalan, J.; Tong, L.; Hassanzadeh, H. R.; Wang, M. D. Multimodal Deep Learning Models for Early Detection of Alzheimer's Disease Stage. *Sci. Rep.* **2021**, *11* (1), 3254.
(56) Bossa, M. N.; Sahli, H. A Multidimensional ODE-Based Model of Alzheimer's Disease Progression. *Sci. Rep.* **2023**, *13* (1), 3162.
(57) Zhang, Z.; Huang, H.; Shen, D. Integrative Analysis of Multi-Dimensional Imaging Genomics Data for Alzheimer's Disease Prediction. *Front. Aging Neurosci.* **2014**, *6*, No. 260, DOI: 10.3389/fnagi.2014.00260.
(58) Jung, C.-R.; Lin, Y.-T.; Hwang, B.-F. Ozone, Particulate Matter, and Newly Diagnosed Alzheimer's Disease: A Population-Based Cohort Study in Taiwan. *J. Alzheimer's Dis.* **2015**, *44* (2), 573−584.
(59) Singh S, A.; Suresh, S.; Singh, A.; Chandran, L.; Vellapandian, C. Perspectives of Ozone Induced Neuropathology and Memory Decline in Alzheimer's Disease: A Systematic Review of Preclinical Evidences. *Environ. Pollut.* **2022**, *313*, 120136.
(60) Singh S, A.; Suresh, S.; Vellapandian, C. OZONE-INDUCED NEUROTOXICITY: IN VITRO AND IN VIVO EVIDENCE. *Ageing Res. Rev.* **2023**, *91*, No. 102045.
(61) Oudin, A.; Forsberg, B.; Adolfsson, A. N.; Lind, N.; Modig, L.; Nordin, M.; Nordin, S.; Adolfsson, R.; Nilsson, L.-G. Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study. *Environ. Health Perspect.* **2016**, *124* (3), 306−312.
(62) Dubey, H.; Gulati, K.; Ray, A. Alzheimer's Disease: A Contextual Link with Nitric Oxide Synthase. *Curr. Mol. Med.* **2020**, *20* (7), 505−515.
(63) S, A. S.; Vellapandian, C. Structure of the Blood Brain Barrier and Its Role in the Transporters for the Movement of Substrates across the Barriers. *Curr. Drug Metab.* **2023**, *24* (4), 250−269.
(64) Chang, K.-H.; Chang, M.-Y.; Muo, C.-H.; Wu, T.-N.; Chen, C.-Y.; Kao, C.-H. Increased Risk of Dementia in Patients Exposed to Nitrogen Dioxide and Carbon Monoxide: A Population-Based Retrospective Cohort Study. *PLoS One* **2014**, *9* (8), No. e103078.
(65) Wong, C.-S.; Lin, Y.-C.; Hong, L.-Y.; Chen, T.-T.; Ma, H.-P.; Hsu, Y.-H.; Tsai, S.-H.; Lin, Y.-F.; Wu, M.-Y. Increased Long-Term Risk of Dementia in Patients With Carbon Monoxide Poisoning. *Medicine (Baltimore).* **2016**, *95* (3), No. e2549.
(66) Katsouyanni, K.; Touloumi, G.; Spix, C.; Schwartz, J.; Balducci, F.; Medina, S.; Rossi, G.; Wojtyniak, B.; Sunyer, J.; Bacharova, L.; Schouten, J. P.; Ponka, A.; Anderson, H. R. Short Term Effects of Ambient Sulphur Dioxide and Particulate Matter on Mortality in 12 European Cities: Results from Time Series Data from the APHEA Project. *BMJ.* **1997**, *314* (7095), 1658−1658.
(67) Huang, Y.; Zhang, H.; Lv, B.; Tang, C.; Du, J.; Jin, H. Sulfur Dioxide: Endogenous Generation, Biological Effects, Detection, and Therapeutic Potential. *Antioxid. Redox Signal.* **2022**, *36* (4−6), 256−274.
(68) Younan, D.; Petkus, A. J.; Widaman, K. F.; Wang, X.; Casanova, R.; Espeland, M. A.; Gatz, M.; Henderson, V. W.; Manson, J. E.; Rapp, S. R.; Sachs, B. C.; Serre, M. L.; Gaussoin, S. A.; Barnard, R.; Saldana, S.; Vizuete, W.; Beavers, D. P.; Salinas, J. A.; Chui, H. C.; Resnick, S. M.; Shumaker, S. A.; Chen, J.-C. Particulate Matter and Episodic Memory Decline Mediated by Early Neuroanatomic Biomarkers of Alzheimer's Disease. *Brain* **2020**, *143* (1), 289−302.
(69) O'Piela, D. R.; Durisek, G. R.; Escobar, Y.-N. H.; Mackos, A. R.; Wold, L. E. Particulate Matter and Alzheimer's Disease: An Intimate Connection. *Trends Mol. Med.* **2022**, *28* (9), 770−780.
(70) Stelzmann, R. A.; Norman Schnitzlein, H.; Reed Murtagh, F. An English Translation of Alzheimer's 1907 Paper, Über Eine Eigenartige Erkankung Der Hirnrinde? *Clin. Anat.* **1995**, *8* (6), 429−431.
(71) Lathe, R.; Sapronova, A.; Kotelevtsev, Y. Atherosclerosis and Alzheimer - Diseases with a Common Cause? Inflammation, Oxysterols, Vasculature. *BMC Geriatr.* **2014**, *14* (1), 36.
(72) Boller, F.; Forbes, M. M. History of Dementia and Dementia in History: An Overview. *J. Neurol. Sci.* **1998**, *158* (2), 125−133.
(73) Berrios, G. E. *The History of Mental Symptoms: Descriptive Psychopathology Since the Nineteenth Century*; Cambridge University Press: Cambridge, UK, 1996.
(74) Vatanabe, I. P.; Manzine, P. R.; Cominetti, M. R. Historic Concepts of Dementia and Alzheimer's Disease: From Ancient Times to the Present. *Rev. Neurol. (Paris).* **2020**, *176* (3), 140−147.
(75) Mesulam, M.-M. *Principles of Behavioral and Cognitive Neurology*, 2nd ed.; Oxford University Press: New York NY, 2000.
(76) Qin, W.; Ho, L.; Wang, J.; Peskind, E.; Pasinetti, G. M. S100A7, a Novel Alzheimer's Disease Biomarker with Non-Amyloidogenic α-

Secretase Activity Acts via Selective Promotion of ADAM-10. *PLoS One* **2009**, *4* (1), No. e4183.
(77) Takeuchi, M.; Sato, T.; Takino, J.; Kobayashi, Y.; Furuno, S.; Kikuchi, S.; Yamagishi, S. Diagnostic Utility of Serum or Cerebrospinal Fluid Levels of Toxic Advanced Glycation End-Products (TAGE) in Early Detection of Alzheimer's Disease. *Med. Hypotheses* **2007**, *69* (6), 1358−1366.
(78) Kilian, J. *The Effects of Airborne Ultra-Fine Particulate Exposure on Cognition and Neuropathology in an Amyloid Model of Alzheimer's Disease*. Ph.D. Thesis, University of Caifornia, Irvine, CA, 2020.
(79) Hashimoto, M.; Rockenstein, E.; Crews, L.; Masliah, E. Role of Protein Aggregation in Mitochondrial Dysfunction and Neurodegeneration in Alzheimer's and Parkinson's Diseases. *NeuroMolecular Med.* **2003**, *4* (1−2), 21−36.
(80) Danielsson, J.; Andersson, A.; Jarvet, J.; Gräslund, A. 15N Relaxation Study of the Amyloid β-Peptide: Structural Propensities and Persistence Length. *Magn. Reson. Chem.* **2006**, *44* (S1), S114−S121.
(81) Tomaselli, S.; Esposito, V.; Vangone, P.; van Nuland, N. A. J.; Bonvin, A. M. J. J.; Guerrini, R.; Tancredi, T.; Temussi, P. A.; Picone, D. The α-to-β Conformational Transition of Alzheimer's Aβ-(1−42) Peptide in Aqueous Media Is Reversible: A Step by Step Conformational Analysis Suggests the Location of β Conformation Seeding. *ChemBioChem.* **2006**, *7* (2), 257−267.
(82) Ohnishi, S.; Takano, K. Amyloid Fibrils from the Viewpoint of Protein Folding. *Cell. Mol. Life Sci.* **2004**, *61* (5), 511−524.
(83) Wenk, G. L. Neuropathologic Changes in Alzheimer's Disease. *J. Clin. Psychiatry* **2003**, *64* (Suppl9), 7−10.
(84) Tiraboschi, P.; Hansen, L. A.; Thal, L. J.; Corey-Bloom, J. The Importance of Neuritic Plaques and Tangles to the Development and Evolution of AD. *Neurology* **2004**, *62* (11), 1984−1989.
(85) Bouras, C.; Hof, P. R.; Giannakopoulos, P.; Michel, J.-P.; Morrison, J. H. Regional Distribution of Neurofibrillary Tangles and Senile Plaques in the Cerebral Cortex of Elderly Patients: A Quantitative Evaluation of a One-Year Autopsy Population from a Geriatric Hospital. *Cereb. Cortex* **1994**, *4* (2), 138−150.
(86) Holtzman, D. M.; Bales, K. R.; Paul, S. M.; DeMattos, R. B. Aβ Immunization and Anti-Aβ Antibodies: Potential Therapies for the Prevention and Treatment of Alzheimer's Disease. *Adv. Drug Delivery Rev.* **2002**, *54* (12), 1603−1613.
(87) Rabinovici, G. D. Dominantly Inherited Alzheimer's Disease: A Compass for Drug Development. *Nat. Med.* **2021**, *27* (7), 1148−1150.
(88) Yin, Y. I.; Bassit, B.; Zhu, L.; Yang, X.; Wang, C.; Li, Y.-M. γ-Secretase Substrate Concentration Modulates the Aβ42/Aβ40 Ratio. *J. Biol. Chem.* **2007**, *282* (32), 23639−23644.
(89) Deng, Y.; Tarassishin, L.; Kallhoff, V.; Peethumnongsin, E.; Wu, L.; Li, Y.-M.; Zheng, H. Deletion of Presenilin 1 Hydrophilic Loop Sequence Leads to Impaired -Secretase Activity and Exacerbated Amyloid Pathology. *J. Neurosci.* **2006**, *26* (14), 3845−3854.
(90) Lauritzen, I.; Pardossi-Piquard, R.; Bauer, C.; Brigham, E.; Abraham, J.-D.; Ranaldi, S.; Fraser, P.; St-George-Hyslop, P.; Le Thuc, O.; Espin, V.; Chami, L.; Dunys, J.; Checler, F. The -Secretase-Derived C-Terminal Fragment of APP, C99, But Not A, Is a Key Contributor to Early Intraneuronal Lesions in Triple-Transgenic Mouse Hippocampus. *J. Neurosci.* **2012**, *32* (46), 16243−16255.
(91) Lauritzen, I.; Pardossi-Piquard, R.; Bourgeois, A.; Pagnotta, S.; Biferi, M.-G.; Barkats, M.; Lacor, P.; Klein, W.; Bauer, C.; Checler, F. Intraneuronal Aggregation of the β-CTF Fragment of APP (C99) Induces Aβ-Independent Lysosomal-Autophagic Pathology. *Acta Neuropathol.* **2016**, *132* (2), 257−276.
(92) Nixon, R. A. Amyloid Precursor Protein and Endosomal-lysosomal Dysfunction in Alzheimer's Disease: Inseparable Partners in a Multifactorial Disease. *FASEB J.* **2017**, *31* (7), 2729−2743.
(93) Willem, M.; Tahirovic, S.; Busche, M. A.; Ovsepian, S. V.; Chafai, M.; Kootar, S.; Hornburg, D.; Evans, L. D. B.; Moore, S.; Daria, A.; Hampel, H.; Müller, V.; Giudici, C.; Nuscher, B.; Wenninger-Weinzierl, A.; Kremmer, E.; Heneka, M. T.; Thal, D. R.; Giedraitis, V.; Lannfelt, L.; Müller, U.; Livesey, F. J.; Meissner, F.; Herms, J.; Konnerth, A.; Marie, H.; Haass, C. η-Secretase Processing of APP Inhibits Neuronal Activity in the Hippocampus. *Nature* **2015**, *526* (7573), 443−447.
(94) Baranger, K.; Bonnet, A. E.; Girard, S. D.; Paumier, J.-M.; García-González, L.; Elmanaa, W.; Bernard, A.; Charrat, E.; Stephan, D.; Bauer, C.; Moschke, K.; Lichtenthaler, S. F.; Roman, F. S.; Checler, F.; Khrestchatisky, M.; Rivera, S. MT5-MMP Promotes Alzheimer's Pathogenesis in the Frontal Cortex of 5xFAD Mice and APP Trafficking in Vitro. *Front. Mol. Neurosci.* **2017**, *9*, No. 163, DOI: 10.3389/fnmol.2016.00163.
(95) Dunys, J.; Valverde, A.; Checler, F. Are N- and C-Terminally Truncated Aβ Species Key Pathological Triggers in Alzheimer's Disease? *J. Biol. Chem.* **2018**, *293* (40), 15419−15428.
(96) Wiltfang, J.; Esselmann, H.; Bibl, M.; Hüll, M.; Hampel, H.; Kessler, H.; Frölich, L.; Schröder, J.; Peters, O.; Jessen, F.; Luckhaus, C.; Perneczky, R.; Jahn, H.; Fiszer, M.; Maler, J. M.; Zimmermann, R.; Bruckmoser, R.; Kornhuber, J.; Lewczuk, P. Amyloid β Peptide Ratio 42/40 but Not Aβ42 Correlates with Phospho-Tau in Patients with Low- and High-CSF Aβ40 Load. *J. Neurochem.* **2007**, *101* (4), 1053−1059.
(97) Saunders, A. M.; Strittmatter, W. J.; Schmechel, D.; St. George-Hyslop, P. H.; Pericak-Vance, M. A.; Joo, S. H.; Rosi, B. L.; Gusella, J. F.; Crapper-MacLachlan, D. R.; Alberts, M. J.; Hulette, C.; Crain, B.; Goldgaber, D.; Roses, A. D. Association of Apolipoprotein E Allele 4 with Late-Onset Familial and Sporadic Alzheimer's Disease. *Neurology* **1993**, *43* (8), 1467−1467.
(98) Corder, E. H.; Saunders, A. M.; Strittmatter, W. J.; Schmechel, D. E.; Gaskell, P. C.; Small, G. W.; Roses, A. D.; Haines, J. L.; Pericak-Vance, M. A. Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families. *Science (80-.).* **1993**, *261* (5123), 921−923.
(99) Ashford, J. W. APOE Genotype Effects on Alzheimer's Disease Onset and Epidemiology. *J. Mol. Neurosci.* **2004**, *23* (3), 157−166.
(100) Corder, E. H.; Saunders, A. M.; Risch, N. J.; Strittmatter, W. J.; Schmechel, D. E.; Gaskell, P. C.; Rimmler, J. B.; Locke, P. A.; Conneally, P. M.; Schmader, K. E.; Small, G. W.; Roses, A. D.; Haines, J. L.; Pericak-Vance, M. A. Protective Effect of Apolipoprotein E Type 2 Allele for Late Onset Alzheimer Disease. *Nat. Genet.* **1994**, *7* (2), 180−184.
(101) Serrano-Pozo, A.; Qian, J.; Monsell, S. E.; Betensky, R. A.; Hyman, B. T. APOE E2 Is Associated with Milder Clinical and Pathological Alzheimer Disease. *Ann. Neurol.* **2015**, *77* (6), 917−929.
(102) Deane, R.; Sagare, A.; Hamm, K.; Parisi, M.; Lane, S.; Finn, M. B.; Holtzman, D. M.; Zlokovic, B. V. ApoE Isoform−Specific Disruption of Amyloid β Peptide Clearance from Mouse Brain. *J. Clin. Invest.* **2008**, *118* (12), 4002−4013.
(103) Ryman, D. C.; Acosta-Baena, N.; Aisen, P. S.; Bird, T.; Danek, A.; Fox, N. C.; Goate, A.; Frommelt, P.; Ghetti, B.; Langbaum, J. B. S.; Lopera, F.; Martins, R.; Masters, C. L.; Mayeux, R. P.; McDade, E.; Moreno, S.; Reiman, E. M.; Ringman, J. M.; Salloway, S.; Schofield, P. R.; Sperling, R.; Tariot, P. N.; Xiong, C.; Morris, J. C.; Bateman, R. J. Symptom Onset in Autosomal Dominant Alzheimer Disease: A Systematic Review and Meta-Analysis. *Neurology* **2014**, *83* (3), 253−260.
(104) Pastorino, L.; Sun, A.; Lu, P.-J.; Zhou, X. Z.; Balastik, M.; Finn, G.; Wulf, G.; Lim, J.; Li, S.-H.; Li, X.; Xia, W.; Nicholson, L. K.; Lu, K. P. The Prolyl Isomerase Pin1 Regulates Amyloid Precursor Protein Processing and Amyloid-β Production. *Nature* **2006**, *440* (7083), 528−534.
(105) Lim, J.; Ping Lu, K. Pinning down Phosphorylated Tau and Tauopathies. *Biochim. Biophys. Acta - Mol. Basis Dis.* **2005**, *1739* (2−3), 311−322.
(106) Braak, H.; Braak, E. Frequency of Stages of Alzheimer-Related Lesions in Different Age Categories. *Neurobiol. Aging* **1997**, *18* (4), 351−357.
(107) Wang, J.-Z.; Gao, X.; Wang, Z.-H. The Physiology and Pathology of Microtubule-Associated Protein Tau. *Essays Biochem.* **2014**, *56*, 111−123.

(108) Alonso, A. d. C.; Grundke-Iqbal, I.; Iqbal, K. Alzheimer's Disease Hyperphosphorylated Tau Sequesters Normal Tau into Tangles of Filaments and Disassembles Microtubules. *Nat. Med.* **1996**, *2* (7), 783−787.
(109) Buée, L.; Bussière, T.; Buée-Scherrer, V.; Delacourte, A.; Hof, P. R. Tau Protein Isoforms, Phosphorylation and Role in Neurodegenerative Disorders11These Authors Contributed Equally to This Work. *Brain Res. Rev.* **2000**, *33* (1), 95−130.
(110) Fath, T.; Eidenmüller, J.; Brandt, R. Tau-Mediated Cytotoxicity in a Pseudohyperphosphorylation Model of Alzheimer's Disease. *J. Neurosci.* **2002**, *22* (22), 9733−9741.
(111) Liu, S. J.; Zhang, J. Y.; Li, H. L.; Fang, Z. Y.; Wang, Q.; Deng, H. M.; Gong, C. X.; Grundke-Iqbal, I.; Iqbal, K.; Wang, J. Z. Tau Becomes a More Favorable Substrate for GSK-3 When It Is Prephosphorylated by PKA in Rat Brain. *J. Biol. Chem.* **2004**, *279* (48), 50078−50088.
(112) Parnetti, L.; Lanari, A.; Amici, S.; Gallai, V.; Vanmechelen, E.; Hulstaert, F. CSF Phosphorylated Tau Is a Possible Marker for Discriminating Alzheimer's Disease from Dementia with Lewy Bodies. *Neurol. Sci.* **2001**, *22* (1), 77−78.
(113) Itoh, N.; Arai, H.; Urakami, K.; Ishiguro, K.; Ohno, H.; Hampel, H.; Buerger, K.; Wiltfang, J.; Otto, M.; Kretzschmar, H.; Moeller, H.-J.; Imagawa, M.; Kohno, H.; Nakashima, K.; Kuzuhara, S.; Sasaki, H.; Imahori, K. Large-Scale, Multicenter Study of Cerebrospinal Fluid Tau Protein Phosphorylated at Serine 199 for the Antemortem Diagnosis of Alzheimer's Disease. *Ann. Neurol.* **2001**, *50* (2), 150−156.
(114) Arai, H.; Ishiguro, K.; Ohno, H.; Moriyama, M.; Itoh, N.; Okamura, N.; Matsui, T.; Morikawa, Y.; Horikawa, E.; Kohno, H.; Sasaki, H.; Imahori, K. CSF Phosphorylated Tau Protein and Mild Cognitive Impairment: A Prospective Study. *Exp. Neurol.* **2000**, *166* (1), 201−203.
(115) Chalermpalanupap, T.; Kinkead, B.; Hu, W. T.; Kummer, M. P.; Hammerschmidt, T.; Heneka, M. T.; Weinshenker, D.; Levey, A. I. Targeting Norepinephrine in Mild Cognitive Impairment and Alzheimer's Disease. *Alzheimers. Res. Ther.* **2013**, *5* (2), 21.
(116) Burke, W. J.; Kristal, B. S.; Yu, B. P.; Li, S. W.; Lin, T.-S. Norepinephrine Transmitter Metabolite Generates Free Radicals and Activates Mitochondrial Permeability Transition: A Mechanism for DOPEGAL-Induced Apoptosis. *Brain Res.* **1998**, *787* (2), 328−332.
(117) Li, S. W.; Lin, T.-S.; Minteer, S.; Burke, W. J. 3,4-Dihydroxyphenylacetaldehyde and Hydrogen Peroxide Generate a Hydroxyl Radical: Possible Role in Parkinson's Disease Pathogenesis. *Mol. Brain Res.* **2001**, *93* (1), 1−7.
(118) Ferreira-Vieira, T. H.; Guimaraes, I. M.; Silva, F. R.; Ribeiro, F. M. Alzheimer's Disease: Targeting the Cholinergic System. *Curr. Neuropharmacol.* **2016**, *14* (1), 101−115.
(119) He, Z.; Li, X.; Wang, Z.; Tu, S.; Feng, J.; Du, X.; Ni, J.; Li, N.; Liu, Q. Esculentoside A Alleviates Cognitive Deficits and Amyloid Pathology through Peroxisome Proliferator-Activated Receptor γ-Dependent Mechanism in an Alzheimer's Disease Model. *Phytomedicine* **2022**, *98*, No. 153956.
(120) Zhao, J.; Yu, L.; Xue, X.; Xu, Y.; Huang, T.; Xu, D.; Wang, Z.; Luo, L.; Wang, H. Diminished A7 Nicotinic Acetylcholine Receptor (A7nAChR) Rescues Amyloid-β Induced Atrial Remodeling by Oxi-CaMKII/MAPK/AP-1 Axis-Mediated Mitochondrial Oxidative Stress. *Redox Biol.* **2023**, *59*, No. 102594.
(121) He, Z.; Li, X.; Wang, Z.; Cao, Y.; Han, S.; Li, N.; Cai, J.; Cheng, S.; Liu, Q. Protective Effects of Luteolin against Amyloid Beta-Induced Oxidative Stress and Mitochondrial Impairments through Peroxisome Proliferator-Activated Receptor γ-Dependent Mechanism in Alzheimer's Disease. *Redox Biol.* **2023**, *66*, No. 102848.
(122) Bhatia, V.; Sharma, S. Role of Mitochondrial Dysfunction, Oxidative Stress and Autophagy in Progression of Alzheimer's Disease. *J. Neurol. Sci.* **2021**, *421*, No. 117253.
(123) Leyane, T. S.; Jere, S. W.; Houreld, N. N. Oxidative Stress in Ageing and Chronic Degenerative Pathologies: Molecular Mechanisms Involved in Counteracting Oxidative Stress and Chronic Inflammation. *Int. J. Mol. Sci.* **2022**, *23* (13), 7273.
(124) Kowalczyk, P.; Sulejczak, D.; Kleczkowska, P.; Bukowska-Ośko, I.; Kucia, M.; Popiel, M.; Wietrak, E.; Kramkowski, K.; Wrzosek, K.; Kaczyńska, K. Mitochondrial Oxidative Stress—A Causative Factor and Therapeutic Target in Many Diseases. *Int. J. Mol. Sci.* **2021**, *22* (24), 13384.
(125) de Oliveira, M. R.; Nabavi, S. M.; Braidy, N.; Setzer, W. N.; Ahmed, T.; Nabavi, S. F. Quercetin and the Mitochondria: A Mechanistic View. *Biotechnol. Adv.* **2016**, *34* (5), 532−549.
(126) Wang, W.-W.; Han, R.; He, H.-J.; Li, J.; Chen, S.-Y.; Gu, Y.; Xie, C. Administration of Quercetin Improves Mitochondria Quality Control and Protects the Neurons in 6-OHDA-Lesioned Parkinson's Disease Models. *Aging (Albany. NY).* **2021**, *13* (8), 11738−11751.
(127) Zhang, L.; Chang, R. C.-C.; Chu, L.-W.; Mak, H. K.-F. Current Neuroimaging Techniques in Alzheimer's Disease and Applications in Animal Models. *Am. J. Nucl. Med. Mol. Imaging* **2012**, *2* (3), 386−404.
(128) Colton, C. A.; Wilcock, D. M.; Wink, D. A.; Davis, J.; Van Nostrand, W. E.; Vitek, M. P. The Effects of NOS2 Gene Deletion on Mice Expressing Mutated Human AβPP. *J. Alzheimer's Dis.* **2008**, *15* (4), 571−587.
(129) Nabeshi, H.; Oikawa, S.; Inoue, S.; Nishino, K.; Kawanishi, S.; Nabeshi, H.; Oikawa, S.; Inoue, S.; Nishino, K.; Kawanishi, S. Proteomic Analysis for Protein Carbonyl as an Indicator of Oxidative Damage in Senescence-Accelerated Mice. *Free Radic. Res.* **2006**, *40* (11), 1173−1181.
(130) Yuan, A.; Halabicky, O.; Rao, H.; Liu, J. Lifetime Air Pollution Exposure, Cognitive Deficits, and Brain Imaging Outcomes: A Systematic Review. *Neurotoxicology* **2023**, *96*, 69−80.
(131) Dhenain, M.; El Tannir El Tayara, N.; Wu, T.-D.; Guégan, M.; Volk, A.; Quintana, C.; Delatour, B. Characterization of in Vivo MRI Detectable Thalamic Amyloid Plaques from APP/PS1Mice. *Neurobiol. Aging* **2009**, *30* (1), 41−53.
(132) Yang, D.; Xie, Z.; Stephenson, D.; Morton, D.; Hicks, C. D.; Brown, T. M.; Sriram, R.; O'Neill, S.; Raunig, D.; Bocan, T. Volumetric MRI and MRS Provide Sensitive Measures of Alzheimer's Disease Neuropathology in Inducible Tau Transgenic Mice (RTg4510). *Neuroimage* **2011**, *54* (4), 2652−2658.
(133) Risacher, S. L.; Saykin, A. J. Neuroimaging and Other Biomarkers for Alzheimer's Disease: The Changing Landscape of Early Detection. *Annu. Rev. Clin. Psychol.* **2013**, *9* (1), 621−648.
(134) Johnson, K. A.; Fox, N. C.; Sperling, R. A.; Klunk, W. E. Brain Imaging in Alzheimer Disease. *Cold Spring Harb. Perspect. Med.* **2012**, *2* (4), a006213−a006213.
(135) Kuntner, C.; Kesner, A. L.; Bauer, M.; Kremslehner, R.; Wanek, T.; Mandler, M.; Karch, R.; Stanek, J.; Wolf, T.; Müller, M.; Langer, O. Limitations of Small Animal PET Imaging with [18F]FDDNP and FDG for Quantitative Studies in a Transgenic Mouse Model of Alzheimer's Disease. *Mol. Imaging Biol.* **2009**, *11* (4), 236−240.
(136) Ikonomovic, M. D.; Klunk, W. E.; Abrahamson, E. E.; Mathis, C. A.; Price, J. C.; Tsopelas, N. D.; Lopresti, B. J.; Ziolko, S.; Bi, W.; Paljug, W. R.; Debnath, M. L.; Hope, C. E.; Isanski, B. A.; Hamilton, R. L.; DeKosky, S. T. Post-Mortem Correlates of in Vivo PiB-PET Amyloid Imaging in a Typical Case of Alzheimer's Disease. *Brain* **2008**, *131* (6), 1630−1645.
(137) Maeda, J.; Ji, B.; Irie, T.; Tomiyama, T.; Maruyama, M.; Okauchi, T.; Staufenbiel, M.; Iwata, N.; Ono, M.; Saido, T. C.; Suzuki, K.; Mori, H.; Higuchi, M.; Suhara, T. Longitudinal, Quantitative Assessment of Amyloid, Neuroinflammation, and Anti-Amyloid Treatment in a Living Mouse Model of Alzheimer's Disease Enabled by Positron Emission Tomography. *J. Neurosci.* **2007**, *27* (41), 10957−10968.
(138) Villa, C.; Lavitrano, M.; Salvatore, E.; Combi, R. Molecular and Imaging Biomarkers in Alzheimer's Disease: A Focus on Recent Insights. *J. Pers. Med.* **2020**, *10* (3), 61.
(139) Kincses, Z. T.; Király, A.; Veréb, D.; Vécsei, L. Structural Magnetic Resonance Imaging Markers of Alzheimer's Disease and Its Retranslation to Rodent Models. *J. Alzheimer's Dis.* **2015**, *47* (2), 277−290.

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631

(140) Masliah, E.; Sisk, A.; Mallory, M.; Games, D. Neurofibrillary Pathology in Transgenic Mice Overexpressing V717F β-Amyloid Precursor Protein. *J. Neuropathol. Exp. Neurol.* **2001**, *60* (4), 357−368.
(141) Song, S.-K.; Kim, J. H.; Lin, S.-J.; Brendza, R. P.; Holtzman, D. M. Diffusion Tensor Imaging Detects Age-Dependent White Matter Changes in a Transgenic Mouse Model with Amyloid Deposition. *Neurobiol. Dis.* **2004**, *15* (3), 640−647.
(142) O'Donnell, L. J.; Westin, C.-F. An Introduction to Diffusion Tensor Image Analysis. *Neurosurg. Clin. N. Am.* **2011**, *22* (2), 185−196.
(143) Assaf, Y.; Pasternak, O. Diffusion Tensor Imaging (DTI)-Based White Matter Mapping in Brain Research: A Review. *J. Mol. Neurosci.* **2008**, *34* (1), 51−61.
(144) Vanhoutte, G.; Pereson, S.; Delgado y Palacios, R.; Guns, P.-J.; Asselbergh, B.; Veraart, J.; Sijbers, J.; Verhoye, M.; Van Broeckhoven, C.; Van der Linden, A. Diffusion Kurtosis Imaging to Detect Amyloidosis in an APP/PS1Mouse Model for Alzheimer's Disease. *Magn. Reson. Med.* **2013**, *69* (4), 1115−1121.
(145) Szabó, N.; Kincses, Z. T.; Párdutz, Á.; Tajti, J.; Szok, D.; Tuka, B.; Király, A.; Babos, M.; Vörös, E.; Bomboi, G.; Orzi, F.; Vécsei, L. White Matter Microstructural Alterations in Migraine: A Diffusion-Weighted MRI Study. *Pain* **2012**, *153* (3), 651−656.
(146) Rosas, H. D.; Tuch, D. S.; Hevelone, N. D.; Zaleta, A. K.; Vangel, M.; Hersch, S. M.; Salat, D. H. Diffusion Tensor Imaging in Presymptomatic and Early Huntington's Disease: Selective White Matter Pathology and Its Relationship to Clinical Measures. *Mov. Disord.* **2006**, *21* (9), 1317−1325.
(147) O'Dwyer, L.; Lamberton, F.; Bokde, A. L. W.; Ewers, M.; Faluyi, Y. O.; Tanner, C.; Mazoyer, B.; O'Neill, D.; Bartley, M.; Collins, D. R.; Coughlan, T.; Prvulovic, D.; Hampel, H. Multiple Indices of Diffusion Identifies White Matter Damage in Mild Cognitive Impairment and Alzheimer's Disease. *PLoS One* **2011**, *6* (6), No. e21745.
(148) Hattori, T.; Ito, K.; Aoki, S.; Yuasa, T.; Sato, R.; Ishikawa, M.; Sawaura, H.; Hori, M.; Mizusawa, H. White Matter Alteration in Idiopathic Normal Pressure Hydrocephalus: Tract-Based Spatial Statistics Study. *Am. J. Neuroradiol.* **2012**, *33* (1), 97−103.
(149) LeBihan, D. IVIM Method Measures Diffusion and Perfusion. *Diagn. Imaging* **1990**, *12* (6), 133−136.
(150) Fornari, E.; Maeder, P.; Meuli, R.; Ghika, J.; Knyazeva, M. G. Demyelination of Superficial White Matter in Early Alzheimer's Disease: A Magnetization Transfer Imaging Study. *Neurobiol. Aging* **2012**, *33* (2), 428.e7−428.e19.
(151) Reveley, C.; Seth, A. K.; Pierpaoli, C.; Silva, A. C.; Yu, D.; Saunders, R. C.; Leopold, D. A.; Ye, F. Q. Superficial White Matter Fiber Systems Impede Detection of Long-Range Cortical Connections in Diffusion MR Tractography. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112* (21), E2820−E2828, DOI: 10.1073/pnas.1418198112.
(152) Le Bihan, D. Looking into the Functional Architecture of the Brain with Diffusion MRI. *Nat. Rev. Neurosci.* **2003**, *4* (6), 469−480.
(153) Mori, S.; Crain, B. J.; Chacko, V. P.; Van Zijl, P. C. M. Three-Dimensional Tracking of Axonal Projections in the Brain by Magnetic Resonance Imaging. *Ann. Neurol.* **1999**, *45* (2), 265−269.
(154) Reginold, W.; Luedke, A. C.; Itorralba, J.; Fernandez-Ruiz, J.; Islam, O.; Garcia, A. Altered Superficial White Matter on Tractography MRI in Alzheimer's Disease. *Dement. Geriatr. Cogn. Dis. Extra* **2016**, *6* (2), 233−241.
(155) Jbabdi, S.; Johansen-Berg, H. Tractography: Where Do We Go from Here? *Brain Connect.* **2011**, *1* (3), 169−183.
(156) Tuch, D. S.; Reese, T. G.; Wiegell, M. R.; Wedeen, V. J. Diffusion MRI of Complex Neural Architecture. *Neuron* **2003**, *40* (5), 885−895.
(157) Tuch, D. S. Q-Ball Imaging. *Magn. Reson. Med.* **2004**, *52* (6), 1358−1372.
(158) Wedeen, V. J.; Wang, R. P.; Schmahmann, J. D.; Benner, T.; Tseng, W. Y. I.; Dai, G.; Pandya, D. N.; Hagmann, P.; D'Arceuil, H.; de Crespigny, A. J. Diffusion Spectrum Magnetic Resonance Imaging (DSI) Tractography of Crossing Fibers. *Neuroimage* **2008**, *41* (4), 1267−1277.
(159) Le Bihan, D. Apparent Diffusion Coefficient and Beyond: What Diffusion MR Imaging Can Tell Us about Tissue Structure. *Radiology* **2013**, *268* (2), 318−322.
(160) Basser, P. J.; Mattiello, J.; LeBihan, D. MR Diffusion Tensor Spectroscopy and Imaging. *Biophys. J.* **1994**, *66* (1), 259−267.
(161) Beaulieu, C. The Basis of Anisotropic Water Diffusion in the Nervous System - a Technical Review. *NMR Biomed.* **2002**, *15* (7−8), 435−455.
(162) Jensen, J. H.; Helpern, J. A.; Ramani, A.; Lu, H.; Kaczynski, K. Diffusional Kurtosis Imaging: The Quantification of Non-Gaussian Water Diffusion by Means of Magnetic Resonance Imaging. *Magn. Reson. Med.* **2005**, *53* (6), 1432−1440.
(163) Hui, E. S.; Cheung, M. M.; Qi, L.; Wu, E. X. Towards Better MR Characterization of Neural Tissues Using Directional Diffusion Kurtosis Analysis. *Neuroimage* **2008**, *42* (1), 122−134.
(164) Van Cauter, S.; Veraart, J.; Sijbers, J.; Peeters, R. R.; Himmelreich, U.; De Keyzer, F.; Van Gool, S. W.; Van Calenbergh, F.; De Vleeschouwer, S.; Van Hecke, W.; Sunaert, S. Gliomas: Diffusion Kurtosis MR Imaging in Grading. *Radiology* **2012**, *263* (2), 492−501.
(165) Lu, H.; Jensen, J. H.; Ramani, A.; Helpern, J. A. Three-Dimensional Characterization of Non-Gaussian Water Diffusion in Humans Using Diffusion Kurtosis Imaging. *NMR Biomed.* **2006**, *19* (2), 236−247.
(166) Zhuo, J.; Xu, S.; Proctor, J. L.; Mullins, R. J.; Simon, J. Z.; Fiskum, G.; Gullapalli, R. P. Diffusion Kurtosis as an in Vivo Imaging Marker for Reactive Astrogliosis in Traumatic Brain Injury. *Neuroimage* **2012**, *59* (1), 467−477.
(167) Arab, A.; Wojna-Pelczar, A.; Khairnar, A.; Szabó, N.; Ruda-Kucerova, J. Principles of Diffusion Kurtosis Imaging and Its Role in Early Diagnosis of Neurodegenerative Disorders. *Brain Res. Bull.* **2018**, *139*, 91−98.
(168) Steven, A. J.; Zhuo, J.; Melhem, E. R. Diffusion Kurtosis Imaging: An Emerging Technique for Evaluating the Microstructural Environment of the Brain. *Am. J. Roentgenol.* **2014**, *202* (1), W26−W33.
(169) Kantarci, K. 1 H Magnetic Resonance Spectroscopy in Dementia. *Br. J. Radiol.* **2007**, *80* (special_issue_2), S146−S152.
(170) Ross, B. D.; Bluml, S.; Cowan, R.; Danielsen, E.; Farrow, N.; Tan, J. In Vivo MR Spectroscopy of Human Dementia. *Neuroimaging Clin. N. Am.* **1998**, *8* (4), 809−822.
(171) Zhang, X.; Tian, Y.; Zhang, C.; Tian, X.; Ross, A. W.; Moir, R. D.; Sun, H.; Tanzi, R. E.; Moore, A.; Ran, C. Near-Infrared Fluorescence Molecular Imaging of Amyloid Beta Species and Monitoring Therapy in Animal Models of Alzheimer's Disease. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112* (31), 9734−9739.
(172) Akasaka, T.; Watanabe, H.; Ono, M. In Vivo Near-Infrared Fluorescence Imaging Selective for Soluble Amyloid β Aggregates Using y-Shaped BODIPY Derivative. *J. Med. Chem.* **2023**, *66*, 14029.
(173) Rajasekhar, K.; Narayanaswamy, N.; Murugan, N. A.; Viccaro, K.; Lee, H.-G.; Shah, K.; Govindaraju, T. Aβ Plaque-Selective NIR Fluorescence Probe to Differentiate Alzheimer's Disease from Tauopathies. *Biosens. Bioelectron.* **2017**, *98*, 54−61.
(174) Liu, Y.; Zhuang, D.; Wang, J.; Huang, H.; Li, R.; Wu, C.; Deng, Y.; Hu, G.; Guo, B. Recent Advances in Small Molecular Near-Infrared Fluorescence Probes for a Targeted Diagnosis of the Alzheimer Disease. *Analyst* **2022**, *147* (21), 4701−4723.
(175) Valenzuela, M. J.; Sachdev, P. Magnetic Resonance Spectroscopy in AD. *Neurology* **2001**, *56* (5), 592−598.
(176) Mills, N. L.; Donaldson, K.; Hadoke, P. W.; Boon, N. A.; MacNee, W.; Cassee, F. R.; Sandström, T.; Blomberg, A.; Newby, D. E. Adverse Cardiovascular Effects of Air Pollution. *Nat. Clin. Pract. Cardiovasc. Med.* **2009**, *6* (1), 36−44.
(177) Calderón-Garcidueñas, L.; Reynoso-Robles, R.; González-Maciel, A. Combustion and Friction-Derived Nanoparticles and Industrial-Sourced Nanoparticles: The Culprit of Alzheimer and Parkinson's Diseases. *Environ. Res.* **2019**, *176*, No. 108574.

(178) Fan, H.; Zhao, C.; Yang, Y.; Yang, X. Spatio-Temporal Variations of the PM2.5/PM10 Ratios and Its Application to Air Pollution Type Classification in China. *Front. Environ. Sci.* **2021**, *9*, No. 692440, DOI: 10.3389/fenvs.2021.692440.
(179) VALAVANIDIS, A.; FIOTAKIS, K.; VLACHOGIANNI, T. Airborne Particulate Matter and Human Health: Toxicological Assessment and Importance of Size and Composition of Particles for Oxidative Damage and Carcinogenic Mechanisms. *J. Environ. Sci. Heal. Part C* **2008**, *26* (4), 339−362.
(180) Loane, C.; Pilinis, C.; Lekkas, T. D.; Politis, M. Ambient Particulate Matter and Its Potential Neurological Consequences. *Rev. Neurosci.* **2013**, *24* (3), 323−335, DOI: 10.1515/revneuro-2013-0001.
(181) Calderón-Garcidueñas, L.; Mora-Tiscareño, A.; Ontiveros, E.; Gómez-Garza, G.; Barragán-Mejía, G.; Broadway, J.; Chapman, S.; Valencia-Salazar, G.; Jewells, V.; Maronpot, R. R.; Henríquez-Roldán, C.; Pérez-Guillé, B.; Torres-Jardón, R.; Herrit, L.; Brooks, D.; Osnaya-Brizuela, N.; Monroy, M. E.; González-Maciel, A.; Reynoso-Robles, R.; Villarreal-Calderon, R.; Solt, A. C.; Engle, R. W. Air Pollution, Cognitive Deficits and Brain Abnormalities: A Pilot Study with Children and Dogs. *Brain Cogn.* **2008**, *68* (2), 117−127.
(182) Guo, Z.; Cupples, L. A.; Kurz, A.; Auerbach, S. H.; Volicer, L.; Chui, H.; Green, R. C.; Sadovnick, A. D.; Duara, R.; DeCarli, C.; Johnson, K.; Go, R. C.; Growdon, J. H.; Haines, J. L.; Kukull, W. A.; Farrer, L. A. Head Injury and the Risk of AD in the MIRAGE Study. *Neurology* **2000**, *54* (6), 1316−1323.
(183) Hamanaka, R. B.; Mutlu, G. M. Particulate Matter Air Pollution: Effects on the Cardiovascular System. *Front. Endocrinol.* **2018**, *9*, No. 680, DOI: 10.3389/fendo.2018.00680.
(184) Sacks, J. D.; Stanek, L. W.; Luben, T. J.; Johns, D. O.; Buckley, B. J.; Brown, J. S.; Ross, M. Particulate Matter−Induced Health Effects: Who Is Susceptible? *Environ. Health Perspect.* **2011**, *119* (4), 446−454.
(185) Bell, M. L.; Zanobetti, A.; Dominici, F. Evidence on Vulnerability and Susceptibility to Health Risks Associated With Short-Term Exposure to Particulate Matter: A Systematic Review and Meta-Analysis. *Am. J. Epidemiol.* **2013**, *178* (6), 865−876.
(186) Levesque, S.; Taetzsch, T.; Lull, M. E.; Kodavanti, U.; Stadler, K.; Wagner, A.; Johnson, J. A.; Duke, L.; Kodavanti, P.; Surace, M. J.; Block, M. L. Diesel Exhaust Activates and Primes Microglia: Air Pollution, Neuroinflammation, and Regulation of Dopaminergic Neurotoxicity. *Environ. Health Perspect.* **2011**, *119* (8), 1149−1155.
(187) Block, M. L.; Wu, X.; Pei, Z.; Li, G.; Wang, T.; Qin, L.; Wilson, B.; Yang, J.; Hong, J. S.; Veronesi, B. Nanometer Size Diesel Exhaust Particles Are Selectively Toxic to Dopaminergic Neurons: The Role of Microglia, Phagocytosis, and NADPH Oxidase. *FASEB J.* **2004**, *18* (13), 1618−1620.
(188) Calderón-Garcidueñas, L.; Solt, A. C.; Henríquez-Roldán, C.; Torres-Jardón, R.; Nuse, B.; Herritt, L.; Villarreal-Calderón, R.; Osnaya, N.; Stone, I.; García, R.; Brooks, D. M.; González-Maciel, A.; Reynoso-Robles, R.; Delgado-Chávez, R.; Reed, W. Long-Term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid β-42 and α-Synuclein in Children and Young Adult. *Toxicol. Pathol.* **2008**, *36* (2), 289−310.
(189) Livingston, G.; Sommerlad, A.; Orgeta, V.; Costafreda, S. G.; Huntley, J.; Ames, D.; Ballard, C.; Banerjee, S.; Burns, A.; Cohen-Mansfield, J.; Cooper, C.; Fox, N.; Gitlin, L. N.; Howard, R.; Kales, H. C.; Larson, E. B.; Ritchie, K.; Rockwood, K.; Sampson, E. L.; Samus, Q.; Schneider, L. S.; Selbæk, G.; Teri, L.; Mukadam, N. Dementia Prevention, Intervention, and Care. *Lancet* **2017**, *390* (10113), 2673−2734.
(190) Landrigan, P. J.; Fuller, R.; Acosta, N. J. R.; Adeyi, O.; Arnold, R.; Basu, N.; Baldé, A. B.; Bertollini, R.; Bose-O'Reilly, S.; Boufford, J. I.; Breysse, P. N.; Chiles, T.; Mahidol, C.; Coll-Seck, A. M.; Cropper, M. L.; Fobil, J.; Fuster, V.; Greenstone, M.; Haines, A.; Hanrahan, D.; Hunter, D.; Khare, M.; Krupnick, A.; Lanphear, B.; Lohani, B.; Martin, K.; Mathiasen, K. V.; McTeer, M. A.; Murray, C. J. L.; Ndahimananjara, J. D.; Perera, F.; Potočnik, J.; Preker, A. S.; Ramesh, J.; Rockström, J.; Salinas, C.; Samson, L. D.; Sandilya, K.; Sly, P. D.; Smith, K. R.; Steiner, A.; Stewart, R. B.; Suk, W. A.; van Schayck, O. C. P.; Yadama, G. N.; Yumkella, K.; Zhong, M. The Lancet Commission on Pollution and Health. *Lancet* **2018**, *391* (10119), 462−512.
(191) Kampa, M.; Castanas, E. Human Health Effects of Air Pollution. *Environ. Pollut.* **2008**, *151* (2), 362−367.
(192) THRON, R. Direct and Indirect Exposure to Air Pollution. *Otolaryngol. - Head Neck Surg.* **1996**, *114* (2), 281−285.
(193) Platt, S. M.; Haddad, I. E.; Pieber, S. M.; Huang, R.-J.; Zardini, A. A.; Clairotte, M.; Suarez-Bertoa, R.; Barmet, P.; Pfaffenberger, L.; Wolf, R.; Slowik, J. G.; Fuller, S. J.; Kalberer, M.; Chirico, R.; Dommen, J.; Astorga, C.; Zimmermann, R.; Marchand, N.; Hellebust, S.; Temime-Roussel, B.; Baltensperger, U.; Prévôt, A. S. H. Two-Stroke Scooters Are a Dominant Source of Air Pollution in Many Cities. *Nat. Commun.* **2014**, *5* (1), 3749.
(194) Calderón-Garcidueñas, L.; Leray, E.; Heydarpour, P.; Torres-Jardón, R.; Reis, J. Air Pollution, a Rising Environmental Risk Factor for Cognition, Neuroinflammation and Neurodegeneration: The Clinical Impact on Children and Beyond. *Rev. Neurol. (Paris).* **2016**, *172* (1), 69−80.
(195) Yolton, K.; Dietrich, K.; Auinger, P.; Lanphear, B. P.; Hornung, R. Exposure to Environmental Tobacco Smoke and Cognitive Abilities among U.S. Children and Adolescents. *Environ. Health Perspect.* **2005**, *113* (1), 98−103.
(196) Calderón-Garcidueñas, L.; Serrano-Sierra, A.; Torres-Jardón, R.; Zhu, H.; Yuan, Y.; Smith, D.; Delgado-Chávez, R.; Cross, J. V.; Medina-Cortina, H.; Kavanaugh, M.; Guilarte, T. R. The Impact of Environmental Metals in Young Urbanites' Brains. *Exp. Toxicol. Pathol.* **2013**, *65* (5), 503−511.
(197) Bandyopadhyay, A. Neurological Disorders from Ambient (Urban) Air Pollution Emphasizing UFPM and PM2.5. *Curr. Pollut. Reports* **2016**, *2* (3), 203−211.
(198) Calderón-Garcidueñas, L.; Mora-Tiscareño, A.; Franco-Lira, M.; Zhu, H.; Lu, Z.; Solorio, E.; Torres-Jardón, R.; D'Angiulli, A. Decreases in Short Term Memory, IQ, and Altered Brain Metabolic Ratios in Urban Apolipoprotein E4 Children Exposed to Air Pollution. *J. Alzheimer's Dis.* **2015**, *45* (3), 757−770.
(199) Segarra, A. B.; Banegas, I.; Prieto, I.; Ramirez-Sanchez, M. [Brain Asymmetry and Dopamine: Beyond Motor Implications in Parkinson's Disease and Experimental Hemiparkinsonism]. *Rev. Neurol.* **2016**, *63* (9), 415−421.
(200) Segarra, A.; Prieto, I.; Martínez-Cañamero, M.; Ramírez-Sánchez, M. Is There a Link between Depression, Neurochemical Asymmetry and Cardiovascular Function? *AIMS Neurosci.* **2020**, *7* (4), 360−372.
(201) Hahad, O.; Lelieveld, J.; Birklein, F.; Lieb, K.; Daiber, A.; Münzel, T. Ambient Air Pollution Increases the Risk of Cerebrovascular and Neuropsychiatric Disorders through Induction of Inflammation and Oxidative Stress. *Int. J. Mol. Sci.* **2020**, *21* (12), 4306.
(202) Elder, A.; Gelein, R.; Silva, V.; Feikert, T.; Opanashuk, L.; Carter, J.; Potter, R.; Maynard, A.; Ito, Y.; Finkelstein, J.; Oberdörster, G. Translocation of Inhaled Ultrafine Manganese Oxide Particles to the CentralNervous System. *Environ. Health Perspect.* **2006**, *114* (8), 1172−1178.
(203) Lucas, S.-M.; Rothwell, N. J.; Gibson, R. M. The Role of Inflammation in CNS Injury and Disease. *Br. J. Pharmacol.* **2006**, *147* (S1), S232−S240.
(204) Shen, H. H. Microbes on the Mind. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112* (30), 9143−9145.
(205) Block, M. L.; Elder, A.; Auten, R. L.; Bilbo, S. D.; Chen, H.; Chen, J.-C.; Cory-Slechta, D. A.; Costa, D.; Diaz-Sanchez, D.; Dorman, D. C.; Gold, D. R.; Gray, K.; Jeng, H. A.; Kaufman, J. D.; Kleinman, M. T.; Kirshner, A.; Lawler, C.; Miller, D. S.; Nadadur, S. S.; Ritz, B.; Semmens, E. O.; Tonelli, L. H.; Veronesi, B.; Wright, R. O.; Wright, R. J. The Outdoor Air Pollution and Brain Health Workshop. *Neurotoxicology* **2012**, *33* (5), 972−984.

(206) Jew, K.; Herr, D.; Wong, C.; Kennell, A.; Morris-Schaffer, K.; Oberdörster, G.; O'Banion, M. K.; Cory-Slechta, D. A.; Elder, A. Selective Memory and Behavioral Alterations after Ambient Ultrafine Particulate Matter Exposure in Aged 3xTgAD Alzheimer's Disease Mice. *Part. Fibre Toxicol.* **2019**, *16* (1), 45.
(207) Sunyer, J.; Esnaola, M.; Alvarez-Pedrerol, M.; Forns, J.; Rivas, I.; López-Vicente, M.; Suades-González, E.; Foraster, M.; Garcia-Esteban, R.; Basagaña, X.; Viana, M.; Cirach, M.; Moreno, T.; Alastuey, A.; Sebastian-Galles, N.; Nieuwenhuijsen, M.; Querol, X. Association between Traffic-Related Air Pollution in Schools and Cognitive Development in Primary School Children: A Prospective Cohort Study. *PLOS Med.* **2015**, *12* (3), No. e1001792.
(208) Chang, Y.-C.; Daza, R.; Hevner, R.; Costa, L. G.; Cole, T. B. Prenatal and Early Life Diesel Exhaust Exposure Disrupts Cortical Lamina Organization: Evidence for a Reelin-Related Pathogenic Pathway Induced by Interleukin-6. *Brain. Behav. Immun.* **2019**, *78*, 105−115.
(209) Peeples, L. How Air Pollution Threatens Brain Health. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117* (25), 13856−13860.
(210) Calderón-Garcidueñas, L.; Cross, J. V.; Franco-Lira, M.; Aragón-Flores, M.; Kavanaugh, M.; Torres-Jardón, R.; Chao, C.-K.; Thompson, C.; Chang, J.; Zhu, H.; D'Angiulli, A. Brain Immune Interactions and Air Pollution: Macrophage Inhibitory Factor (MIF), Prion Cellular Protein (PrP(C)), Interleukin-6 (IL-6), Interleukin 1 Receptor Antagonist (IL-1Ra), and Interleukin-2 (IL-2) in Cerebrospinal Fluid and MIF in Serum Differenti. *Front. Neurosci.* **2013**, *7*, 183.
(211) Vrahatis, A. G.; Skolariki, K.; Krokidis, M. G.; Lazaros, K.; Exarchos, T. P.; Vlamos, P. Revolutionizing the Early Detection of Alzheimer's Disease through Non-Invasive Biomarkers: The Role of Artificial Intelligence and Deep Learning. *Sensors* **2023**, *23* (9), 4184.
(212) Fujita, K.; Katsuki, M.; Takasu, A.; Kitajima, A.; Shimazu, T.; Maruki, Y. Development of an Artificial Intelligence-Based Diagnostic Model for Alzheimer's Disease. *Aging Med.* **2022**, *5* (3), 167−173.
(213) Nasrumminallah, M.; Rehan, F.; Sawairah, M. Using Artificial Intelligence Technology- for Diagnosing Alzheimer's Disease before Emerging of Symptoms. *J. Pak. Med. Assoc.* **2023**, *73* (2), 456−456.
(214) Davodabadi, A.; Daneshian, B.; Saati, S.; Razavyan, S. Mathematical Model and Artificial Intelligence for Diagnosis of Alzheimer's Disease. *Eur. Phys. J. Plus* **2023**, *138* (5), 474.
(215) Bayat, S.; Roe, C. M.; Schindler, S.; Murphy, S. A.; Doherty, J. M.; Johnson, A. M.; Walker, A.; Ances, B. M.; Morris, J. C.; Babulal, G. M. Everyday Driving and Plasma Biomarkers in Alzheimer's Disease: Leveraging Artificial Intelligence to Expand Our Diagnostic Toolkit. *J. Alzheimer's Dis.* **2023**, *92* (4), 1487−1497.
(216) Sekaran, K.; Alsamman, A. M.; George Priya Doss, C.; Zayed, H. Bioinformatics Investigation on Blood-Based Gene Expressions of Alzheimer's Disease Revealed ORAI2 Gene Biomarker Susceptibility: An Explainable Artificial Intelligence-Based Approach. *Metab. Brain Dis.* **2023**, *38* (4), 1297−1310.
(217) Khachaturian, A. S.; Dengel, A.; Dočkal, V.; Hroboň, P.; Tolar, M. Editorial: Accelerating Innovations for Enhanced Brain Health. Can Artificial Intelligence Advance New Pathways for Drug Discovery for Alzheimer's and Other Neurodegenerative Disorders? *J. Prev. Alzheimer's Dis.* **2023**, *10*, 1−4.
(218) Gunes, S.; Aizawa, Y.; Sugashi, T.; Sugimoto, M.; Rodrigues, P. P. Biomarkers for Alzheimer's Disease in the Current State: A Narrative Review. *Int. J. Mol. Sci.* **2022**, *23* (9), 4962.
(219) Mirkin, S.; Albensi, B. C. Should Artificial Intelligence Be Used in Conjunction with Neuroimaging in the Diagnosis of Alzheimer's Disease? *Front. Aging Neurosci.* **2023**, *15*, No. 1094233, DOI: 10.3389/fnagi.2023.1094233.
(220) Finney, C. A.; Delerue, F.; Gold, W. A.; Brown, D. A.; Shvetcov, A. Artificial Intelligence-Driven Meta-Analysis of Brain Gene Expression Identifies Novel Gene Candidates and a Role for Mitochondria in Alzheimer's Disease. *Comput. Struct. Biotechnol. J.* **2023**, *21*, 388−400.
(221) Sadegh-Zadeh, S.-A.; Fakhri, E.; Bahrami, M.; Bagheri, E.; Khamsehashari, R.; Noroozian, M.; Hajiyavand, A. M. An Approach toward Artificial Intelligence Alzheimer's Disease Diagnosis Using Brain Signals. *Diagnostics* **2023**, *13* (3), 477.
(222) Ziyad, S. R.; Alharbi, M.; Altulyan, M. Artificial Intelligence Model for Alzheimer's Disease Detection with Convolution Neural Network for Magnetic Resonance Images. *J. Alzheimer's Dis.* **2023**, *93* (1), 235−245.
(223) Yao, Z.; Wang, H.; Yan, W.; Wang, Z.; Zhang, W.; Wang, Z.; Zhang, G. Artificial Intelligence-Based Diagnosis of Alzheimer's Disease with Brain MRI Images. *Eur. J. Radiol.* **2023**, *165*, No. 110934.

https://doi.org/10.1021/acsomega.3c06328
ACS Omega 2024, 9, 8615−8631