Influence of Woodsmoke Exposure on Molecular Mechanisms Underlying Alzheimer's Disease: Existing Literature and Gaps in Our Understanding

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ABSTRACT: Woodsmoke poses a significant health risk as a growing component of ambient air pollution in the United States. While there is a long history of association between woodsmoke exposure and diseases of the respiratory, circulatory, and cardiovascular systems, recent evidence has linked woodsmoke exposure to cognitive dysfunction, including Alzheimer's disease dementia. Alzheimer's disease is a progressive neurodegenerative disorder with largely idiopathic origins and no known cure. Here, we explore the growing body of literature which relates woodsmoke-generated and ambient air pollution particulate matter exposure to Alzheimer's disease (AD) onset or exacerbation, in the context of an inflammation-centric view of AD. Epigenetic modifications, specifically changes in DNA methylation patterns, are well documented following woodsmoke exposure and have been shown to influence disease-favoring inflammatory cascades, induce oxidative stress, and modulate the immune response in vitro, in vivo, and in humans following exposure to air pollution. Though the current status of the literature does not allow us to draw definitive conclusions linking these events, this review highlights the need for additional work to fill gaps in our understanding of the directionality, causality, and susceptibility throughout the life course.

KEYWORDS: Epigenetics, Alzheimer's disease, woodsmoke, wildfire smoke, DNA methylation, dementia, inflammation, air pollution

Background

An estimated 9 out of 10 individuals live where air quality exceeds World Health Organization guidelines.[1] This is the result of high levels of ambient air pollution (AAP) which is made up of components from naturally occurring (ie, wildfires) or anthropogenic (ie, traffic-related air pollution, prescribed burns) sources. While airborne pollutants vary by source, season, and location, it is well established that particulate matter (PM) smaller than 2.5 μm in diameter ($PM_{2.5}$) is of great importance to human health due to penetration of lung alveoli.[2] The toxic potential of particles generated from different sources is likely to be unique and thus it is important to independently consider the health impacts and associated mechanisms of major sources. Wildfire smoke (WFS) is demonstrated to be a major source of AAP PM, contributing as much as 70% of $PM_{2.5}$ in the western United States (US) on days when regulatory limits are exceeded.[3] Importantly, projections indicate that as early as the year 2100 WFS could derive greater than 50% of total $PM_{2.5}$ for the entire US.[4] Alongside WFS, anthropogenic woodsmoke (AWS) has been estimated to contribute between 56 to 77% of $PM_{2.5}$ in western communities in the winter.[5] Geographical effects of total woodsmoke (TWS: comprised of WFS and AWS) air pollution extend beyond immediate regions where biomass combustion occurs due to the ability of smoke particulate to travel great distances.

The health burden associated with smoke exposure is of concern as increased wildfire prevalence is expected with warmer, drier environments concurrent with climate change. Unfortunately, common methods of wildfire prevention (eg, prescribed burning to reduce fuel sources) are themselves contributors of AWS air pollution. With mitigation measures factored in, US deaths directly attributed to WFS are still expected to double as early as 2050.[4] In addition to mortality, exposure to TWS has been correlated with morbidities such as cancer, cardiovascular disease, and respiratory syndromes. Recently, AWS exposure has also been associated with central nervous system (CNS) dysfunction, including Alzheimer's disease (AD) dementia.[6]

AD is a progressive neurodegenerative disorder characterized by hallmark pathological markers such as senile amyloid-beta (Aβ) plaques and neurofibrillary tau tangles (NFTs), as well as neuroinflammation, synaptic dysfunction, and neuronal cell death, which collectively results in marked cognitive impairment.[7] AD accounts for 50% to 75% of all known dementias.[8] According to the Centers for Disease Control, AD is the 5th leading cause of death among the elderly, impacting nearly 5 million Americans over 65, a number which is expected to triple by 2060.[9] Despite advances in our understanding of AD pathology, there remains no effective treatment or cure. Because of this, research efforts have transitioned from a treatment approach to attempting preventative measures. While this push to better understand etiology has resulted in the characterization of a heritable subtype of AD, the majority of cases remain idiopathic in nature.[10] Identifying modifiable risk factors and associated mechanisms could aid in the prevention of AD and help curb the rising tide of the disease.

The molecular mechanisms that underlie the onset of morbidity following TWS exposure are not well understood, especially as they differ from total AAP exposure. One promising theory is that combination of inflammation, oxidative stress, and epigenetic modifications might link airborne pollutant inhalation and subsequent disease pathogenesis. Several reviews have been conducted which explore the potential for environmental effect on epigenetic patterns to modify disease pathogenesis, including AD.[11-17] Additionally, reviews have been conducted which explore the association between AAP exposure and onset of AD or dementia.[18-23] Very recently, a review has assessed the effects of exposure to bushfire smoke on brain health.[24] Taken together, these existing articles demonstrate the growing body of literature which supports interplay between molecular mechanisms, including epigenetics, which underlie disease onset and occur following air pollution exposure. More work is needed to characterize the ability of TWS constituents, individually or as a whole, to influence epigenetics mechanisms that underlie AD though recent publications have suggested the plausibility of this relationship. Specifically, Wang et al.[13] postulates that epigenetic modifications might help to explain the link between formaldehyde (a component of TWS) exposure and subsequent onset of AD.

Traditional approaches to address the nature of this relationship have been largely siloed with public health researchers reporting epidemiologic data, molecular biologists studying epigenetics and pathological progression, and chemists or environmental scientists characterizing PM makeup and air pollution exposure events. However, recent cross-disciplinary efforts have allowed for the emergence of a new perspective. Our review seeks to explore existing literature and apply this novel lens to better understand how exposure to TWS and molecular mechanisms believed to be involved in AD onset are interrelated by referencing data from in vitro and in vivo models, as well as data from human epidemiologic analyses. While others have reviewed air pollution broadly, or traffic-related air pollution specifically, we here cite the expected increase in the contribution of wood smoke to cumulative ambient air pollution as rationale which warrants evaluation of the status of the science and identification of major gaps in knowledge regarding links between TWS exposure and AD.

Total woodsmoke characterization

The most prevalent component of WFS by mass is $PM_{2.5}$ which is composed of: sulfate, nitrate, ammonium, chloride, elemental/organic carbon, and other air pollutants.[25] These components are subject to variation based on geographic location, season, and fuel source.[3,26] Likewise, AWS contains highly variable levels of air pollutants depending upon the fuel source, conditions surrounding combustion,[27,28] and the type of fire actively burning (ie, smolder, active flame).[29] Some groups have described exposure assessment techniques that can be used to distinguish between the contribution of diesel emissions or

woodsmoke to AAP[30,31] As a result, reporting source apportionment of $PM_{2.5}$ is essential to accurately assess implications of exposure. Source apportionment studies provide strong evidence for the consideration of TWS as a unique contributor to AAP.[32] For example, data indicate that biomass combustion including TWS more strongly correlates with respiratory disease compared to motor vehicle sources,[33] whereas motor vehicle sources relative to AWS have been more strongly linked to cancer risk.[34] Importantly, AAP exposure in studies that do not report source apportionment for $PM_{2.5}$ may contain TWS pollutants depending on the location and season. Because of this, some studies reporting AAP exposure data have been included in this review.

Woodsmoke exposure

Determining how TWS-derived particles come into contact with CNS tissue, or whether direct contact is necessary to induce AD-related outcomes, remains a challenge associated with this work (Figure 1). One potential for direct exposure is through uptake during inhalation. While no studies have demonstrated this in models exposed to TWS PM, recent work has documented the ability of iron soot, a product of biomass combustion, to enter the CNS directly via olfactory nerve bundles and subsequently travel to the brain.[51] Another potential pathway that has been proposed is that following TWS inhalation, PM passes through the lung-blood barrier and drives systemic inflammation, which leads to attenuation of the blood-brain barrier (BBB). While this has not been demonstrated in studies of WFS-derived PM, there are reports of altered BBB permeability following AAP exposure.[58,59] Additionally, AWS has been demonstrated to activate the nuclear factor kappa B (NF-kB) pathway as well as increase the release of tumor necrosis factor alpha (TNF-α) in mouse peritoneal macrophages.[56] This cascade leads to the systemic release of proinflammatory cytokines (IL-1β, 6, 12, 18) and is known to regulate BBB structural integrity.[60] NF-kB mediated inflammation has also been reported in the lung, blood, and brain following AAP exposure in male wild-type (C57BL/6) mice.[49] Collectively, this demonstrates the potential for induction of systemic inflammatory cascades, driven by inhalation exposure, to sufficiently increase BBB permeability which could allow TWS particles to directly interact with neurons or microglia. While this is an attractive theory, additional work is required to characterize the specific nature of TWS particle access to CNS tissue, or if an alternate indirect mechanism negates the need for direct PM contact (ie, inflammatory mediators generated following inhalation of TWS particles travel to the brain and drive AD pathogenesis).

Woodsmoke and neurodegeneration

Notwithstanding full elucidation of TWS PM toxicokinetics related to CNS tissue, it is clear from the literature that both AAP and AWS exposures are associated with increased AD
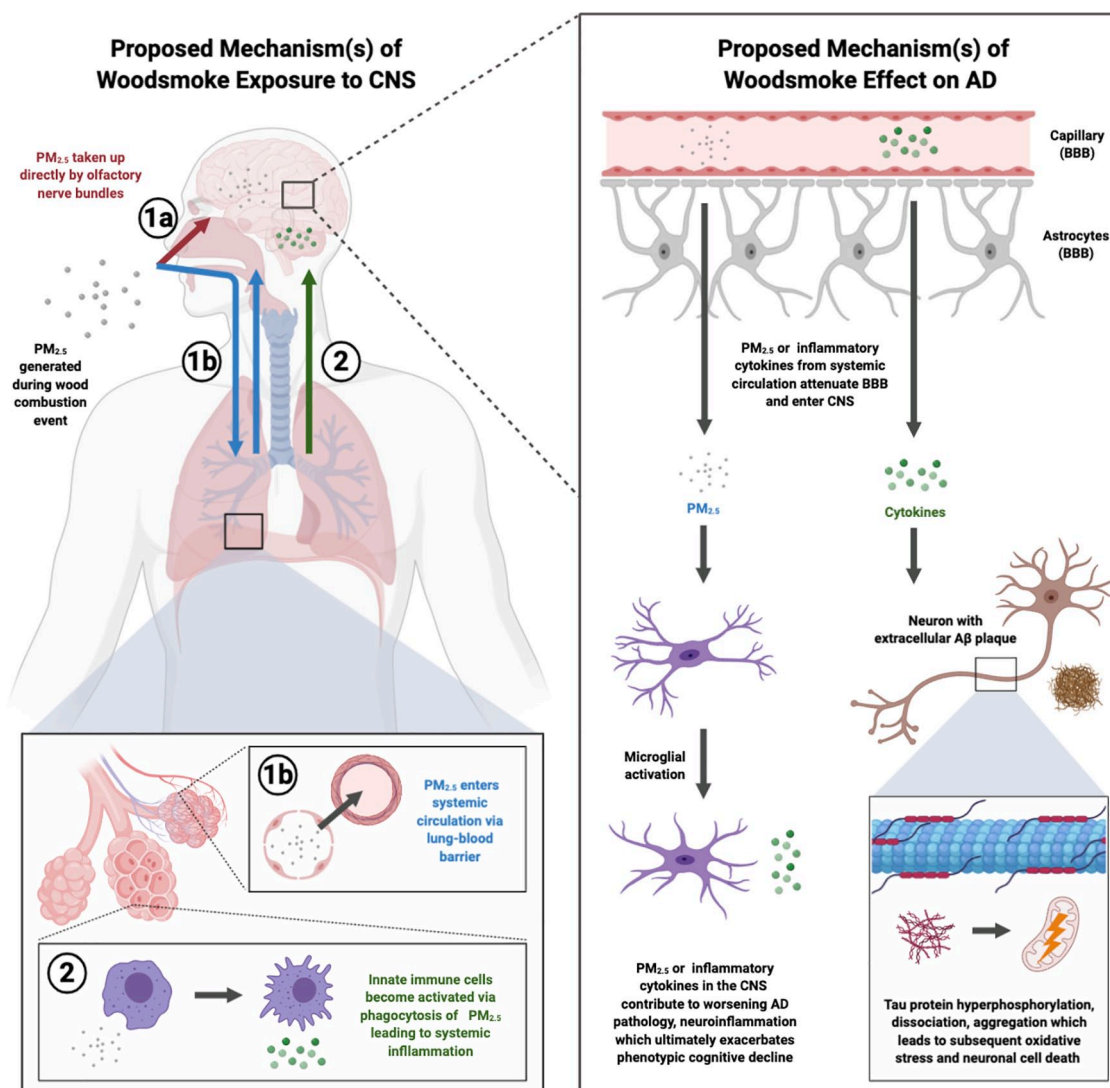
Figure 1. Working model demonstrating potential direct (1a and b) or indirect route (2) of CNS exposure to Total Woodsmoke (TWS) PM, inflammation-mediated progression of AD, and contribution to hallmark pathology. (1a) PM$_{2.5}$ enters the brain directly via the olfactory tract. (1b) PM$_{2.5}$ enters the lung during inhalation and crosses the lung blood barrier, entering into systemic inflammation and allowing direct access to the BBB. (2) PM$_{2.5}$ is inhaled, phagocytosed by innate immune cells, and induces systemic inflammation which can indirectly affect the BBB. Exposure event subsequently attenuates BBB integrity and CNS tissue becomes susceptible to exacerbation of AD pathology, neuroinflammation. While these pathways are discussed here as independent, the true exposure route may be a combination of these pathways.
Abbreviations: Aβ, amyloid beta; CNS, central nervous system; AD, Alzheimer's disease; BBB, blood-brain barrier; PM, particulate matter.
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onset.[6,35-37] Attempts to characterize molecular explanations for AD onset have largely followed the thought that senile plaques and NFTs are driving factors in pathogenesis. Research published on this front has led to the development of the "amyloid hypothesis," which was held as the general consensus surrounding AD onset for many years.[61] Drug design studies targeting various components in amyloid hypothesis pathways have demonstrated little promise in clinical trials. As such, a shift favoring other theories regarding disease origin has occurred.[62] The emergence of an inflammation-centric view of AD has demonstrated significant promise in recent years.[63] Accordingly, we here assess TWS influence on AD in this context.

While no literature currently demonstrates a clear causative molecular mechanism to explain the correlation between either TWS or AAP exposure and AD onset, there are many individual investigations that characterize inflammatory or cell stress pathway activation following an exposure event. These specific physiological changes are relevant to the pathogenesis of AD and are summarized in Table 1. Studies assessing occupational health risks in firefighters have found that acute AWS exposure is associated with systemic inflammation.[38,39] Similar observations have been made in mouse or cell models.[49,50,55] Li et. al.[55] speculate that the mechanism underlying cellular toxicity following exposure-induced inflammation is linked to mitochondrial dysfunction as evidenced by reactive oxygen

Table 1. Citations from primary literature articles reviewed which assess AAP or TWS exposure in humans, animal models, or cell lines. Numbers correspond to the manuscript bibliography.

AUTHOR	MODEL	EXPOSURE DURATION	EXPOSURE TIMEPOINT	EXPOSURE ASSESSMENT/ METHOD	EXPOSURE TYPE	OUTCOMES RELEVANT TO REVIEW TOPIC
Oudin et al.[6]	Human (n = 1806)	~15y	Adult and Elderly	Estimated	AWS (PM2.5)	Woodsmoke PM2.5 correlates with AD risk
Wu et al.[35]	Human (n = 871)	~12y	Elderly	Estimated	AAP (PM10, O3)	AAP exposure correlates with AD, VaD risk
Li et al.[36]	Human (n = 2340)	5y	Adult and Elderly	Estimated	AAP (PM2.5)	AAP exposure correlated with allergic rhinitis onset, AD risk
Chang et al.[37]	Human (n = 29547)	~12y	Adult and Elderly	Estimated	AAP (NO2, CO)	NO2 and CO exposure correlates with dementia risk
Hejl et al.[38]	Human (n = 12)	1 mo	Adult	Personal air monitor	AWS (CO, PM2.5)	Acute AWS exposure correlates with increase in IL-8
Unosson et al.[39]	Human (n = 14)	3h	Adult	Whole-body	AWS (PM1)	Acute AWS exposure correlates with pathologic CV symptoms
Cerza et al.[40]	Human (n = 21 548)	~12y	Elderly	Estimated	AAP (NO2, O3, PM10, PM2.5)	AAP exposure correlates with dementia hospitalization
Lee et al.[41]	Human (n = 645)	1 mo to 1 y	Elderly	Estimated	AAP (PM2.5)	AAP exposure correlates with neuropsychiatric symptoms in AD, MCI
Younan et al.[42]	Human (n = 998)	3y	Elderly	Estimated	AAP (PM2.5)	AAP exposure correlates with cognitive dysfunction
Guxens et al.[43]	Human (n = 783)	Gestation (9 mo)	In Utero	Estimated	AAP (NO2, PM10, PM2.5)	Fetal AAP exposure correlates with abnormal brain development
Dai et al.[44]	Human (n = 646)	1 y	Elderly	Estimated	AAP (PM2.5)	PM2.5 exposure correlates with changes in epigenome-wide DNA methylation
Mostafavi et al.[45]	Human (n = 157)	24h	Adult and Elderly	Personal air monitor	AAP (PM2.5, PM0.3)	Acute AAP exposure correlates with changes in DNA methylation
Gondalia et al.[46]	Human (n = 8397)	Daily and monthly	Adult and Elderly	Estimated	AAP (PM10, PM2.5)	AAP exposure correlates with differential DNA methylation, including in AD-relevant genes
Jew et al.[47]	3×Tg AD mouse (n = 10)	2 wk	Elderly	Whole-body	AAP (PM0.1)	AAP exposure correlates with cognitive dysfunction
Cacciottolo et al.[48]	EFAD mouse (n = 10)	10-15 wk	Adult	Whole-body	AAP (PM2.5)	AAP exposure correlates with worsened AD pathological phenotype, dementia risk

(Continued)

Table 1. (Continued)

AUTHOR	MODEL	EXPOSURE DURATION	EXPOSURE TIMEPOINT	EXPOSURE ASSESSMENT/ METHOD	EXPOSURE TYPE	OUTCOMES RELEVANT TO REVIEW TOPIC
Ku et al.[49]	C57/BL6 mouse (n = 6)	4 wk	Adult	Oropharyngeal aspiration	AAP (PM2.5)	AAP exposure correlates with systemic inflammation, cognitive dysfunction
Pardo et al.[50]	C57/BL6 mouse (n = 6)	Single Exposure	Adult	Nose only	Wood tar aerosols	AWS component exposure correlates with inflammation *in vivo*
Hopkins et al.[51]	C57/BL6 mouse (n = 20)	5 wk	Adult	Whole-body	Iron-soot aerosol	Iron-soot particles found in olfactory nerve tracts, olfactory bulb
Cory-Slechta et al.[52]	C57/BL6 mouse (n = 10)	2 wk	Perinatal	Whole-body	AAP (PM0.1)	Fetal AAP exposure correlates with cognitive dysfunction in males
Black et al.[53]	Rhesus macaques (n = 25)	3 y	Perinatal	Estimated	WFS (PM2.5)	Early life WFS exposure correlates with peripheral immune cell dysfunction later in life
Jang et al.[54]	3×Tg AD mouse (ex vivo) Neuro2A mouse cells	24 h	Elderly Mice for *ex vivo*	Culture media	AAP (PM4)	AAP exposure resulted in microglial activation, PARP-1 mediated Aβ levels in hippocampus
Ku et al.[49]	Primary hippocampal mouse cells	24 h	Perinatal neurons	Culture media	AAP (PM2.5)	AAP exposure correlates with systemic inflammation, cognitive dysfunction
Pardo et al.[50]	Human bronchial epithelial cells	5 and 24 h	Adult cells	Culture media	Wood tar aerosols	AWS component exposure correlates with cytotoxicity *in vitro*
Li et al.[55]	Primary hippocampal mouse cells	24 h	Perinatal neurons	Culture media	AAP (PM2.5)	AAP exposure correlates with inflammatory, disease-favorable phenotype
Leonard et al.[56]	Peritoneal macrophage mouse cells	30 min-24 h	Adult cells	Culture media	AWS	AWS exposure correlates with oxidative stress, NF-kB mediated inflammation
Hesselbach et al.[57]	Human bronchial epithelial cells	5 wk	Adult cells	Culture media	AWS (PM2.5)	AWS exposure resulted in a global hypomethlyation, disease-relevant differential methylation

Abbreviations: AD, Alzheimer's disease; AAP, ambient air pollution; AWS, anthropogenic woodsmoke; WFS, wildfire smoke; VaD, Vascular dementia; MCI, mild cognitive impairment; PM, particulate matter.

species (ROS) formation and oxidative stress. This is plausible given that ROS and NF-kB are known regulators of one another[64] and have been implicated in AD risk.[65] Alternatively, AAP exposed mouse cells display overexpression of cyclooxygenase-2 (COX-2) mediated by ROS formation following NF-kB activation. COX-2 is known to aggravate inflammation and plays a role in worsening AD pathology.[66] Both of these molecular mechanisms represent a potential pathway for exposure-induced inflammation or cell stress cascades to result in cellular damage or cytotoxicity.

In addition to AD risk, chronic AAP exposure has been correlated with exacerbation of symptoms and increased incidence of hospitalization for those with dementia.[40] Lee et al.[41] found that, in patients with mild cognitive impairment (MCI) or AD, high levels of exposure to AAP $PM_{2.5}$ worsens neuropsychiatric symptoms. Furthermore, elderly females with elevated residential AAP $PM_{2.5}$ exposure exhibit accelerated declines in executive functions, including immediate recall and new learning.[42] Changes in cognition not only decrease the quality of life for the patient suffering from AD but also extend the impact of AD on society. Worsening neuropsychiatric state and decline in executive function increases caregiver burden[67] and furthers the economic impact of AD.[68] These implications strengthen the need for more extensive experimentation surrounding TWS exposure in the context of AD.

Complementing epidemiologic data suggesting a link between exposure to environmental air pollutants and altered AD phenotype, animal and cell models have been employed to investigate potential mechanistic links (Table 1). To date, these experiments are limited exclusively to the analysis of cumulative AAP[47,48,54] but future studies should investigate PM from unique sources, namely TWS or even individual PM generating events—prescribed burns, residential wood burning, wildfires. Two different transgenic AD mouse models[69,70] have been used to explore AAP exposure effect on dementia onset or progression. In both cases, increased tissue pathological load and eventual clinical presentation worsened following inhalation of the toxicant. These data demonstrate that exposure events have the potential to exacerbate the clinical progression of AD, independent of genetic predisposition to the disease.

In addition to identifying how TWS PM mechanistically influences CNS function, establishing windows of susceptibility, particularly during early life will be important for mitigating disease risk. Data suggests that human in utero exposure to AAP may significantly delay neurological development and impair cognitive function.[43] Similarly, mouse pups exposed to AAP at timepoints representative of third trimester pregnancy in humans were found to display decrement in learning and memory.[52] Both deficits in CNS structure and executive function are believed to have an association with the risk of AD onset or worsened disease phenotype.[71] Accordingly, TWS-induced CNS dysfunction could be partly explained by the developmental origins of health and disease (DOHaD)

hypothesis[72] which posits that early life exposure events can shape disease risk throughout the lifespan. There is a significant lack of existing research to explore the cumulative effects of exposure throughout the life course. We have identified 4 time points which seem to have distinct outcomes when assessed individually for exposure (Figure 2). Our understanding regarding windows of susceptibility to TWS will hopefully be expanded in the coming years following efforts to prospectively track health outcomes following major wildfire events such as the Camp Fire of 2018 which took place in California (eg, WHAT-Now-California study being led by researchers at UC Davis).

Some limited information from the animal literature suggests that early life exposure to TWS may impact inflammatory processes implicated in AD risk. Non-human primates exposed to WFS-derived PM in infancy presented with modulation of immune response measured using peripheral blood mononuclear cells (PBMCs) during adolescence.[53] This included a dampened response to toll-like receptor (TLR) stimulation and downstream signaling through NF-kB. Important in the context of AD, microglia expressing TLRs (TLR2, 4, and 9)[73] are thought to help recognize and phagocytose neurotoxic pathology (ie, Aβ plaques).[74] Attenuation of innate immune response may occur in microglia as observed in PBMCs, and if so, there is potential for this to mediate TWS-derived PM effect on AD etiology. Furthermore, it is known that PBMCs are recruited to the brain when microglia become overwhelmed in AD.[75] If parenchymal Aβ load or TWS PM-induced neuroinflammation cause sufficient strain on microglia clearance ability, the recruitment of PBMCs that have been "damaged" by TWS exposure (as seen in the rhesus macaque following exposure) might significantly hinder the ability to clear parenchymal AD pathology and result in neuronal death. This hypothesized mechanism of macrophage-related AD disease risk has not been fully demonstrated and thus remains speculative.

Woodsmoke and epigenetics

Another appealing mechanism commonly evaluated as a conduit between exposure and disease is epigenetic alterations. Epigenetics can be defined as heritable features that affect gene expression, without altering the DNA sequence directly. The most well-characterized epigenetic modification is DNA methylation, which is the addition of a methyl group to a 5' cytosine in a cytosine-guanine dinucleotide (CpG). DNA hypermethylation at CpG islands is typically associated with repression of gene transcription. Leading up to and shortly after birth, waves of DNA methylation patterns are established in a region or gene-specific fashion, and these patterns are inherently cell-specific.[76] Unlike the genetic sequence, DNA methylation patterns are believed to remain plastic throughout the life span.[77] Differential DNA methylation has been demonstrated to be especially impactful at in utero or perinatal time
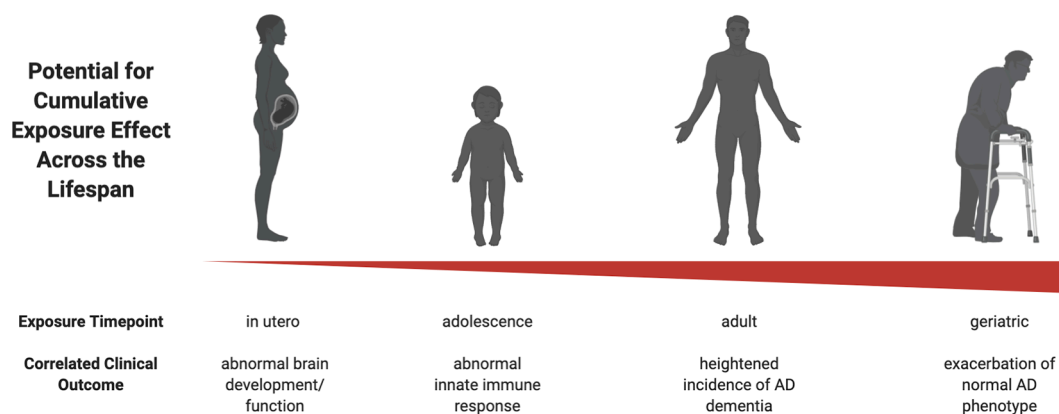
Figure 2. Representative time points of TWS exposure with potential for individual exposure events or cumulative effects to result in ultimate age-related phenotype.
Abbreviation: AD, Alzheimer's disease.
Image created using BioRender.com.

points,[78] in support of the DOHaD hypothesis. Further work is necessary to implicate these timepoints in AD risk following TWS exposure, though early AAP exposure has been demonstrated to affect neural developmental trajecotry.[79] The dynamic nature of DNA methylation presents a way for environmental exposure to alter functional protein levels and affect system physiology. Recently, novel data has associated epigenetic modification with the onset of AD.[80,81] Notably, global DNA hypomethylation—often linked to chromatin stability—has been implicated in AD onset.[82] Review articles[14,15] have explored potential reasons why CNS tissue is susceptible to DNA methylation changes citing reasons such as the large number of genes involved in the complex regulation of CNS development and maintenance relative to other tissues. Indeed, it has also been reported that in studies of AD discordance between monozygotic twins, differential DNA methylation profiles can be detected in PBMCs.[83] While the directionality of this phenomenon was not definitive in that study, this demonstrates novel evidence in support of further characterization of DNA methylation profiles in the context of AD risk. Notably, DNA methylation also serves as a potential target for therapeutic interventions[84] and could ultimately help to mitigate disease risk.

Changes in DNA methylation following AAP and TWS exposure have been well demonstrated.[44-46,57] While the differential DNA methylation patterns reported here have not been demonstrated to have a definitive causative effect on AD, they are involved in the inflammatory pathways that are currently held as central mechanisms of disease onset and/or progression (Table 1). For instance, differential methylation of the gene coding for cAMP-regulated phosphoprotein 21 *(ARPP21)* was associated with acute AAP PM exposure.[46] Aberrant expression of *ARPP21* occurs with altered entorhinal cortical (EC) thickness which is known to correlate with worsened cognitive performance and exacerbation of AD progression.[85] In another study assessing epigenome-wide methylation of buffy coat DNA, AAP $PM_{2.5}$ was associated with methylation of genes involved in immune cell maturation and function.[44] Additionally, differential CpG methylation in human peripheral blood samples has been related to immune system modulation with respect to 24-h AAP $PM_{2.5}$ levels.[45] Innate immune system activation has been extensively studied as a potential link between peripheral inflammation and neuroinflammation in neurodegenerative disease[73] and theories surrounding exposure-induced aberrant innate immune response contribution to neurodegeneration have been addressed in this review.

Discussion

Here, we review the growing body of literature regarding the impact of air pollution on public health, and more specifically linking TWS exposure to AD onset. This focused evaluation is necessary and timely given the dramatic shift that is expected in air pollution source contribution from industrial/automobile to TWS. We have cited examples of plausible molecular mechanisms whereby exposure-induced differential DNA methylation may alter AD risk, exacerbate other disease-relevant processes, and ultimately influence the phenotypic presentation.

Notably, comparing health outcomes from studies assessing effects of AAP, WFS, AWS, and traffic-related air pollution (TRAP) presents a major challenge because the composition of exposure constituents is inherently highly variable from sample to sample. Even comparing results from 2 studies that claim to measure the same source of pollution (eg, WFS) is problematic because of the complexity introduced by weather, geography, and fuel source. Also, many studies are conducted using estimates of PM exposure gathered from sparsely located governmental sites due to limitations in more localized data gathering methods which can include instrument availability or cost as well as participant recruitment. It is important to consider that there are inconsistencies in the way that estimated exposure models are generated[86] and these methods may be particularly problematic in the rural west due to low sampler density. Additional consideration should also be given to the effect of TWS "ageing," or the change in chemical composition as

smoke spreads outward from the fire source.[87] These factors highlight a need for better characterization of the toxicity of individual TWS components and mixtures under multiple environmental conditions. Our review also revealed inconsistencies in the way comorbidities and relevant disease status were recorded. Thus, when conducting future population health studies, researchers must consider health status and relevant AD risk factors in the population to improve interpretability and reproducibility of findings.

The implication that modifiable environmental exposures could drive disease onset or other aspects of pathogenesis raises the potential for interventions by which to ameliorate AD risk. At a population level, heightened awareness of the health threat posed by smoke exposure, coupled with increased efforts to reduce climate change and continued monitoring of air quality, would aid in the prevention of TWS generating events. At the individual level, some have posited that the impact of environmental toxicant exposure and subsequent development of dementia could be reversible.[22] If DNA methylation is determined to be a mechanistic driver of pathogenesis, then the modification of disease-favoring states could reduce lifelong disease risk or heritability. Considering the link between TWS exposure and inflammation, a potential therapeutic might have broader applications to more neurodegenerative disorders in addition to AD.

Candidate gene methylation patterns represent potential disease biomarkers, especially if they could be detected in an accessible sample (eg, blood) before the progression of debilitating pathology. Mounting evidence exists to suggest that peripheral lymphocytes demonstrate AD-like inflammatory profiles before the onset of cognitive decline and independently of senile plaque or NFT pathology.[88,89] In this way, exploration of differential DNA methylation patterns following exposure events in AD-relevant gene regions using peripheral samples (ie, buffy-coat DNA) may be useful as a minimally invasive diagnostic biomarker even if there is not found to be a causal involvement in neurodegenerative pathogenesis.

Model systems that complement epidemiological studies will be key to bolstering our understanding of the influence of woodsmoke on neuronal health. Future work using animal and cell models should investigate these molecular changes with varying study design endpoints to assess the efficacy of prediction regarding the ultimate disease phenotype. The relative scale of aging for rodents coupled with the ease of genetic manipulation will allow more rapid exploration of different exposure durations and constituents, at varying time points, to generate data in support of a causal relationship.

Conclusion

The directionality and causality of the complex relationship between TWS exposure and the molecular underpinnings of neurodegenerative disease are not clear, yet predictions that TWS exposure will increase nationwide in the coming decades warrants further efforts to this end. The model proposed here

demonstrates multiple ways that TWS exposure may influence AD onset and/or progression including through peripheral modulation of innate immune signaling, attenuation of the blood-brain barrier, and ultimately neuroinflammation leading to the parenchymal susceptibility to hallmark AD pathologies. Exposure timepoint, duration, and composition of TWS PM may distinctively influence the aforementioned pathways. TWS exposure events warrant further independent study from other AAP sources in the context of molecular mechanisms, specifically aberrant DNA methylation, underlying neuroinflammation, and AD.

AUTHORS' CONTRIBUTION
LM conceived the review topic and AS and LM contributed to the literature review as well as manuscript writing and editing.

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