Fine Particulate Matter, Neuropathologies, & Dementia

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Abstract

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Neurodegenerative disorders, including Alzheimer's disease (AD) and related dementias (ADRD), affect over 47 million people worldwide, and this number is anticipated to reach 131.5 million by 2050. Because no medication successfully reverses the course of dementia, researchers are focusing increasing efforts on prevention by addressing potentially modifiable risk factors. Recent evidence suggests that air pollution, a ubiquitous environmental exposure, may be linked to neurodegeneration and dementia. This project aimed to advance the state of the science on this topic through biologically-based epidemiological analyses.

In the first aim, using a cohort from the University of Washington Alzheimer's Disease Research Center, I evaluated the association between long and short-term $PM_{2.5}$ exposure and biomarkers of vascular injury (E-selectin, vascular cell adhesion molecule-1 (VCAM-1)) in the cerebrospinal fluid (CSF). This question is important to investigate because of the growing evidence of the role of cerebrovascular disease in dementia as well as well-established linkages between air pollution and cardiovascular disease. Our analyses indicated that, among cognitively normal individuals, a 5 ug/m^3 increase in 1-yr and 7-day $PM_{2.5}$ exposure was associated with elevated VCAM-1 (beta (95% CI) for 1-year: 51.8 (6.5, 97.1) ng/ml; 7-day: 35.4 (9.7, 61.1) ng/ml) and that a 5 ug/m^3 increase in 1-yr $PM_{2.5}$ exposure was associated with

elevated e-selectin (53.3 (11.0, 95.5) pg/ml). We found no consistent associations between pollution and markers of vascular injury in the CSF among cognitively impaired individuals. Overall, our results in cognitively normal individuals are aligned with prior research linking $PM_{2.5}$ to vascular damage in other biofluids as well as emerging evidence of the role of $PM_{2.5}$ in neurodegeneration. Our null results among cognitively impaired individuals are unsurprising, given that the influence of internal disease processes would be more important than external $PM_{2.5}$ exposures in contributing to vascular injury.

In the second aim, I utilized autopsy specimens to conduct a novel analysis evaluating the association between $PM_{2.5}$ exposure and AD stage at death. After addressing differential selection into the autopsy cohort through inverse-probability weighting, we estimated that each 1 ug/m^3 increase in 10-year average $PM_{2.5}$ prior to death was associated with a suggestive increase in the odds of higher CERAD score (OR: 1.35 (0.90, 1.90)). There was no association with Braak score (OR: 0.99 (0.64, 1.47), and there was a suggestive inverse association with odds of higher simulated ABC score (OR: 0.79 (0.49, 1.19). However, for all outcomes, the confidence intervals included the null.

In the third aim, I evaluated the association between long term average $PM_{2.5}$ exposure and incidence of dementia (AD and all-cause). This study leveraged 40 years of exposure information based on a newly developed spatiotemporal model as well as research quality diagnosis data. We estimated that a 1 ug/m^3 increase in 10-year moving average of $PM_{2.5}$ was associated with a 1.16 (1.03, 1.31) increase in the hazard of all-cause dementia. Results from secondary analyses of AD-subtype dementia were slightly attenuated (1.11 (0.97, 1.27)). These results providing additional evidence of the neurodegenerative effects of $PM_{2.5}$ pollution.

Overall, this work advances our scientific understanding of the mechanisms and risk factors for dementia. Findings of this research can inform policies to reduce exposure to air pollution, which could decrease the burden of environmental-related dementia across the population.

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Chapter 1: Introduction

Neurodegenerative diseases, including Alzheimer's Disease (AD) and related dementias (ADRD), pose a growing burden on our rapidly aging society.[1,2] Understanding the mechanisms and risk factors of these conditions is a key public health priority. Increasing evidence has linked air pollution (AP), such as fine particulate matter ($PM_{2.5}$), to neurodegeneration, including decreased cognitive performance,[3-8] accelerated cognitive decline,[9,10] and dementia.[11-14] Yet, further work is needed to more thoroughly investigate the possible mechanisms by which $PM_{2.5}$ can promote pathophysiologic neurodegenerative processes as well as to substantiate the growing evidence that suggests an association between $PM_{2.5}$ and dementia. Given that $PM_{2.5}$ exposure is widespread and modifiable, this research could have important implications for the development of public health-protective policies.

My project takes an innovative, integrated and interdisciplinary approach to this research question. The first two aims directly assess possible pathological mechanisms by which $PM_{2.5}$ may contribute to neurodegeneration, using two different subpopulations with specific biological samples of interest. My third aim broadens to address disease incidence, the measure of ultimate public health significance, in a population-based cohort and will help elucidate whether effects vary by exposure time scale. Together, these molecular and population-based epidemiological analyses will contribute strong, inter-related evidence on the role of $PM_{2.5}$ exposure on neurodegeneration.

Aim 1: Biomarkers of damage and early disease in the cerebrospinal fluid (CSF)

The CSF is a colorless fluid that is in direct contact with the brain. As such, CSF biomarkers can be used to detect biochemical changes in the brain. Alterations in levels of endothelial injury markers, such as e-selectin and vascular cell adhesion molecule-1 (VCAM-1), have been detected in the cerebrospinal fluid (CSF) of individuals with Alzheimer's disease (AD) and vascular dementia,[15-24] as have characteristic AD markers such as β-amyloid$_{1-42}$ (Aβ_{1-42})[25-27] and tau proteins (total tau and phosphorylated tau (p-tau)).[26,28,29] Changes in these biomarkers are predictive of future neurodegeneration and/or disease progression for individuals both normal[30-33] and with mild cognitive impairment (MCI)[34-40] at baseline. Limited studies to date have found associations between exposure to $PM_{2.5}$ and CSF Aβ_{1-42} levels, among other markers, in children and young adults.[41,42] However, no studies have evaluated the association between exposure to $PM_{2.5}$ and key biomarkers of vascular injury in the CSF of an adult population. In the context of ADRD research, it is relevant to evaluate vascular injury in the CSF because of the growing understanding of the linkages between vascular disease and dementia.[43,44] We will address this research question using data from the University of Washington (UW) Alzheimer's Disease Research Center (ADRC) cohort.

Aim 2: Biomarkers of AD pathologies in brain tissue from normal and diseased individuals

β-amyloid$_{1-42}$ (Aβ_{1-42}) plaques and tau aggregations (neurofibrillary tangles) are the characteristic pathologic markers of AD.[45] Several studies have documented aggregations of Aβ_{1-42}, among other molecular changes, in brain tissue from children, young adults, and canines exposed to high levels of air pollution.[46-49] Experimental laboratory studies also demonstrate evidence of changes in these molecular markers after exposure to air pollution and/or inhaled metals.[50-52] However, no studies to date have evaluated the association between exposure to

$PM_{2.5}$ and these AD biomarkers in the brains of diseased and cognitively normal aging individuals, who may be particularly susceptible to neurodegeneration. Our study fills this crucial gap using data from the Adult Changes in Thought (ACT) study. An important component of this work is addressing the selection bias present when utilizing an autopsy sample, which may not be representative of the general population.

My analysis also addresses whether APOE-ε4 status, a polymorphism linked to decreased age of dementia onset and increased dementia severity,[53-56] modifies the association between $PM_{2.5}$ exposure and the neuropathological markers of interest. Because of its role in the transport of cholesterol and related lipids, APOE is central to neurogenesis, plasticity, & repair.[53] Additionally, APOE influences antioxidant capacity, inflammatory response, and vascular health. [57,58] If $PM_{2.5}$ contributes to the development of AB plaques through oxidative stress and neuroinflammation, then individuals with one or two copies of the e4 allele may be more susceptible to the neurotoxic effects of $PM_{2.5}$. Limited prior studies of air pollution and cognitive decline or dementia risk suggests that effects of air pollution exposure may be more pronounced in carriers of the ε4 allele,[46,47,59-63] though other studies do not support effect modification by ε4.[64] Evaluating whether APOE ε4 status affects susceptibility to $PM_{2.5}$ related neurodegeneration could provide important insight into mechanism.

Aim 3: Risk of AD and all-cause dementia

Emerging evidence suggests an association between exposure to AP, such as $PM_{2.5}$, and risk of AD and other dementias.[11,13,64] This aim builds on the first two aims, which explore

biological mechanisms, to address the fundamental public health question: how incidence of AD and all-cause dementia is influenced by long term (10-year) $PM_{2.5}$ exposure among individuals in the ACT cohort. Our study has important advantages over prior studies, including access to 40 years of exposure data and research quality outcome ascertainment.

Overarching hypotheses

Growing evidence has linked ambient air pollution (AP), a complex mixture of particles and gases, to adverse neurological outcomes, such as accelerated cognitive decline and dementia.[11,12,64-69] This work focuses on $PM_{2.5}$, which may promote neurodegeneration by triggering inflammation and oxidative stress in the central nervous system directly (through translocation of particles and associated metals to the brain) or indirectly (through overflow of inflammatory and oxidative stress signals from the peripheral circulation).[65,69,70] Because of both of these biologically plausible pathways, I hypothesize that exposure to $PM_{2.5}$ will be associated with alterations in markers of cerebrovascular injury, AD markers in the brain at autopsy, and increased incidence of AD and all-cause dementia. My overarching hypothesis is based on the theories that 1) $PM_{2.5}$ is associated with increased oxidative stress and inflammation-related vascular injury in other biological matrices[71-75], and 2) cerebral oxidative stress, inflammation, and cerebrovascular damage may lead to cognitive decline and dementia.[43,44,76-80]

Chapter 2: Fine particulate matter exposure and cerebrospinal fluid markers of vascular injury[1]

[1] Reprinted from Journal of Alzheimer's Disease, Vol. 71, no. 3. Rachel M Shaffer, Lianne Sheppard, Elaine R Peskind, Jing Zhang, Sara D Adar, Ge Li, Fine Particulate Matter Exposure and Cerebrospinal Fluid Markers of Vascular Injury, Pages 1015-1025., Copyright (2019), with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-190563

ABSTRACT

Background**:** Cerebrovascular diseases play an important role in dementia. Air pollution is associated with cardiovascular disease, with growing links to neurodegeneration. Prior studies demonstrate associations between fine particulate matter ($PM_{2.5}$) and biomarkers of endothelial injury in the blood, however, no studies have evaluated these biomarkers in cerebrospinal fluid (CSF).

Objective**:** We evaluate associations between short-term and long-term $PM_{2.5}$ exposure with CSF vascular cell adhesion molecule-1 (VCAM-1) and e-selectin in cognitively normal and mild cognitive impairment (MCI)/Alzheimer's disease (AD)) individuals.

Methods: We collected CSF from 133 community volunteers at VA Puget Sound between 2001-2012. We assigned short-term $PM_{2.5}$ from central monitors and long-term $PM_{2.5}$ based on annual average exposure predictions linked to participant addresses. We performed analyses stratified by cognitive status and adjusted for key covariates with tiered models. Our primary exposure windows for the short-term and long-term analyses were 7-day and 1-year averages, respectively.

Results**:** Among cognitively normal individuals, a 5 ug/m^3 increase in 7-day and 1-year average $PM_{2.5}$ was associated with elevated VCAM-1 (7-day: 35.4 (9.7, 61.1) ng/ml; 1-year: 51.8 (6.5, 97.1) ng/ml). A 5 ug/m^3 increase in 1-yr average $PM_{2.5}$, but not 7-day average, was associated with elevated e-selectin (53.3 (11.0, 95.5) pg/ml). We found no consistent associations among MCI/AD individuals.

Conclusions**:** We report associations between short-term and long term $PM_{2.5}$ and CSF biomarkers of vascular damage in cognitively normal adults. These results are aligned with prior

research linking $PM_{2.5}$ to vascular damage in other biofluids as well as emerging evidence of the role of $PM_{2.5}$ in neurodegeneration.

INTRODUCTION

Growing evidence suggests that cerebrovascular damage, such as microvascular injury and stroke, may contribute to cognitive impairment and dementia.[81,82] Specifically, based on the vascular contributions to cognitive impairment and dementia (VCID) hypothesis, a substantial proportion of neurodegeneration and cognitive decline is actually due to vascular insults, which can also occur concomitantly with Alzheimer's disease (AD) pathology.[83]

Vascular disease morbidity and mortality is strongly linked to fine particulate matter air pollution ($PM_{2.5}$) exposure.[84,85] There are several plausible mechanisms by which $PM_{2.5}$ could impact vascular health, including systemic oxidative stress and inflammation leading to endothelial damage.[84] Vascular cell adhesion molecule-1 (VCAM-1) and e-selectin are adhesion molecules expressed by endothelial cells in response to injury and inflammation.[20,21] Elevations in these markers reflect vascular injury and are associated with hypertension, atherosclerosis, and dysregulation of cerebral blood flow.[86,87] Prior epidemiological studies indicate associations between exposure to air pollution, such as $PM_{2.5}$, and these and other biomarkers of vascular damage in plasma and serum.[88-99] $PM_{2.5}$ has also been linked to cerebrovascular damage, such as stroke.[100]

Cerebrospinal fluid (CSF), which is derived from blood plasma and circulates within the cerebral ventricular system, can be used to detect biochemical changes and understand pathological disease processes in the brain during life. For example, alterations in e-selectin and VCAM-1 have been detected in the CSF of individuals with AD and vascular dementia.[15-23] Yet, despite the well-recognized link between $PM_{2.5}$ and vascular injury and the role of vascular

injury in dementia, no prior studies have evaluated the association between $PM_{2.5}$ and these biomarkers of endothelial injury in the CSF of adult populations.

To address this scientific gap, we conduct a novel study to evaluate the associations between short-term (days/months) and long-term (years) $PM_{2.5}$ exposure with both VCAM-1 and e-selectin in the CSF. Our interest in short-term time windows was informed by prior research indicating associations between $PM_{2.5}$ exposure over days or weeks and changes in these biomarkers of vascular injury in the blood.[88-99] We investigated long-term time windows to evaluate a potential chronic inflammatory response, which has also been suggested by studies of $PM_{2.5}$ and blood-based biomarkers.[98] Since individuals with mild cognitive impairment (MCI) or AD often also already exhibit vascular pathologies, we stratified our analyses by cognitive status (cognitively normal vs. MCI/AD). Our *a priori* focus was on the cognitively normal subgroup, because we hypothesized that the disease process in existing MCI/AD cases would likely drive endothelial injury to a relatively greater extent than $PM_{2.5}$.

Given the hypothesized role of cerebrovascular injury and neuroinflammation in dementia and neurodegeneration,[43,83] understanding whether $PM_{2.5}$ is linked with CSF biomarkers of vascular injury may provide evidence to support the link between air pollution exposure and cognitive impairments and dementia.[12,65,69]

METHODS

The cohort included 133 individuals enrolled in studies at the University of Washington (UW) Alzheimer's Disease Research Center (ADRC) between 2001-2012 (Table S1). All procedures were approved by the UW Institutional Review Board (IRB) (01-8926-V & 01173),

and all individuals or legal authorized representatives for AD participants provided written consent prior to enrollment in the study. Participants were classified as having no cognitive impairment, MCI, or AD at consensus conference based on clinical evaluations supported by neuropsychological testing. Exclusion criteria included major neurological diagnoses (other than MCI/AD) that could affect cognitive function (stroke, Parkinson's disease, multiple sclerosis, history of moderate or severe head injury), major psychiatric disorder (schizophrenia, major affective disorder, posttraumatic stress disorder), unstable medical conditions, illegal drug use, and alcohol use disorder.

CSF samples were obtained through lumbar puncture with standardized procedures as published previously.[101] All samples were kept frozen at -80°C prior to analysis at the VA Puget Sound. E-selectin and VCAM-1 were measured with the Human Premixed Multi-Analyte Kit (R&D Systems, Minneapolis, MN, USA).[102] Apolipoprotein (APOE) genotype was assessed through a restriction digest method.[103] All assays were performed blinded to clinical diagnosis.

Short-term (days, month) average $PM_{2.5}$ exposure was estimated from a single central site monitor in the Seattle-Beacon Hill neighborhood (AQS ID 530330080) using measurements from a mass-based federal reference method (FRM).[104] When no FRM data were available, we used data from a federal equivalent method (FEM) instrument, the tapered element oscillating microbalance (TEOM), at the same or neighboring site that were calibrated to the FRM. $PM_{2.5}$ may vary by temperature and season. Thus, to control for the temporal confounding, daily $PM_{2.5}$ concentration was "pre-whitened" (pre-adjusted) for temperature (3 degrees of freedom (df)) and time (8 df/year (yr)), and these residuals were used in the inferential analyses. This pre-whitening method has been demonstrated as an effective approach for adjusting for

seasonality in evaluating the health effects of short-term pollutant exposures in cohort studies.[105] In contrast to these short-term exposure estimates from the central site, long-term (years) average $PM_{2.5}$ exposure was estimated through yearly national model predictions based on participant address, which were geocoded using ArcMap version 10.5.1. More specifically, $PM_{2.5}$ exposure was estimated with universal kriging using a land use regression for the mean model and an exponential covariance for the geostatistical smoothing. Input data came from a national network of monitoring stations, as described previously.[106] Yearly averages were estimated as a weighted average based on the date of lumbar puncture.

All inferential analyses were stratified by cognitive status (cognitively normal vs. MCI/AD). For short-term $PM_{2.5}$ exposures, we focused on the effects of 7-day averages (prior to CSF draw) with VCAM-1 and e-selectin. This window was selected based on prior studies of $PM_{2.5}$ and blood biomarkers of vascular injury. Sensitivity analyses considered alternative exposure averaging periods (2-day, 5-day, 1-month prior to CSF draw), other pre-whitening spline specifications (12 df/year for time), and restriction to exposure data from the Beacon Hill monitor only. Exploratory analyses considered potential interaction effects of age[107,108] and diabetes;[94,96,109-111] however, because of small sample size in the diabetes subgroup, we were unable to perform the latter analysis and therefore considered effect modification of age only. For long-term $PM_{2.5}$ exposures, we focused on the effects of 1-yr averages with VCAM-1 and e-selectin. This time window allowed us to investigate potential chronic inflammatory responses. We also conducted sensitivity analyses to consider other exposure averaging periods (5-yr, 10-yr, 20-yr), adjustment for year, and to drop individuals for whom we only had P.O. box address information.

We conducted multivariable adjusted linear regression for all analyses. Based on information from relevant scientific literature, we included the following covariates and/or precision variables in a tiered model approach: age (yrs);[19,112] smoking status;[19] sex;[19,112] education (yrs);[113,114] apolipoprotein E4 (APOE-ε4) status (at least 1 copy of E4 vs. no copies of E4),[19,112] body mass index (BMI),[19] hypertension,[112,115-118] coronary heart disease,[112] and diabetes.[112,119,120] The latter three variables are potential intermediates in the causal pathway and therefore were not included in the main model. While we report results from all models below, our *a priori* model (model 2) adjusted for age, smoking, and sex. To allow for comparison to prior studies on air pollution and vascular injury as well as on AD and CSF biomarkers, we provide raw numerical estimates of mean change (i.e. the estimated beta regression coefficient) and as well as percent change estimates scaled to the mean outcome value for each subgroup. All exposure effect estimates were scaled to 5 ug/m^3 for reporting.

All data analysis was performed using R version 3.6.0.

RESULTS

Descriptive Statistics

Among the cognitively normal individuals (n = 73), average (standard deviation (SD)) age was 71.7 (8.0) years and average (SD) years of education was 15.9 (2.5). There were roughly equal proportions of males and females (males = 50.7%), and slightly more than half of this subgroup were past smokers (53.4%) (none were current smokers). Most cognitively normal individuals (69.9%) did not have any copies of APOE-ε4 allele. Average (SD) CSF VCAM-1 and e-selectin concentrations among this subgroup were 126.4 (56.8) ng/ml and 62.6 (48.4) pg/ml,

respectively. Inter-individual variability in exposure was higher for the short-term averages than for the long-term averages.

Among the dementia/MCI individuals (n=60), average (SD) age was 69.9 (9.7) years, and average (SD) years of education was 16.2 (3.0). There were slightly more males than females in this subgroup (males = 55.0%), and 43% were past smokers (none were current smokers). In contrast to the cognitively normal subgroup, most individuals in this subgroup (66.7%) had one or more copies of APOE-ε4. Average (SD) CSF VCAM-1 and e-selectin concentrations in this subgroup were 139.2 (57.5) ng/ml and 58.9 (44.0) pg/ml, respectively. Inter-individual variability in exposure was higher for the 2-7 day averages than for the long-term averages.

VCAM-1

Among the cognitively normal subgroup, a 5 ug/m^3 increase in 7-day average $PM_{2.5}$ was associated with increased CSF VCAM-1 (*a priori* adjusted: 35.4 (9.7, 61.1) ng/ml) (Figure 1; Table S2). Results were robust to restriction to Beacon Hill monitor data only and using a 12-df spline adjustment for year. Effect estimates for the 2-day and 5-day average periods were consistent with the 7-day average effect; however, estimates were attenuated and consistent with a range of effects for the 1-month average period. There was no evidence of effect modification by age.

We also estimated positive associations between 1-yr average $PM_{2.5}$ and CSF VCAM-1 among cognitively normal individuals (Figure 1; Table S2). Based on our *a priori* adjustment model (model 2), a 5 ug/m^3 increase in 1-yr average $PM_{2.5}$ was associated with a 51.8 (6.5, 97.1) ng/ml increase in CSF VCAM-1. Estimates were slightly strengthened with increased covariate adjustment. Results were somewhat attenuated but overall robust to sensitivity analyses evaluating other long-term exposure periods (5-yr, 10-yr, 20-yr) and dropping PO box

individuals. Effect estimates were strengthened when year of cohort enrollment was added to the analytical model.

Among the MCI/AD subgroup, estimates for 7-day and 1-year average $PM_{2.5}$ were positive yet consistent with a wide range of effects (7-day: 16.2 (-8.5, 40.8) ng/ml; 1-year: 17.1 (-33.9, 68.2) ng/ml (Table S4). There was no evidence of effect modification by age. In sensitivity analyses, 2-day average $PM_{2.5}$ was associated with increased VCAM-1 (21.7 (1.2, 42.2) ng/ml), but other results were consistent with the primary analyses. Sensitivity analyses evaluating other long-term exposure periods (5-yr, 10-yr, 20-yr), adding adjustment for enrollment year, and dropping individuals with PO box addresses only were also consistent with the primary results.

E-selectin

Our analysis of 7-day average $PM_{2.5}$ and e-selectin was inconclusive (-1.8 (-27.1, 23.4) pg/ml) in the cognitively normal subgroup (Figure 2; Table S3). We observed similar results in sensitivity analyses. There was no evidence of effect modification by age.

However, we estimated positive associations between 1-yr average $PM_{2.5}$ and e-selectin. Based on our *a priori* model, a 5 ug/m^3 increase in 1-yr average $PM_{2.5}$ was associated with a 53.3 (11.0, 95.5) pg/ml increase in CSF e-selectin (Figure 2; Table S3). In sensitivity analyses evaluating other long-term exposure periods, results from the 5-yr and 10-yr averages were consistent with results from the 1-yr average; restriction to individuals without PO box addresses strengthened the observed associations. Effect estimates were slightly attenuated when year of cohort enrollment was added to the analytical model; however, conclusions from the *a priori* model were consistent the primary model.

Among the MCI/AD subgroup, estimates for 7-day and 1-year average $PM_{2.5}$ were consistent with a wide range of effects (7-day: -9.5 (-28.2, 9.1) pg/ml; 1-year: 23.0 (-15.1, 61.2) pg/ml) (Table S5). Sensitivity analyses evaluating other exposure periods, adding adjustment for enrollment year, and dropping individuals with PO box addresses only were consistent with the primary results.

DISCUSSION

To our knowledge, this is the first study to evaluate the association between $PM_{2.5}$ exposure and CSF biomarkers of endothelial injury. Among cognitively normal individuals, we estimate that 7-day and 1-year average $PM_{2.5}$ exposure is associated with increased CSF VCAM-1, and that 1-year average $PM_{2.5}$ is associated with increased CSF e-selectin. Among individuals with existing MCI/AD, associations were inconclusive for both short-term and long-term $PM_{2.5}$ exposure and the selected biomarkers.

Some prior epidemiological studies have evaluated the association between $PM_{2.5}$ and these biomarkers of endothelial injury in other biofluids, such as serum and plasma. While CSF and blood are not directly comparable, we provide results from these prior studies as context for our findings (Table 2). Most of these studies report associations between short-term exposure to $PM_{2.5}$ and VCAM-1, in alignment with our results. However, our percent change estimate for VCAM-1 among cognitively normal individuals (28.0 (7.7, 48.3) %) was larger than those reported for comparable time periods in prior work. To our knowledge, only one prior study has considered $PM_{2.5}$ in relation to e-selectin;[98] estimates from this study are several orders of magnitude larger than what we observed in our analyses of $PM_{2.5}$ and e-selectin (7-day: -1.8 (-27.1, 23.4) pg/ml; 1-year: 53.3 (11.0, 95.5) pg/ml).

Results from experimental studies evaluating these biomarkers in other biofluids have been mixed. In mice, 9-month exposure to $PM_{2.5}$ was not associated with increased VCAM-1 in the temporal cortex.[51] In one *in vitro* study using a human umbilical vein cell line, $PM_{2.5}$ exposure resulted in a dose-dependent increase in VCAM-1 expression. This elevated VCAM-1 was attenuation by co-treatment with a scavenger of reactive oxidative species (ROS), demonstrating the role of oxidative stress in $PM_{2.5}$-related endothelial inflammation.[121] Another study using the same cell line yielded inconsistent effects on VCAM-1 but a dose-dependent increase in expression of E-selectin.[122]

Further context for our results can be obtained through comparison with prior limited research on other predictors for these CSF biomarkers; these studies report effect estimates in the range of our estimate associated with a 5 ug/m^3 increase in 1-yr $PM_{2.5}$ (51.8 (6.5, 97.1) ng/ml). In a previous study utilizing a cohort with partial overlap to ours, individuals with diabetes had higher CSF VCAM-1 than those without the condition (61.0 (28.0, 95.0) ng/ml). Similarly, an increase in age from 50 to 75 years was associated with a 66.0 (30.0, 102.0) ng/ml increase in CSF VCAM-1.[112] In our own dataset using the *a priori* model among the cognitively normal cohort, a 25-year increase in age was associated with a 87.5 (51.7, 123.3) ng/ml increase in CSF VCAM-1. It should also be noted that another study, also using a cohort with partial overlap to ours, did not report differences in CSF VCAM-1 or e-selectin by smoking status.[19] This is perhaps counterintuitive given the known links between smoking and endothelial injury.[123] Yet, while smoking is often used to represent high air pollution exposure scenarios, some studies do not report links to changes in serum VCAM-1,[124,125] indicating the possibility of different mechanisms of action or the presence of adaptation.

Nevertheless, our results indicating positive associations between $PM_{2.5}$ and CSF biomarkers of endothelial injury among cognitively normal individuals are consistent with much of the prior epidemiological research and the general scientific consensus that $PM_{2.5}$ is associated with inflammation and endothelial injury.[84] Our novel findings suggest potential cerebrovascular and neuroinflammation effects from $PM_{2.5}$ among cognitively normal individuals; however, we were unable to determine whether these changes also occurred in the systemic circulation. These results are aligned with research suggesting that short-term $PM_{2.5}$ is linked to increased cerebrovascular resistance and decreased cerebral blood flow velocity.[126] Given the growing recognition of the role of vascular injury and neuroinflammation in neurodegeneration,[43,83] including recent findings suggesting associations between CSF VCAM-1 and CSF tau,[127,128] these cerebrovascular and inflammation changes may provide evidence to support the link between $PM_{2.5}$, cognitive decline, and dementia.[12,65,69]

Our inconclusive results among individuals classified as MCI/AD are not surprising. Increasing evidence indicates the importance of vascular pathways and the presence of endothelial dysfunction in dementia.[15,19-21,43,83] Thus, in individuals with MCI or AD, existing pathological processes related to cerebrovascular injury may play a more important role in mediating VCAM-1 and e-selectin expression than $PM_{2.5}$ exposure – and thus would obscure any potential $PM_{2.5}$ effects.

This study has several limitations. First, there is possible exposure misclassification for both long-term and short-term exposures to $PM_{2.5}$. With respect to long-term averages, we only had access to a single address for each individual from which to estimate exposures. This address may not represent actual participant address over longer time periods, which could

have resulted in exposure misclassification – particularly for our 10-and 20-year exposure measures. However, our concerns about exposure misclassification are somewhat mitigated given that our primary exposure period for the long-term analysis was focused on 1-yr average exposures. Effects of possible exposure misclassification due to use of PO box rather than residential address was addressed through sensitivity analyses, as described above, which indicated consistent or strengthened associations with restriction to residential address only. For our short-term analysis, we focused only on temporal variation. Ignoring spatial variability may result in some exposure misclassification;[105,129] however, properly addressing spatial variation at the daily scale is a challenge that might have offset the benefits of incorporating it, and temporal variation is the more important determinant of variability at this scale. There is also possible residual confounding in our study. We did not have access to several covariates, such as socioeconomic status (SES), secondhand smoke exposure, medication use, and sleep quality, that may be linked to the exposure, outcomes, or factors that would affect our measurements of the outcomes.[92,130-137] In one prior study among diabetics, associations between $PM_{2.5}$ and plasma VCAM-1 were stronger in those not taking statins compared to the full population (Table 2),[96] yet we were not able to account for statin use. The closest approximation to SES that we had was education level, which may not fully capture the effects of SES in the causal pathway. Future studies evaluating this question should seek to integrate these variables. Finally, this cohort is a small convenience sample based in the Puget Sound region, and results may not be generalizable.

Despite these limitations, our study has important strengths. We evaluated both short-term and long-term exposure $PM_{2.5}$ in relation to CSF biomarkers of endothelial injury, neither

of which had been investigated previously despite the well-documented vascular effects of $PM_{2.5}$. By including both of these exposure periods, we capture variation that is predominantly spatial (long-term) and temporal (short-term). With our pre-whitening approach for the short-term $PM_{2.5}$ analysis, we were able to address most of the confounding on a short time scale that is difficult to remove in a cohort study – particularly those with small sample sizes. Finally, our findings are particularly meaningful because they suggest that $PM_{2.5}$ may have effects on cerebrovascular injury and related neuroinflammation at even the low levels observed in the Puget Sound region. Prior research on $PM_{2.5}$ also suggests effects on biomarkers of endothelial injury, functional cerebrovascular changes, vascular disease and mortality at low exposure levels.[91,126,138-140]

To our knowledge, our study is the first to evaluate the associations between short-term and long-term $PM_{2.5}$ exposure with biomarkers of endothelial injury in the CSF. Here, we estimated that short-term and long term $PM_{2.5}$ exposure was associated with elevated biomarkers of endothelial injury among cognitively normal individuals; no convincing associations were observed for MCI/AD individuals. The clinical significance of these effects among cognitively normal individuals is unknown. Nevertheless, in the context of the growing recognition of the role of vascular injury in neurodegeneration and dementia,[43,83,128] our results may provide evidence to support the link between air pollution and cognitive decline or dementia.[12,65,69]

TABLES & FIGURES

	Cognitively Normal (n=73)	**MCI/AD (n=60)**
Covariates	continuous: mean (SD); categorical: n(%)	
Age (yrs)	71.7 (8.0)	69.9 (9.7)
Education (yrs)	15.9 (2.5)	16.2 (3.0)
Male	37 (50.7)	33 (55.0)
Former smoker	39 (53.4)	26 (43.3)
APOE-ε4 status		
0	51 (69.9)	18 (30.0)
1	22 (30.1)	40 (66.7)
NA	0 (0.0)	2 (3.3)
Body mass index (BMI) (kg/m^2)	26.3 (3.3)	25.4 (3.8)
Coronary artery disease	0 (0.0)	2 (3.3)
Diabetes	1 (1.4)	1 (1.7)
Hypertension	7 (9.6)	10 (16.7)
Outcome variables (mean (sd))		
VCAM-1 (ng/ml)	126.4 (56.8)	139.2 (57.6)
e-selectin (pg/ml)	62.6 (48.4)	58.9 (44.0)
$PM_{2.5}$ (ug/m^3) average (mean (sd))		
Short-term[1]		
2-day	7.8 (4.2)	7.5 (4.2)
5-day	7.7 (2.9)	7.6 (3.9)
7-day[2]	7.8 (2.6)	7.6 (3.5)
30-day	7.7 (2.1)	7.4 (1.8)
Long-term		
1-year[2]	8.3 (1.4)	7.8 (1.4)
5-year	8.8 (1.5)	8.2 (1.5)
10-year	9.6 (1.6)	8.9 (1.6)
20-year	11.2 (1.7)	10.5 (1.8)

Table 1: Descriptive statistics on UW ADRC cohort, stratified by cognitive status

1 Short-term exposure values are unadjusted (not pre-whitened)
2 Primary exposure period for inferential analyses

Author	**Study Cohort/Location**	**$PM_{2.5}$ increment** (ug/m_3)	**Blood biomarker**	**Avg. Period: Effect Estimate** (% change (95% CI) or mean change (95% CI)
Bind et al, 2012 [88]	Veterans Administration Normative Aging Study / Boston, MA, USA	7.1	Plasma VCAM-1	4-hour, 24-hour, 3-28 day: 2-5%[1]
Wilker et al, 2011 [91]	Veterans Administration Normative Aging Study / Boston, MA, USA	4.3	Serum VCAM-1	7-day: 2.5 (0.6, 4.5) %
Pope et al, 2016 [99]	Provo, UT, USA	10	Plasma VCAM-1	24-hour: 0.5%[1]; (also reported as 2.3 (0.3, 4.3) ng/ml increase)
O'Neill et al, 2007 [96]	Boston, MA; diabetics only	7.6	Plasma VCAM-1	<u>All diabetics</u> Same-day: 6.9 (-2.9, 17.6) % 2-day: 8.2 (-1.4, 18.7) % 3-day: 6.9 (-1.7, 16.3) % 4-day: 6.5 (-1.2,14.7) % 5-day: 8.6 (0.1, 17.8) % 6-day: 11.8 (3.5, 20.7) % <u>Excluding statin users</u> Same-day: 10.3 (-0.6, 22.4) % 2-day: 15.0 (3.8, 27.5) % 3-day: 14.6 (3.9, 26.3) % 4-day: 15.2 (4.5, 26.8) % 5-day: 16.2 (5.8, 27.6) % 6-day: 17.7 (7.8, 28.5) %
Madrigano et al, 2010 [95]	Veterans Administration Normative Aging Study / Boston, MA, USA	10	Plasma VCAM-1	1-day: 1.0 (-1.1, 3.2) % 2-day: 1.7 (-0.9, 4.3) % 3-day: 0.4 (-2.6, 3.3) %
Liu et al, 2017 [97]	Shanghai, China	27.4	Serum VCAM-1	24-hour: 12%[2]
Delfino et al, 2008 [92]	Los Angeles, CA, USA	11.5[3]	Plasma VCAM-1	Same-day: 3.4 (-7.5, 14.2) ng/ml 2-day: 8.7 (-8.6, 26.0) ng/ml 3-day: 6.1 (-18.6, 30.7) ng/ml 4-day: -2.8 (-31.8, 26.2) ng/ml
Hajat et al, 2015 [98]	Multi-Ethnic Study of Atherosclerosis (MESA) / Baltimore, MD; Chicago, IL; Winston-Salem, NC; Los Angeles, CA; New York, NY; St. Paul, MN, USA	5	Serum E-selectin	Same-day: 600 (60, 1140) pg/ml Day-prior: 390 (-130, 910) pg/ml 2-day: 440 (-200, 1080) pg/ml 3-day: -20 (-740, 690) pg/ml 4-day: -370 (-1160, 420) pg/ml 5-day: -330 (-1160, 500) pg/ml 1-year: 1100 (-700, 2800) pg/ml

Table 2: Results from prior epidemiological studies evaluating effects of $PM_{2.5}$ on blood VCAM-1 or E-selectin

[1]Estimated from figure; exact numbers not provided in manuscript
[2] Confidence interval not provided
[3] Estimates for this study were based on $PM_{0.25\text{-}2.5}$ ug/m_3

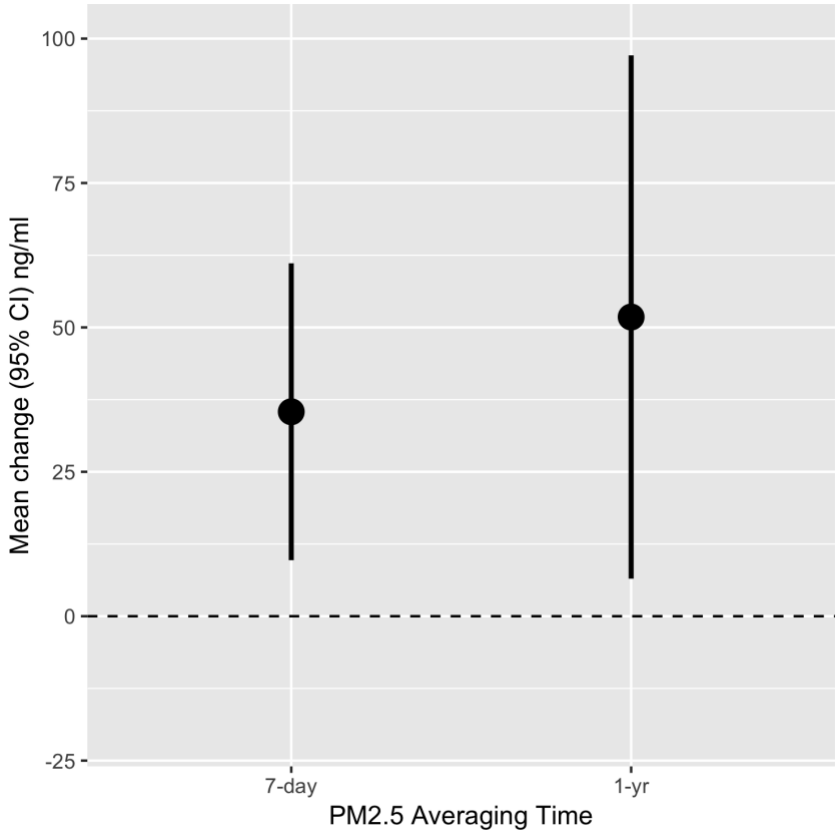

Figure 1: Estimated associations between PM2.5 & VCAM-1 among cognitively normal individuals (*a priori* adjusted model)[1]

[1]Model adjusted for age, smoking, and sex; 7-day exposure accounts for calendar time and temperature with pre-whitening.

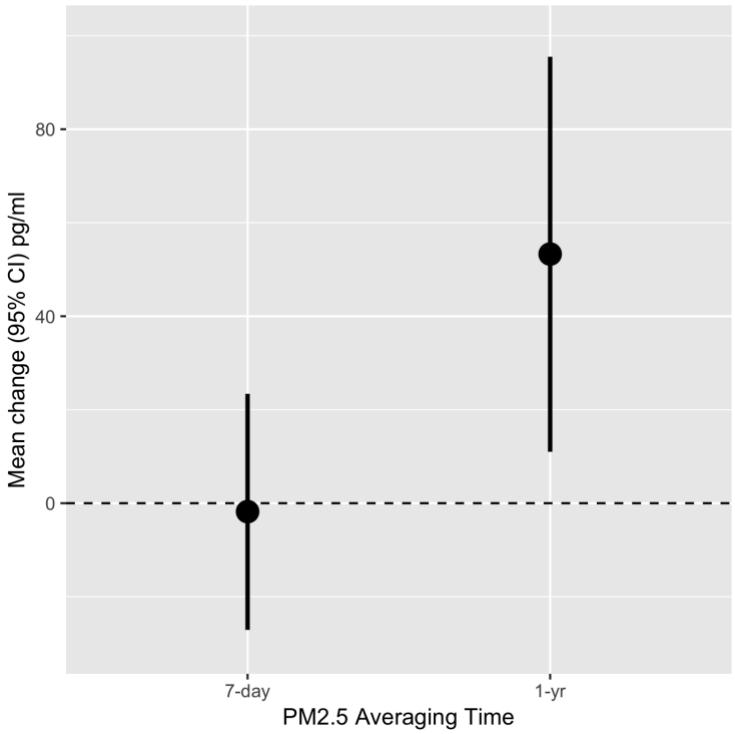

Figure 2: Estimated associations between PM2.5 & E-selectin among cognitively normal individuals (*a priori* adjusted model)[1]

[1]Model adjusted for age, smoking, and sex; 7-day exposure accounts for calendar time and temperature with pre-whitening.

SUPPLEMENTAL INFORMATION

Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2012
# Enrolled	0	12	5	14	26	29	22	16	7	1	1

Table S1: ADRC Cohort Enrollment by Year

	7-day average[3]		1-year average	
Model [2]	Mean change (95% CI) (ng/ml)	% change (95% CI)	Mean change (95% CI) (ng/ml)	% change (95% CI)
Model 1	36.1 (10.6, 61.7)	28.6 (8.4, 48.8)	31.2 (-11.6, 74.0)	24.7 (-9.2, 58.5)
Model 2 *(a priori)*	35.4 (9.7, 61.1)	28.0 (7.7, 48.3)	51.8 (6.5, 97.1)	41.0 (5.1, 76.8)
Model 3	33.5 (7.6, 59.4)	26.5 (6.0, 47.0)	57.2 (11.0, 103.4)	45.3 (8.7, 81.8)
Model 4	31.7 (3.4, 59.9)	25.1 (2.7, 47.4)	56.6 (6.2, 107.0)	44.8 (4.9, 84.6)

Table S2: Estimated associations between short-term and long-term $PM_{2.5}$[1] and VCAM-1 among cognitively normal individuals

[1] Associations scaled to 5 ug/m[3] $PM_{2.5}$
[2] Model 1: age; Model 2: age, smoking, and sex; Model 3: age, smoking, sex, education, APOE-ε4; Model 4: age, smoking, sex, education, APOE-ε4, BMI, hypertension, and diabetes. *Note: Model 4 for the cognitively normal individuals did not include coronary artery disease because no one in this subgroup had been diagnosed with this condition.*
[3] 7-day average exposures account for calendar time and temperature with pre-whitening

	7-day average[3]		1-year average	
Model [2]	Mean change (95% CI) (pg/ml)	% change (95% CI)	Mean change (95% CI) (pg/ml)	% change (95% CI)
Model 1	-1.5 (-26.6, 23.5)	-2.4 (-42.5, 37.5)	37.4 (-2.1, 76.9)	59.7 (-3.4, 122.8)
Model 2 *(a priori)*	-1.8 (-27.1, 23.4)	-2.9 (-43.3, 37.4)	53.3 (11.0, 95.5)	85.1 (17.6, 152.6)
Model 3	0.3 (-25.3, 25.9)	0.5 (-40.4, 41.4)	48.6 (4.5, 92.7)	77.6 (7.2, 148.1)
Model 4	-2.5 (-28.8, 23.7)	-4.0 (-46.0, 37.9)	48.5 (3.4, 93.6)	77.5 (5.4, 149.5)

Table S3: Estimated associations between short-term and long-term $PM_{2.5}$[1] and E-selectin among cognitively normal individuals

[1]Associations scaled to 5 ug/m[3] $PM_{2.5}$
[2] Model 1: age; Model 2: age, smoking, and sex; Model 3: age, smoking, sex, education, APOE-ε4; Model 4: age, smoking, sex, education, APOE-ε4, BMI, hypertension, and diabetes. *Note: Model 4 for the*

cognitively normal individuals did not include coronary artery disease because no one in this subgroup had been diagnosed with this condition.

[3] 7-day average exposures account for calendar time and temperature with pre-whitening

	7-day average[3]		1-year average	
Model [2]	Mean change (95% CI) (ng/ml)	% change (95% CI)	Mean change (95% CI) (ng/ml)	% change (95% CI)
Model 1	12.7 (-12.3, 37.7)	9.1 (-8.8, 27.1)	17.0 (-34.8, 68.8)	12.2 (-25.0, 49.4)
Model 2 *(a priori)*	16.2 (-8.5, 40.8)	11.6 (-6.1, 29.3)	17.1 (-33.9, 68.2)	12.3 (-24.4, 49.0)
Model 3	16.8 (-9.1, 42.6)	12.1 (-6.5, 30.6)	21.2 (-34.7, 77.1)	15.2 (-24.9, 55.4)
Model 4	13.6 (-20.4, 47.5)	9.8 (-14.7, 34.1)	24.2 (-39.8, 88.2)	17.4 (-28.6, 63.4)

Table S4: Estimated associations between short-term and long-term $PM_{2.5}$[1] and VCAM-1 among MCI/AD individuals

[1]Associations scaled to 5 ug/m[3] $PM_{2.5}$

[2] Model 1: age; Model 2: age, smoking, and sex; Model 3: age, smoking, sex, education, APOE-ε4; Model 4: age, smoking, sex, education, APOE-ε4, BMI, hypertension, coronary artery disease, and diabetes

[3] 7-day average exposures account for calendar time and temperature with pre-whitening

	7-day average[3]		1-year average	
Model [2]	Mean change (95% CI) (pg/ml)	% change (95% CI)	Mean change (95% CI) (pg/ml)	% change (95% CI)
Model 1	-12.4 (-31.5, 6.7)	-21.0 (-53.5, 11.4)	22.9 (-16.5, 62.4)	38.9 (-28.0, 105.9)
Model 2 *(a priori)*	-9.5 (-28.2, 9.1)	-16.1 (-47.9, 15.4)	23.0 (-15.1, 61.2)	39.0 (-25.6, 103.9)
Model 3	-9.2 (-28.7, 10.3)	-15.6 (-48.7, 17.5)	17.9 (-23.9, 59.7)	30.4 (-40.6, 101.4)
Model 4	-2.7 (-25.2, 19.7)	-4.6 (-42.8, 33.4)	11.1 (-31.0, 53.3)	18.8 (-52.6, 90.5)

Table S5: Estimated associations between short-term and long-term $PM_{2.5}$[1] and E-selectin among MCI/AD individuals

[1]Associations scaled to 5 ug/m[3] $PM_{2.5}$

[2] Model 1: age; Model 2: age, smoking, and sex; Model 3: age, smoking, sex, education, APOE-ε4; Model 4: age, smoking, sex, education, APOE-ε4, BMI, hypertension, coronary artery disease, and diabetes

[3] 7-day average exposures account for calendar time and temperature with pre-whitening

Chapter 3: Fine Particulate Matter and Markers of Alzheimer's Disease Neuropathology

INTRODUCTION

Neurodegenerative diseases, including Alzheimer's Disease (AD) and related dementias (ADRD), pose a growing burden on our rapidly aging society.[1,2] In 2016, dementia was the fifth leading cause of death around the world.[141] The most common cause of dementia is AD, which is characterized by the presence of extracellular β-amyloid$_{1-42}$ (Aβ_{1-42}) plaques and intraneuronal tau aggregations (neurofibrillary tangles (NFTs)), among other alterations, that disrupt cell-to-cell communication and transport and trigger pathologic inflammatory processes.[45,142]

Increasing evidence has linked air pollution, such as fine particulate matter ($PM_{2.5}$), to neurodegeneration and ADRD.[11-14,143] Additionally, several studies have specifically documented aggregations of Aβ_{1-42}, among other pathologic changes, in brain tissue from children, young adults, and canines exposed to high levels of air pollution.[46-49] Experimental laboratory studies also provide evidence of alterations in levels of AD and related molecular markers after exposure to air pollution and/or inhaled metals.[50-52] Current hypotheses suggest that these central nervous system (CNS) effects of $PM_{2.5}$ and other air pollutants may be mediated through direct and/or indirect pathways leading to oxidative stress and inflammation.[65,69,70]

Despite the growing links between air pollution and neurodegeneration as well as the plausible mechanisms to support these associations, no studies to date have evaluated the association between exposure to $PM_{2.5}$ and AD neuropathology at death in older adults: the primary population affected by AD and one that might be particularly sensitive to the effects of $PM_{2.5}$ due to decreased antioxidant defenses in the aging brain.[15,144] Furthermore, the few human studies conducted to date, focusing primarily on children and young adults, have been

descriptive analyses with limited sample size.[46-48] To address this gap, conducted a novel analysis to investigate the association between long-term $PM_{2.5}$ exposure and markers of AD neuropathology at autopsy among participants in the Adult Changes in Thought (ACT) prospective population-based cohort study in Seattle, Washington, USA.[145] The results of this pathophysiological-based epidemiological investigation complement prior studies that have evaluated the clinical outcome of AD and expand upon our understanding of the neurotoxic effects of $PM_{2.5}$.

METHODS

Study Design

The ACT study is a prospective community-based cohort study in Seattle, WA, USA. This cohort is comprised of an urban and suburban elderly (>65 years) population randomly sampled from a well-established health maintenance organization (HMO) (Group Health, now Kaiser Permanente of Washington). Enrollment of cognitively intact (defined as CASI (Cognitive Abilities Screening Instrument) score of > 85 or consensus diagnosis of "not demented" after comprehensive assessment) individuals began in 1994-96 (original cohort, n=2581) and has been expanded to maintain 2000 person-years at-risk per calendar year. Consent for autopsy is optional. It is discussed at study enrollment and follow-up visits; for those who consented, it is confirmed by next-of-kin at the time of participant death, as required by Washington State law. As of the most recent ACT study data freeze in September 2018, 5546 participants have been enrolled, and 832 autopsies have been conducted.

This study was approved by the University of Washington Institutional Review Board.

Exposure Assessment

We assigned $PM_{2.5}$ exposure uniquely based on residential addresses geocoded with ArcMap version 10.5 (Redlands, California) for individuals living within the Puget Sound modeling region covered by our spatiotemporal exposure prediction model. We obtained high quality participant address history from billing records starting in 1989; prior to that date, address data were available from various sources including Group Health/Kaiser Permanente administrative records. Updated addresses, due to participant change of residence, for example, were incorporated when possible. If participants moved out of the spatiotemporal modeling region during the course of our study, no exposure estimates were able to be generated following the move. Additional information on how gaps in address coverage were addressed are detailed in Supplemental Part A.

We estimated annual average $PM_{2.5}$ concentrations based on two-week average concentrations from a hierarchical spatiotemporal prediction model using land use regression (LUR) and geostatistical smoothing, similar to prior published work.[146-148] This new model was developed from $PM_{2.5}$ monitoring data covering the years 1978-2019 across the Puget Sound region in Washington State, including 35 long-term (>2 years) regulatory monitors at 29 sites, 52 sites from research campaigns conducted in 2003-2004 and 2012, and 105 community and study participant home sites (2017-2019) using low-cost sensor measurements (with 5 sites co-located with regulatory monitors). See Supplemental Information for additional model details. For long-term averages at regulatory monitoring locations, the final model had a cross-validated R^2 (R^2_{CV}) of 0.87 and a root mean square error (RMSE) of 1.29 µg/m3; at low-cost measurement sites, the corresponding values were R^2_{CV} = 0.78, RMSE = 0.89 µg/m^3. Using this

final model, we had the ability of predict long-term average $PM_{2.5}$ at participant homes from 1978-2018; based on these data, we created different exposure averaging periods of interest for our analyses.

Outcome Assessment

Preservation and evaluation procedures for autopsied brain tissues have been described previously.[149] Briefly, neuritic plaque density in the cerebral cortex was assessed using the Consortium to Establish a Registry for AD (CERAD) score (none; sparse; moderate; frequent).[150] NFT distribution was assessed by Braak staging (I-II; III-IV; V-VI).[151] Combined AD pathology (plaques and NFTs) was assessed with an ABC score, in line with recent National Institute on Aging-Alzheimer's Association (NIA-AA) recommendations.[152,153] For tissue collected prior to these 2012 recommendations, the ABC score was simulated based on CERAD and Braak score. Because 'intermediate' or 'high' AD neuropathologic change is considered sufficient explanation for dementia,[153] we converted ABC scores to a binary variable ("not/low" vs. "intermediate/high") for our inferential analyses. The simulated score was used for all cases to ensure consistency among participants given the substantial missingness in the raw scores.

Statistical Analysis

Accounting for Selection Bias

Selection bias is a challenge to the generalizability of the analysis.[154,155] To be included in the autopsy dataset, participants had to pass through several stages of selection: enrollment, consent to autopsy, continuation in the study over the course of life, death, and next-of-kin consent to autopsy. To address this issue, we employed Inverse Probability Weighting

(IPW)[156,157] to create stabilized weights for use in the inferential analyses. IPW creates a pseudo-population that allows us to model what would have happened if all individuals were included in the autopsy cohort.

Because our inferential analysis did not evaluate time-varying covariates and all aspects of selection are known at autopsy, we considered all stages of selection together in one model. Missing values of key covariates were replaced with the mode or mean for selection modeling. (Missingness was less than 7% for each of the covariates). We fit a logistic regression model to estimate the probability of inclusion in the autopsy subset, given a final set of covariates as determined by forward selection based on the following starting covariates obtained at baseline: ACT study cohort, age at baseline, birth cohort, gender, race, educational degree, neighborhood median household income, smoking status, alcohol use, regular exercise, APOE-ε 4 status, body mass index (BMI), diabetes, cardiovascular disease, hypertension, multivitamin use, self-rated health, and challenges with instrumental activities of daily living (IADL). While non-linearity was explored for selected variables, such as age, we determined there was no added benefit of these alternatives. Based on the selected model, we computed stabilized weights[156,158] using gender as the numerator. Stabilization is recommended for IPW because standard, non-stabilized weights could be very large (unstable) for observations with low probabilities.[156] Extreme weights were truncated at 10. The distribution of the final stabilized weights was then evaluated to check for positivity violations. The stabilized weights were included as the weights parameter in the inferential analyses.

Inferential Analyses

We conducted ordinal logistic regression to evaluate the association between long-term exposure to $PM_{2.5}$ and Braak and CERAD stage. We conducted logistic regression to evaluate the association between long-term exposure to $PM_{2.5}$ and dichotomized ABC score (none/low vs. intermediate/high). Importantly, we evaluated these outcomes in all individuals, regardless of clinical dementia diagnosis status. Because of the extended period of disease development in AD,[159,160] it is still highly relevant to examine these neuropathologies in cognitively normal individuals. Furthermore, based on the cognitive reserve and brain reserve hypotheses, some individuals may appear cognitively normal despite significant AD-related neuropathology.[161-165]

We addressed potential confounding with detailed covariate data based on baseline (enrollment) information unless otherwise noted below. The following key covariates and precision variables, with missingness filled in with mean or mode as described for the IPW modeling above, were selected in a tiered model approach based on prior scientific literature: model 1 (M1) (crude/minimally adjusted model): gender,[166-168] *APOE* genotype (defined as ≥1 ε4 allele vs. 0 ε4 alleles),[169-172] age at death; [173,174] model 2 (M2) (*a priori* main model): M1 + year of death, educational degree category,[175,176] neighborhood median household income;[137] model 3 (M3) (extended model): M2 + race,[177-179] smoking pack years,[180,181] regular exercise; smoking pack years,[180,181] regular exercise;[182,183] model 4 (M4) (extended + mediation model): M3 + body mass index (BMI) category,[184-186] diabetes,[119,187-189] hypertension,[115,116,190] and cardiovascular disease.[43,191,192] Strong temporal trends in our exposure data informed our decision to use calendar year of death to adjust for confounding by time. Model 4 includes medical comorbidities that may be on the causal pathway. B-splines with three degrees of

freedom were used to model the following covariates: age at death; year of death; smoking pack years.

Our primary analyses focused on the association between 10-year average $PM_{2.5}$ and the outcomes of interest, using the M2 covariates described above. We selected this exposure window because it was the longest averaging period for which we had high confidence in our exposure modeling and address history coverage for the cohort; this extended period mirrors the long disease development and progression in ADRD.[159,193]

In secondary analyses, we evaluated alternative exposure averaging periods (1-yr; 5-yr; 20-yr) as well as an exposure period incorporating a lag time (5-yr with 10-yr lag) given the extended timeline involved in the development of dementia pathologies. We conducted sensitivity analyses to evaluate the impact of using categories for the three variables (age at death, year of death, smoking pack-years) that were modeled as splines in the primary analysis and the impact of the following cohort restrictions: never smokers; non-smoker at baseline; high address imputation quality; and death after year 2000. We also conducted a sensitivity analysis using dichotomous rather than ordered categorical outcomes for Braak and CERAD.

In additional secondary analyses, we evaluated the potential for effect modification between APOE genotype status and $PM_{2.5}$ exposure in the *a priori* model. APOE polymorphisms are strongly linked to AD pathology and risk of AD.[194] The APOE protein, which is encoded by the *APOE* gene, is the main lipid transport protein expressed in the brain. Because of its role in the transport of cholesterol and related lipids, APOE is central to neurogenesis, plasticity, & repair.[53] Additionally, APOE influences antioxidant capacity, inflammatory response, and vascular health. [57,58] If $PM_{2.5}$ contributes to the development of AB plaques and NFTs through

oxidative stress and neuroinflammation, then individuals with one or two copies of the ε4 allele may be more susceptible to the neurotoxic effects of $PM_{2.5}$.

Bootstrapping

The processes described above for both the selection and inferential modeling were implemented on 1000 bootstrap samples drawn with replacement from the original 5546 person dataset. This nonparametric bootstrapping process was implemented in order to generate more accurate standard error estimates.[195] Point estimates were calculated by averaging the results of these replicate regression analyses, and confidence intervals were obtained from the 2.5^{th} and 97.5^{th} percentiles of the empirical bootstrap distribution.

All data analysis was performed using R version 4.0.0.

RESULTS

Descriptive Statistics

Overall, population characteristics of the autopsy cohort were fairly similar to those of the full ACT cohort (Table 1). However, the autopsy cohort was less likely to be comprised of individuals from the latest birth cohort (autopsy: 12%; full ACT: 38%); more likely to be white (autopsy: 94%; full ACT: 89%). more likely to be APOE-ε4 positive (autopsy: 27%; full ACT: 21%); and less likely to be obese (autopsy: 26%; full ACT: 31%). The average (standard deviation (SD) age at entry for individuals in the autopsy cohort was 77 (7) years, and the average (SD) age at death was 89 (7) years.

Exposure coverage and quality information is provided in Supplement Part A. Mean (SD) 10-year average $PM_{2.5}$ from death across the autopsy cohort was 8.2 (1.9) ug/m^3. However, this overall summary masks an important temporal trend across time, as depicted in Figure 1, with 10-year average $PM_{2.5}$ decreasing over time as expected based on secular trends in air pollution. Decomposition of variance indicated that between-year variation (SD: 2.6) was much higher than within-year variation (SD: 0.4) in our dataset. Consequently, controlling for temporal confounding by adjusting for year of death, which focused the inferential analysis on within-year spatial variation, resulted in a decrease in exposure contrast across the population.

With respect to the distribution of outcomes in the autopsy cohort, the most common findings were B3 Braak stage (37%) and frequent CERAD score (29%). There were equal proportions of individuals in the none/low and intermediate/high (simulated) ABC score groups (50%).

Bootstrapping & Selection Modeling

There were an average of 830 autopsies across 1000 bootstrapped samples of the full dataset. The only variable included in all selection models across these bootstrapped datasets was birth cohort. Other commonly selected variables included: ACT cohort, educational degree, race, *APOE* genotype, smoking status, self-rated health, challenges with IADL, and hypertension. After applying these selection models to the IP weight modeling process and prior to truncation, there were, on average, 6 individuals in each dataset with weights above 10. The mean (SD) of stabilized, truncated IP weights across all bootstrapped samples was 0.99, with a range of 0.25 to 10.

Inferential Analyses

In our *a priori* primary analyses using IP-weighting, we estimated that each 1 ug/m^3 increase in 10-year average $PM_{2.5}$ prior to death was associated with a suggestive increase in the odds of worse brain pathology as indicated by higher CERAD score (OR: 1.35 (0.90, 1.90)) (Figure 2). However, there was no association with Braak score (OR: 0.99 (0.64, 1.47), and $PM_{2.5}$ was suggestively associated with less pathology as indicated by a lower odds of the simulated ABC score. However, for all outcomes, the confidence intervals were consistent with a range of effects, including no association, and therefore we cannot draw strong conclusions.

Overall, our results were robust to different modeling strategies. Results from crude models were attenuated while results from more richly adjusted models were similar to the primary models. Results from sensitivity analyses were similar to the primary analysis, though the estimate was larger and confidence intervals much wider when the population was restricted to never smokers for CERAD in particular (See Supplement Figure S5). Similarly, while there was some variation in the effect estimates across different exposure averaging periods, the ranges of the confidence intervals were overlapping with the primary analyses. (See Supplement Figures S6-8). Overall, IP-weighting showed associations that overlapped considerably with unweighted associations though the IP-weighted estimates had larger confidence intervals. There was no evidence of effect medication by *APOE* genotype (APOE interaction p-values: Braak = 0.97; CERAD = 0.09; ABC = 0.24).

DISCUSSION

Our study is the first to evaluate the association between $PM_{2.5}$ and AD neuropathologies using autopsy samples in a population-based prospective cohort study comprised of older adults. While specific point estimates for the outcomes of interest suggest potential associations, the results were inconsistent across outcomes and none of the observed associations could be distinguished from no association.

Prior *in vivo* and *in vitro* experimental studies suggest adverse effects of $PM_{2.5}$ on AD neuropathologies. For example, 9-month $PM_{2.5}$ exposure has been shown to cause early AD-related changes and increased expression of pro-inflammatory enzymes in mice.[51] Three-week and six month exposure to diesel exhaust, a complex mixture of gases and particulates (including $PM_{2.5}$), has been shown to stimulate and/or accelerate AD markers, including plaque formation, in both mice and rats.[196,197] *In vitro* studies have demonstrated that $PM_{2.5}$ leads to increased Aβ levels in *ex vivo* mouse hippocampal tissue[198] and that nano-size traffic-related PM leads to increases in both oxidative stress and Aβ production in mouse neuronal cells.[199]

While there are currently no other prospective cohort studies of air pollution and AD neuropathology at autopsy to our knowledge, previously published descriptive analyses that have documented aggregations of $A\beta_{1\text{-}42}$, among other molecular changes such as those reflecting oxidative stress, in brain tissue from children, young and middle age adults, and canines exposed to high levels of air pollution.[46-49] Yet, it is important to note that these prior data are all based on populations living in Mexico City, which has a yearly average $PM_{2.5}$ concentration of 25 ug/m^3.[49] By contrast, our study population experienced lower exposure concentrations: the overall mean (SD) across all years in our autopsy cohort was 8.3 (1.9) ug/m^3, with a range of 4.8-15.1 ug/m^3. This may partially explain our inconclusive results: we

may not have had enough power to estimate effects of the low exposures experienced by our cohort.

Investigators have used the ACT cohort to evaluate the effect of other exposures on these standardized categorical scores and stages for AD neuropathology, providing another point of comparison for this research. For example, heavy anticholinergic use – which is linked to increased risk of dementia[200] - was associated with a suggestive increase in CERAD score (1.22 (0.81, 1.88)) and a suggestive decrease in Braak stage (0.89 (0.47, 1.66)), but both of these confidence intervals were overlapping with the null. High glucose exposure in the five years prior to death was not associated with elevated Braak stage (RR: 1.06 (0.53, 2.04)) or CERAD score (RR: 1.01 (0.67, 1.51).[201] Our effect estimates are in a similar range to these findings from studies also investigating the impact of known dementia risk factors on AD neuropathology. These results could suggest that the elevated dementia risk from $PM_{2.5}$ (or the other risk factors investigated in prior ACT studies) are mediated through mechanisms other than tau tangles and beta-amyloid plaques.

Another relevant comparison may be found in autopsy studies of smoking and AD neuropathology. In an analysis using a smaller sample from the ACT cohort (N=238), Tsuang et al. reported that compared to moderate smokers (5-50 pack years), never/low smokers (0-5 pack years) had a suggestive elevated risk of higher ABC score (IP-weighted RR: 1.16 (0.55, 2.81), while heavy smokers (>50 pack years) had a suggestive decreased risk (IP-weighted RR: 0.65 (0.17, 2.25), though both estimates had large confidence intervals consistent with a range of effects.[202] In an analysis using the Honolulu-Asia Aging Study with light smokers (0-26.7 pack-years) as the reference category, medium (26.7-40.5 pack-years) and heavy (40.5-55.5 pack-

years) smokers were more likely to have higher counts of neocortical neuritic plaques (count ratios (95% CI); medium: 2.12 (1.17, 3.86), heavy: 2.09 (1.14, 3.84)), though this association was attenuated in very heavy smokers (>55.5–156 pack-years) (1.25 (0.60, 2.58). Associations between smoking intensity and hippocampal NFTs, neocortical NFTs, and hippocampal neuritic plaques, respectively, were mixed, with some effect estimates suggesting adverse effects while other suggesting protective effects; overall, confidence intervals for most of these estimates were overlapping with the null.[203] Most other published studies report null or protective effects of smoking and AD neuropathology.[180,204-206]

A likely reason for these inconclusive and potentially counterintuitive results across all of these smoking studies as well as our study is that these exposures are associated with premature mortality,[207] yet age is associated with neuropathology.[208] Therefore, we cannot rule out the possibility that our results are biased due to the fact that age at death is behaving like a quasi-mediator in the association between $PM_{2.5}$ and AD neuropathology. This can also be perceived as a form of selection bias, where individuals who die earlier from higher intensity exposures would exhibit less severe neuropathology because they died younger than other individuals. While most studies of smoking and AD neuropathology– as well as this current analysis of $PM_{2.5}$ – have included age at death as a covariate, simple adjustment for this mediator may still lead to bias if there are unmeasured confounders that impact both age at death and the outcome of interest.

We did not observe evidence of effect modification by *APOE* genotype. Some prior studies of air pollution and cognitive decline or dementia risk suggests that effects of air pollution exposure may be more pronounced people with $\geq$1 ε4 allele,[46,47,59-63] though other

studies do not support effect modification by *APOE* genotype.[64] Future studies in the area of air pollution and ADRD should continue to evaluate the potential for interaction by *APOE* genotype.

The central, novel contribution of this work is the evaluation of the association between $PM_{2.5}$ and AD neuropathological stages rather than clinical AD diagnosis alone, as has been the focus of prior studies.[11-13,143] AD neuropathology and AD dementia diagnosis may not be aligned in many individuals. Due to the extended period of disease development in AD, plaques and tangles manifest prior to detectable symptoms.[159,160,209,210] In fact, studies suggest that approximately 20-40% of cognitively normal elderly individuals have significant amyloid plaques, [211-215] though this statistic varies by age and *APOE* genotype.[214] Furthermore, based on the cognitive reserve and brain reserve hypotheses, some individuals may appear cognitively normal (ie: receive no clinical AD diagnosis) despite significant AD-related neuropathology.[161-165] Therefore, a study that directly evaluates AD neuropathology provides different information than one relying on incidence data alone.

To evaluate neuropathology, we used standardized, well-accepted stage and score classifications for AD, which allows for comparison to other published studies. Yet, using continuous measures could provide more precision to answer this scientific question. Future analyses could use quantitative measures of neuropathology, such as histelide[216] or Luminex-based[217] approaches.

A major strength of this work is that we utilized a newly developed spatiotemporal exposure prediction model, specifically for the Puget Sound, that provided estimates of residence-based $PM_{2.5}$ for 40 years (1978-2018). This provides extensive exposure history with

which to examine our research question. We complemented this exposure assessment data with detailed address histories available through Group Health/Kaiser Permanente of Washington records, with nearly complete histories since 1989 for the entire cohort and reasonably good coverage prior to 1989. Overall, we were able to estimate 10-year average $PM_{2.5}$ exposures using known address history for 98% of the individuals in the autopsy dataset across the entire study period. Evaluating a long exposure period is crucial for this research question, given the extended period of disease development in ADRD.[159]

Yet, there were also challenges in utilizing an extended exposure history. For example, there were limited monitoring sites across the region during the early years; therefore, the spatial contrasts in our model rely heavily on information from more recent years. This issue is especially important to consider given that by adjusting for year of death in our *a priori* and extended models, we are essentially eliminating the larger between-year temporal contrasts and relying entirely on the smaller within-year spatial contrasts for the inferential analyses: the spatial contrasts during earlier periods may have more bias. Additionally, measurement error concerns aside, these low within-year spatial exposure contrasts likely explain the fairly wide confidence intervals for our results.

Another challenge for our study – as in all cohort studies of elderly populations – is selection bias, which occurs with differential enrollment or attrition of study participants. Overall, the ACT study has an exceptional Completeness of Follow-up Index (95.6%),[218] which minimizes our concern with bias due to selective attrition in general. However, differential enrollment into the autopsy cohort, specifically, could still be an issue. An important strength of this work is that we utilized IP-weighting in our inferential models to minimize the impact of

this selection bias. In the end, we observed minimal impact of this weighting across our analyses.

Finally, we cannot rule out the possibility that our results are biased due to the fact that age at death is behaving like a quasi-mediator in the association between $PM_{2.5}$ and AD neuropathology. As noted above, it is likely that the inconclusive and counterintuitive results from studies of smoking and AD neuropathology are due to the fact that smoking is linked to premature mortality,[207] yet elevated age is associated with increased neuropathology.[208] Thus, individuals who die earlier from higher intensity smoking patterns would exhibit less severe neuropathology. A similar situation could arise with $PM_{2.5}$ exposure, given its well-established link to premature mortality.[219] Advancements in biostatistical methods, including by incorporating tools from the causal inference literature, are needed to address this potential bias and identify alternative estimands.

CONCLUSION

In summary, we report suggestive but inconclusive results regarding the association between long-term $PM_{2.5}$ and AD neuropathology. Our results are similar to other studies of known AD risk factors on AD neuropathology.[201,220] Given the potential bias resulting from mediation by age at death, a future analysis that more appropriately accounts for this factor may provide more accurate effect estimates. Further work is needed in this area, including development of appropriate statistical methods, given the growing evidence of the association between long-term exposure to $PM_{2.5}$ and clinical AD.[12]

TABLES & FIGURES

mean(SD) / n(%)	**Total**	**Autopsy**
	(n=5546)	**(n=832)**
Baseline Age (Years)	74 (6)	77(7)
Age at Death (Years)	87 (7)	89 (7)
ACT Cohort		
Original	2581 (47%)	512 (61%)
Expansion	811 (15%)	188 (23%)
Replacement	2154 (39%)	132 (16%)
Birth Cohort		
1890-1910	637 (11%)	151 (18%)
1915	783 (14%)	206 (25%)
1920	1049 (19%)	220 (26%)
1925	973 (18%)	158 (19%)
1930-1950	2104 (38%)	97 (12%)
≥1 *APOE* ε4 allele	1179 (21%)	224 (27%)
Female	3228 (58%)	480 (58%)
White	4956 (89%)	786 (94%)
Census Tract Median Household Income		
<35,000	528 (10%)	77 (9%)
35,000-49,999	1709 (31%)	262 (31%)
50,000-74,999	2703 (49%)	414 (50%)
>75,000	606 (11%)	79 (9%)
Degree		
None	465 (8%)	65 (8%)
GED/High School	2089 (38%)	356 (43%)
Bachelors	1285 (23%)	197 (24%)
Masters	859 (15%)	109 (13%)
Doctorate	327 (6%)	43 (5%)
Other	521 (9%)	62 (7%)
Smoking Status		
Never	2706 (49%)	372 (45%)
Past	2569 (46%)	411 (49%)
Current	271 (5%)	49 (6%)
Regular Exercise	3969 (72%)	584 (70%)
Body Mass Index (BMI)		
Underweight/Normal	2014 (36%)	327 (39%)

Overweight	1836 (33%)	285 (34%)
Obese	1696 (31%)	220 (26%)
Diabetes	577 (10%)	86 (10%)
Cardiovascular Disease	492 (9%)	92 (11%)
Hypertension	2284 (41%)	314 (38%)
Avg PM2.5 (ug/m3) for the 10-yrs Prior to Death	9.0(2.4)	8.2(1.9)
Braak stage		
0	-	24 (3%)
B1	-	204 (25%)
B2	-	291 (35%)
B3	-	304 (37%)
Missing	-	9 (1%)
CERAD score		
None	-	187 (22%)
Sparse	-	205 (25%)
Moderate	-	199 (24%)
Frequent	-	238 (29%)
Missing	-	3 (0.4%)
ABC score (simulated)		
None/Low	-	414 (50%)
Interm/High	-	412 (50%)
Missing	-	6 (0.7%)

Table 1: Descriptive statistics for full cohort and autopsy cohort

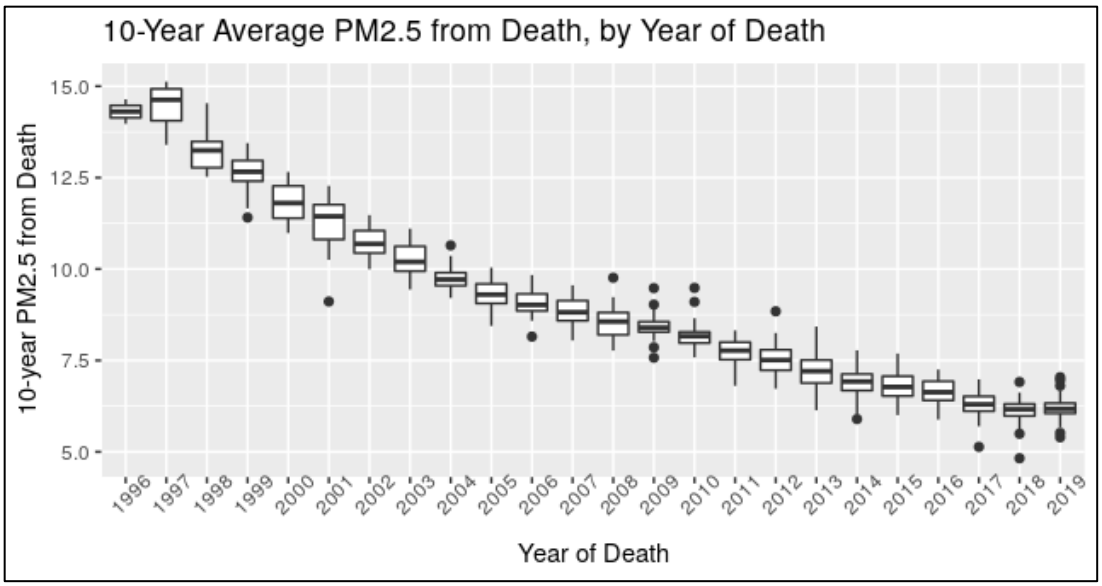

Figure 1: 10-year average $PM_{2.5}$ exposure by Year of Death in the Autopsy Cohort**.** In each boxplot, the middle line represents the median value; the edges of the box represent the 25th and 75th percentiles, and the whiskers extended up to 1.5 times the interquartile range (IQR). Points represent outlier observations outside this range.

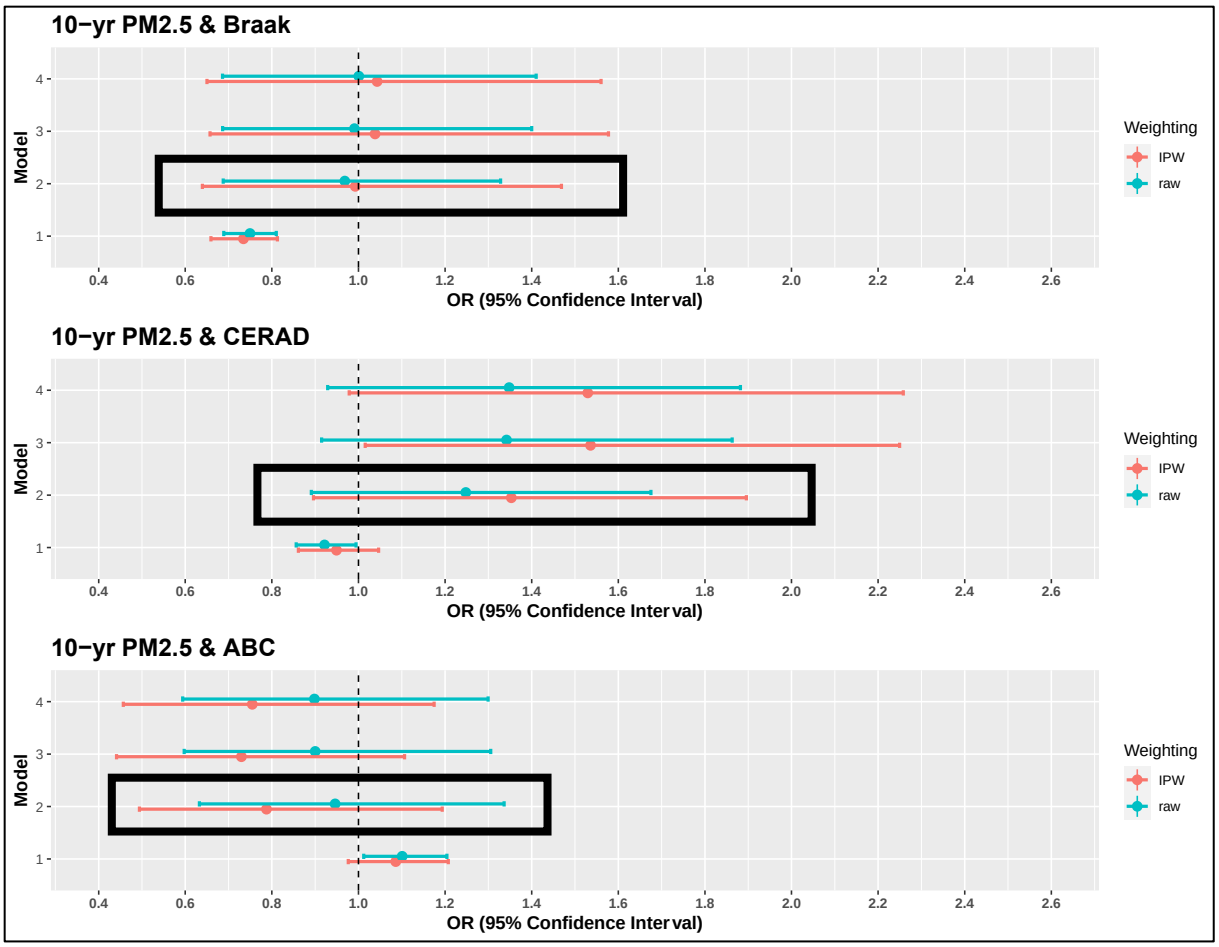

Figure 2: Association between 1 ug/m^3 increase in 10-year average exposure to $PM_{2.5}$ and AD neuropathology at autopsy. Box indicates *a priori* model. M1: gender, APOE-ε4 status, age at death; M2 (*a priori*): M1 + year of death, educational degree, neighborhood median household income; M3: M2 + race, smoking pack years, regular exercise; M4: M3 + BMI, diabetes, hypertension, and cardiovascular disease.

SUPPLEMENTAL INFORMATION

A: Exposure Coverage & Quality

A.1. Additional information on Exposure Model

The spatiotemporal model is comprised of a space-time mean plus residual: the mean model includes terms representing spatially varying long-term average as well as a spatially varying trend. This model can be fit to limited space-time data by utilizing a small number of sites with long-term monitoring to estimate time trends. These trends anchor the seasonal and other short-term variation to estimate spatial contrasts using data from all sites, which are particularly informed by multiple short-term monitoring sites. Because there were limited number of monitoring sites prior to 1999 and no long-term sites that provided data over the entire monitoring period, the Puget Sound model required modifications to the standard modeling approach. Specifically, prior to fitting the model, we subtracted a single smooth long-term trend from log-transformed measurements; this was later added back to the predictions.

The final model includes one time trend to capture spatially-varying seasonal and other short-term fluctuations. The trend was estimated from a singular value decomposition (SVD) of data providing at least two years of monitoring data followed by smoothing using a spline with eight degrees of freedom per year. The spatially varying long-term mean and trend were fit using distinct universal kriging models, each with a mean reflecting land use characteristics that was estimated from over 100 geographic covariates reduced to a single partial least squares (PLS) score. Geographic covariates included proximity variables (including measured distance in meters to major roads, intersections, truck routes, railways, railyards, coastlines, airports and ports) and buffer variables (including those based on major road length, truck route length, land-use category percentage, normalized difference vegetation index (NDVI), and year 2000 population density). Kriging was captured using an exponential variogram.

A.2. Imputation rules and classification

Address histories since 1978 were obtained from a combination of archived Group Health/Kaiser Permanente administrative records and ACT study records. Gaps in individual administrative records were most likely due to temporary changes in health coverage. For this analysis, we imputed missing address history information for two categories of coverage gaps: gaps prior to 1989 (when the bulk of the administrative address history data became available) and gaps after the first available address. Missing addresses were imputed based on available information, and we classified each individual's imputation quality for each year beginning in 1978. Individuals with complete address coverage and those with a short gaps in coverage (up to 2 years) with the same address before and after the gap were classified as having complete address history (score = 1). Individuals with gaps of less than two years and a change of address during this gap were assumed to have moved halfway through the time period; they were classified as having nearly complete address history (score = 2). All other individuals were classified as having less complete address history (score = 3). If address information prior to the first recorded address was missing, we projected the first available address back in time and

assigned a score of 2 for the duration up to the time they were known to live at the available address and a score of 3 for any additional time.

A.3. Descriptive statistics on exposure coverage & quality across the cohort

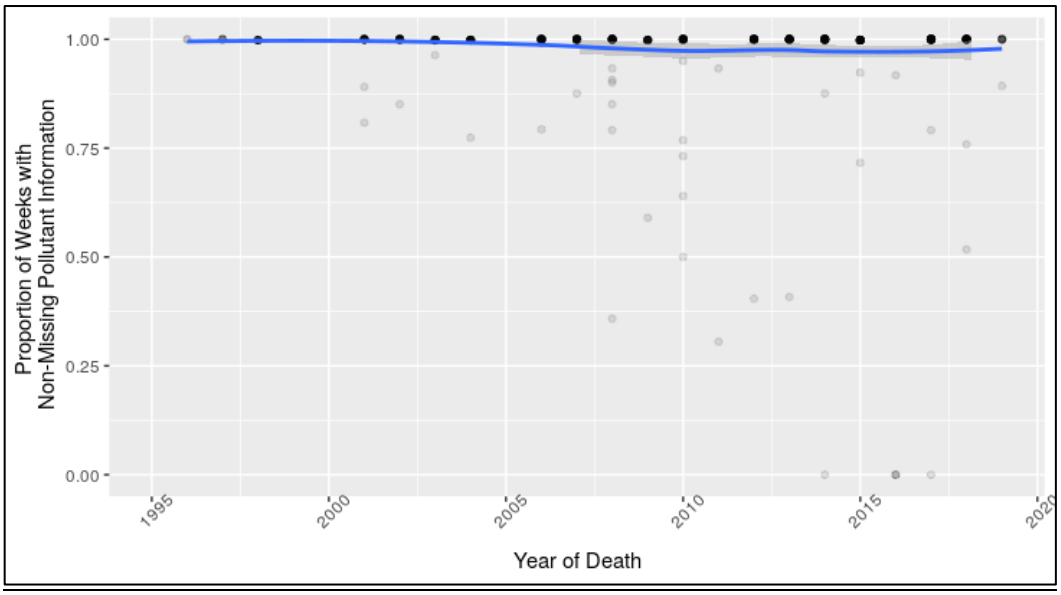

Figure S1: Exposure coverage for 10-year average $PM_{2.5}$; Proportion of weeks with non-missing pollutant information. Pollutant estimates are missing when the participant lived outside of the spatiotemporal modeling region. Individual records appear as gray circles with shading to reflect data density while the blue trend line depicts the average across all individuals in each year..

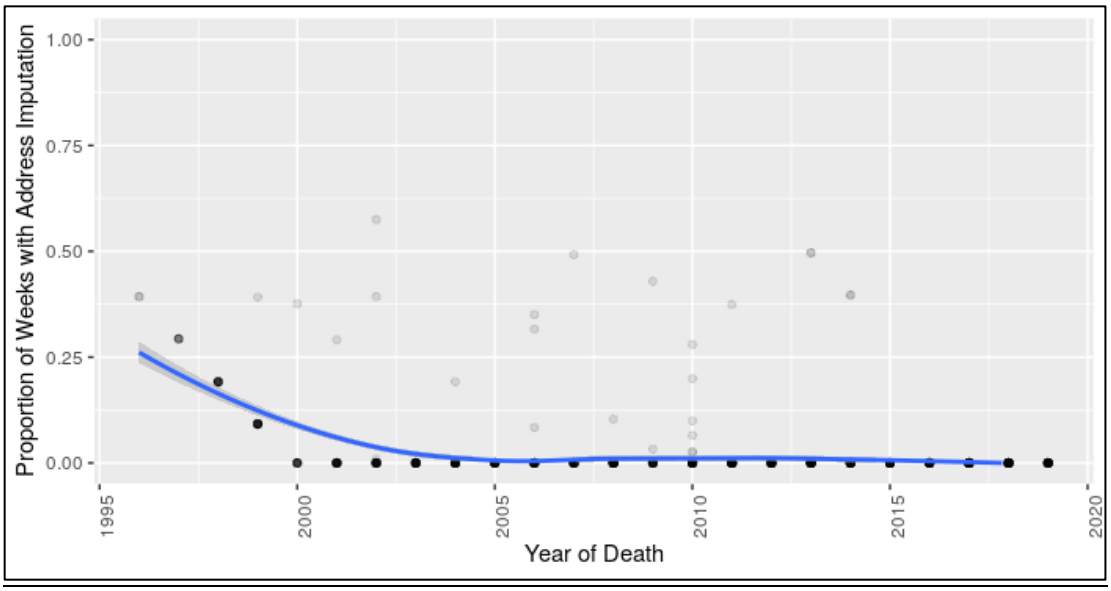

Figure S2: Imputation coverage for 10-year average $PM_{2.5}$; Proportion of weeks with address history imputation. Individual records appear as gray circles with shading to reflect data density while the blue trend line depicts the average across all individuals in each year.

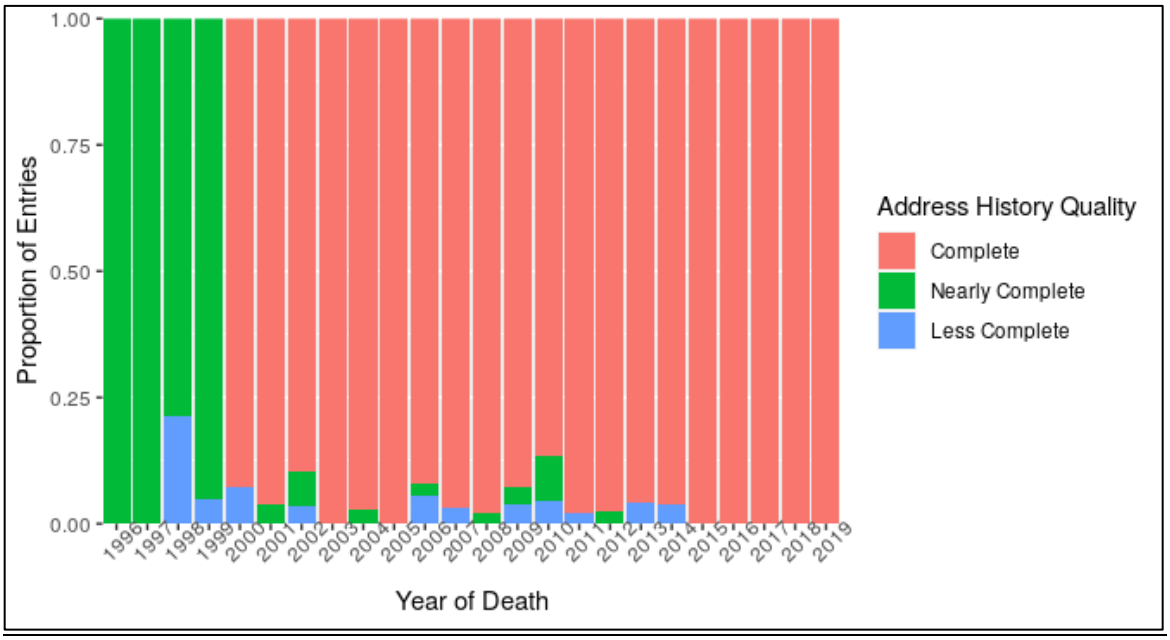

Figure S3: Address history quality for 10-year average $PM_{2.5}$. Proportion of entries corresponding to different levels of imputation quality across the study period.

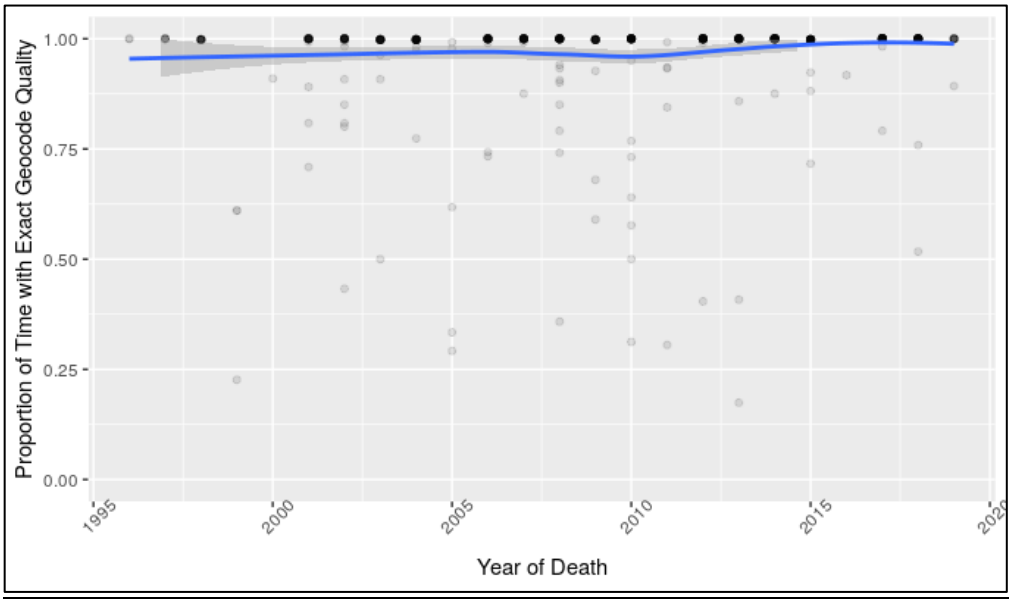

Figure S4: Exact Geocoding Coverage for 10-year Average PM2.5; Proportion of entries with exact geocode quality. Individual records appear as gray circles with shading to reflect data density while the blue trend line depicts the average across all individuals in each year.

B: Secondary and Sensitivity Analyses

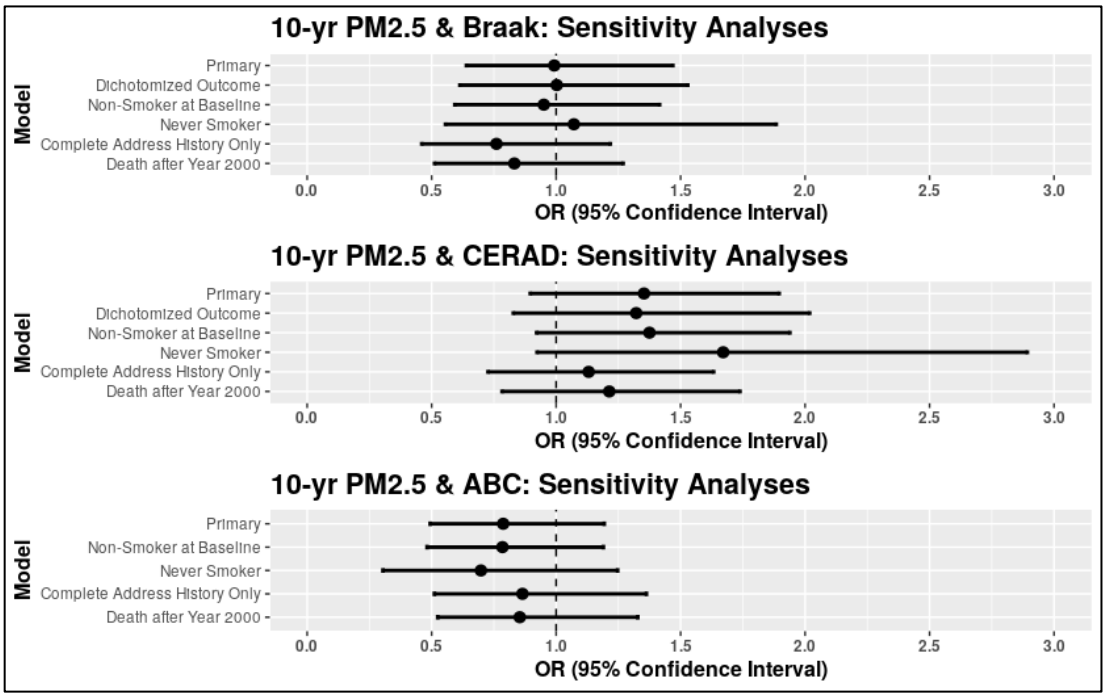

Figure S5: Sensitivity analyses for 1 ug/m^3 increase in 10-year PM2.5 exposure and odds of elevated AD neuropathological score. Sample size reflects average across bootstrapped replicates. Models adjusted for gender, APOE-ε4 status, age at death; year of death, educational degree category, neighborhood median household income.

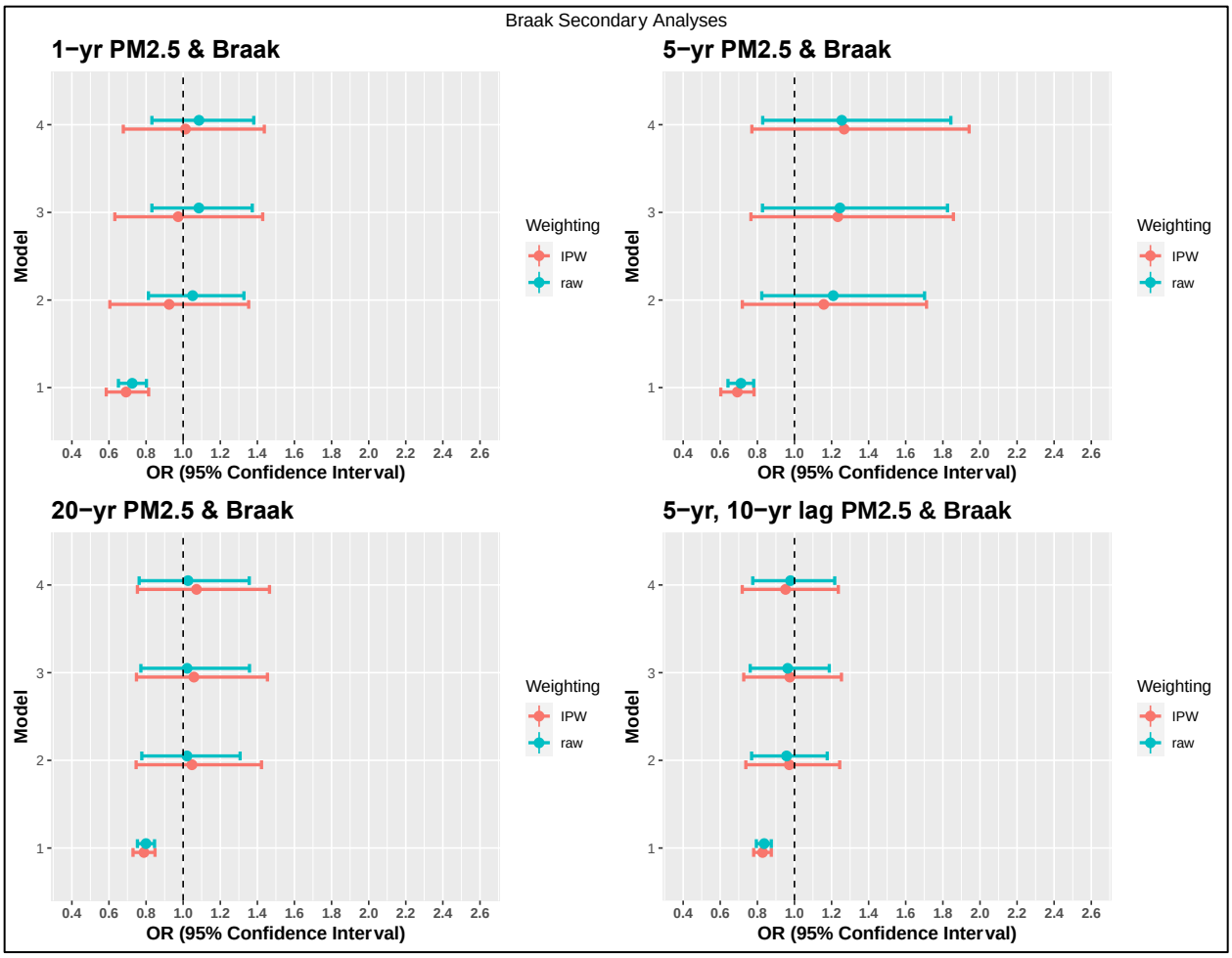

Figure S6: Secondary analyses for 1 ug/m^3 increase in 10-year $PM_{2.5}$ exposure and odds of elevated Braak stage. M1: gender, APOE-ε4 status, age at death; M2 (*a priori*): M1 + year of death, educational degree, neighborhood median household income; M3: M2 + race, smoking pack years, regular exercise; M4: M3 + BMI, diabetes, hypertension, and cardiovascular disease.

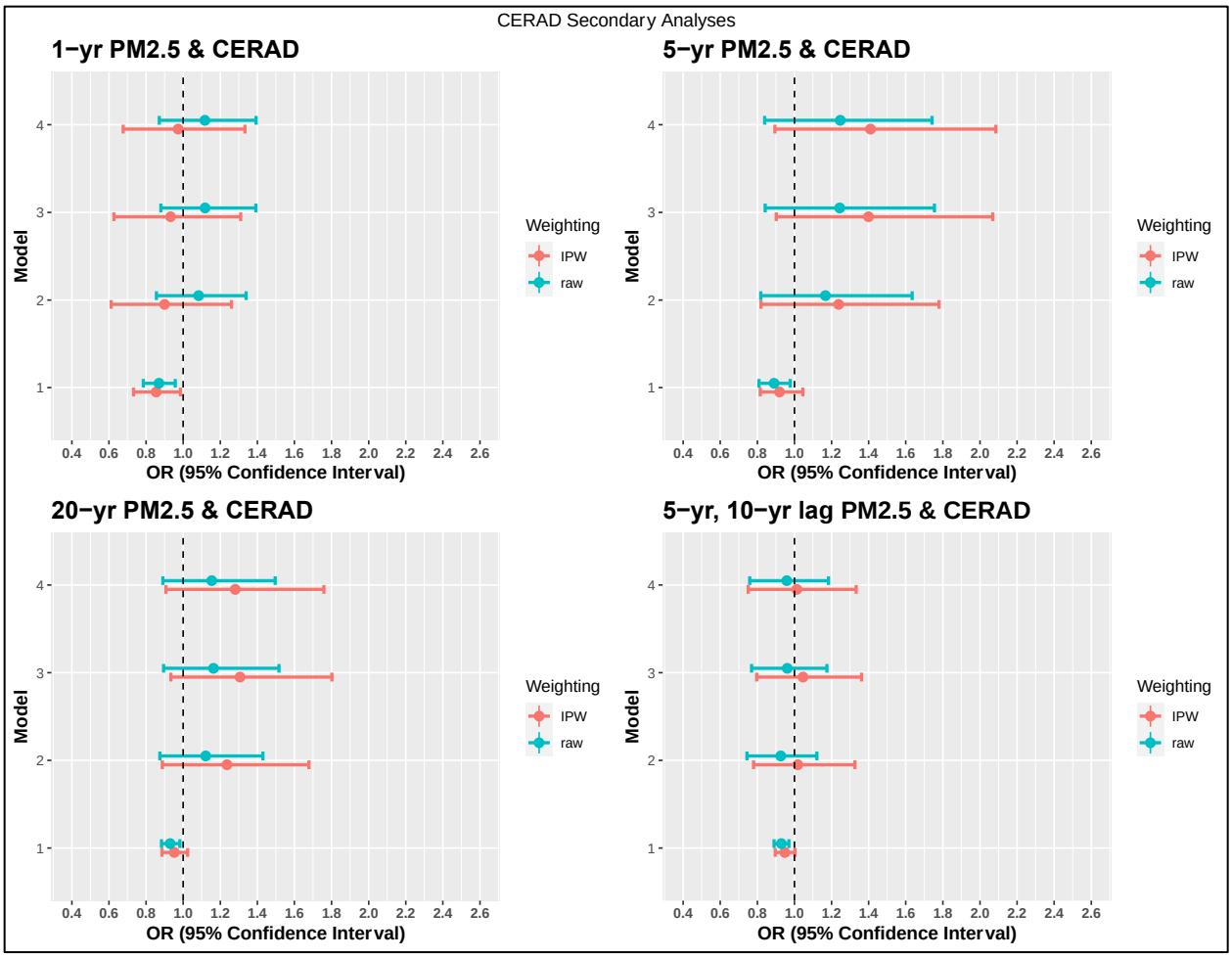

Figure S7: Secondary analyses for 1 ug/m^3 increase in 10-year $PM_{2.5}$ exposure and odds of elevated CERAD stage. M1: gender, APOE-ε4 status, age at death; M2 (*a priori*): M1 + year of death, educational degree, neighborhood median household income; M3: M2 + race, smoking pack years, regular exercise; M4: M3 + BMI, diabetes, hypertension, and cardiovascular disease.

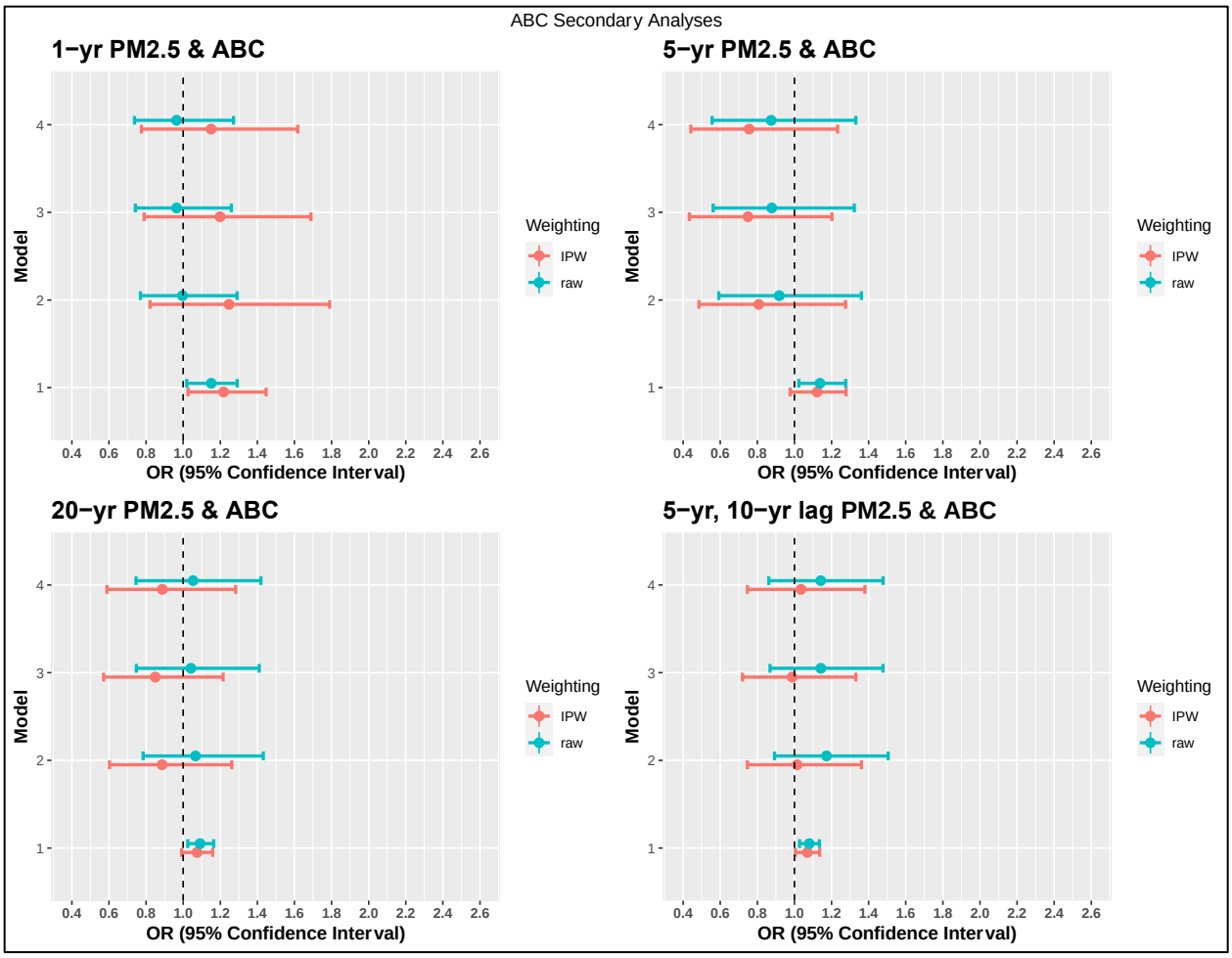

Figure S8: Secondary analyses for 1 ug/m^3 increase in 10-year $PM_{2.5}$ exposure and odds of elevated ABC score. M1: gender, APOE-ε4 status, age at death; M2 (*a priori*): M1 + year of death, educational degree, neighborhood median household income; M3: M2 + race, smoking pack years, regular exercise; M4: M3 + BMI, diabetes, hypertension, and cardiovascular disease.

Chapter 4: Fine Particulate Matter and Dementia Incidence

INTRODUCTION

Neurodegenerative diseases, including Alzheimer's Disease (AD) and related dementias (ADRD), pose a growing burden on our rapidly aging society.[1,2] In 2016, dementia was the fifth leading cause of death around the world.[141] Because no medication successfully alters the course of ADRD, there has been an increasing focus on prevention by addressing potentially modifiable risk factors.

Mounting evidence has linked air pollution to incidence of ADRD.[11-14,62,143,221-223] While air pollution is a complex mixture of particles and gases, fine particulate matter ($PM_{2.5}$) may be a particular concern given its small size – with the ability to penetrate deeply - and potential toxic components. Current hypotheses suggest that the central nervous system (CNS) effects of $PM_{2.5}$ may be mediated through direct and/or indirect pathways leading to oxidative stress and inflammation.[65,69,70]

Several prior studies have evaluated the link between $PM_{2.5}$ and ADRD. In general, all of these studies suggest that elevated exposure to $PM_{2.5}$ is associated with an increased hazard of ADRD, though some of the estimates are consistent with a range of effects.[11,13,62,143,221,222] Yet, limitations in this current body of literature indicate the need for further study. For example, most previous studies evaluated only exposure periods of five years or less, which may not capture the relevant exposure window given the extended development of dementia.[159] Additionally, many studies utilized administrative data to ascertain dementia status; misclassification is a concern when using this approach.[224] Finally, all but two prior analyses utilized calendar time as the time axis in the survival model, which may provide only incomplete

adjustment for the confounding effects of age as compared to using age as the primary time-axis.[225-227]

To address these limitations and existing questions, we utilized a community-based prospective cohort study in the Puget Sound region (the greater Seattle, WA area) to evaluate the association between time-varying, long term average exposure to $PM_{2.5}$ and incidence of ADRD, using age as the time axis in our survival model. A secondary goal was to evaluate the difference between using age and calendar time as the time axis in the Cox model and understand the impact of different ways to control for these covariates in the analysis. Given the ubiquity of air pollution, a better understanding of the potential impact of $PM_{2.5}$ on ADRD could inform policies to reduce exposures across the population.

METHODS

Study Design

The ACT study is a prospective community-based cohort study based in the Puget Sound area. This cohort is comprised of an urban and suburban elderly (≥65 years) population from a well-established HMO (Group Health, now Kaiser Washington). Enrollment of cognitively intact individuals began in 1994-96 (original cohort, n=2581) and has been expanded to maintain 2000 at-risk person-years per calendar year. As of September 2018, 5546 participants have been enrolled. We dropped individuals with no follow-up after the baseline visit and those whose intake date was recorded as occurring after their final visit date; therefore, our final analytical sample included 4744 individuals.

This study was approved by the University of Washington Institutional Review Board.

Exposure Assessment

Annual average $PM_{2.5}$ concentrations linked to residential addresses (geocoded with ArcMap version 10.5) were calculated based on two-week average concentrations obtained from a newly developed hierarchical spatiotemporal prediction model that incorporates both land use regression (LUR) and geostatistical smoothing. This model was based on monitoring data from five types of fine particulate matter monitors covering the years 1978-2019 across the Puget Sound region. See the Supplement for additional model details. We used the final model to predict long-term averages at participant homes from 1978-2018 and create individual-specific time-varying ten-year average exposures for each calendar year of observation. The final model had a cross-validated R^2 (R^2_{CV}) of 0.87 and a root mean square error (RMSE) of 1.29 $\mu g/m^3$ for long-term averages at regulatory monitoring locations; these figures were $R^2_{CV} = 0.78$, RMSE = 0.89 $\mu g/m^3$ at low-cost measurement sites.

Individual $PM_{2.5}$ estimates were assigned based on residential addresses geocoded with ArcMap version 10.5. Estimates were only available for addresses within the spatiotemporal modeling region. High quality participant address history from billing records was available starting in 1989; prior to that date, address information was available from multiple sources including archived Group Health/Kaiser Permanente administrative records. If participants moved during the study period, updated addresses were incorporated when possible. If participants moved out of the spatiotemporal modeling region, no estimates were available for that period. Gaps in address coverage were filled in based on pre-specified imputation coverage rules detailed in Supplemental Part A.

Outcome Assessment

ACT participants had full cognitive assessments during biennial follow-up visits.[145] Individuals who scored 86 or higher on the Cognitive Abilities Screening Instrument (CASI) exam were classified as dementia-free. Individuals who scored lower than 86 underwent standardized evaluations for dementia. Diagnoses were made by consensus conference: dementia diagnosis was based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV,[228] while AD diagnosis (possible/probable) was based on National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria.[229]

Because participants are only observed biennially, we do not have access to the exact date at which they cross the threshold into "dementia." To allow for consistency with non-cases, we assigned the last-visit date as the event onset date. We acknowledge the presence of interval censoring in this approach. However, any attempt to pinpoint a specific date for ADRD diagnosis would be imprecise given that these conditions emerge over several years. In sensitivity analyses, we evaluated the impact of this decision by utilizing an alternative approach routinely used in other survival analyses of the ACT cohort – assigning dementia onset as the midpoint between the last two visits for cases.

Statistical Analysis

We used a Cox proportional hazards model to obtain a hazard ratio (HR) based on time to event (dementia or AD diagnosis). Age was utilized as the time axis, which allows for non-parametric specification of the age effect. Additionally, using age as the time axis automatically adjusts for the confounding effect of age and therefore may be the preferred approach when

evaluating a process such as dementia that is strongly related to aging.[225-227,230] This approach is aligned with prior survival analyses in the ACT cohort.[231-233]

Given the substantial evidence indicating elevated risk of ADRD for carriers of apolipoprotein ε4 genotype,[53-56] we utilized *APOE* genotype (0 vs. ≥1 copies of ε4) as a stratification variable for the Cox models in our analysis. This approach allows each level of this categorical variable to have its own baseline hazard function, which eliminates the proportional hazards condition normally required for the Cox model.

We used inverse probability weighting (IPW) to account for missingness in the *APOE* variable. First, missing values of non-*APOE* covariates (median household income, degree, smoking status, BMI category, diabetes, heart disease, CVD, hypertension) were replaced with the mean category or value of each. (Missingness was less than 2% for each of these covariates). Next, we modeled the probability of a non-missing *APOE* status, using stepwise selection to obtain a final selection model. Finally, we computed stabilized IP weights, using gender in the numerator and the selection model covariates as the denominator, to represent the inverse probability of non-missing *APOE* status. These values were used as weights in the Cox proportional hazards model.

For this analysis, we utilized detailed covariate data collected at or based on baseline (enrollment) information unless otherwise noted below. The rationale for this decision is that our primary goal with covariate adjustment is to unconfound the exposure-outcome relationship; later values of time-varying covariates may have been affected by the exposure of interest. The following key covariates and precision variables, with missingness filled in as described for the IPW modeling above, were selected *a priori* based on prior scientific

literature. We used a tiered model approach to address sensitivity to covariates in our inferential analyses by considering: model 1 (M1): *APOE* genotype stratification only; model 2 (M2) (*a priori*): M1 + gender,[168,234] educational degree category (none; GED/high school; bachelors; master's; doctorate; other) ,[164,175,235,236] year 2000 neighborhood median household income (< $35,000; $35,000-50,000; $50,000-75,000; >$75,000),[137] race (white; non-white),[177-179] time-varying calendar year categories (2-year categories, except for a 3-year category covering the most recent years 2016-2018);[237,238] model 3 (M3): M2 + smoking status (current/former/never),[239,240] regular physical activity;[182,183] model 4 (M4): M3 + vascular health indicators (hypertension, diabetes, cardiovascular disease (CVD), heart disease),[84,119,241-244] and body mass index (BMI) category (underweight; normal; overweight; obese).[245-247] Vascular health indicators and BMI may be on the causal pathway.

The time-varying exposure at each age is defined as the average $PM_{2.5}$ level over the ten calendar years prior to an event onset date for everyone in the risk set at that time. We allowed these exposures to change once per year on January 1; each participant has a corresponding continuous age on this date. For example, a ten-year average $PM_{2.5}$ estimate linked to an event age in the year 2010 would be calculated from $PM_{2.5}$ during the years 2000-2009. We also modified the risk set in our models to account for delayed entry (left truncation), which is crucial in this cohort given the wide range in entry ages for participants.

Our primary analysis focused on the association between 10-year average $PM_{2.5}$ and incidence of all-cause dementia. We selected this exposure window because it was the longest averaging period for which we had high confidence in our exposure modeling and address history coverage for the cohort; this extended period mirrors the long disease development and

progression in ADRD[159,193] As a secondary analysis, we evaluated the association between 10-year average $PM_{2.5}$ and the incidence of AD-specific subtype of dementia as well as potential effect modification by APOE-ε4 status.[59,62] Secondary analyses also evaluated alternative exposure averaging periods (1-yr; 5-yr; 20-yr) as well as exposure periods with lag times incorporated (10-yr with 5-yr lag; 10-yr with 10-yr lag), given the prolonged development and delayed manifestation of dementias.

We conducted multiple additional sensitivity analyses to evaluate the impact of our modeling decisions on the results, such as utilization of the standard ACT study method for classifying onset date (as midpoint between the last two visits for cases); dropping the IP weights from the model; restriction to individuals with complete address history; consideration of 5-20-year categories of birth cohort and 5-year categories of calendar time rather than 2-year categories of calendar time to adjust for temporal confounding (categories shown in Table 1); and utilization of calendar time as the time axis (instead of age). As a post-hoc analysis, we evaluated an interaction of $PM_{2.5}$ with time period.

All analyses were conducted using R version 3.6.3.

RESULTS

Selection Modeling & Inverse Probability (IP) Weighting

The stepwise selection process produced a final selection model with the following covariates: ACT cohort, race, degree, gender, CVD, age at intake, and birth cohort. The mean (standard deviation (SD)) of IP weights across the population was 1.15 (0.56).

Descriptive Statistics

Mean (SD) 10-year average $PM_{2.5}$ exposure across all follow-up years was 10.0 (2.9) $\mu g/m^3$. This simple summary statistic masks important temporal trends: the 1994 mean (SD) was 16.0 (0.8) $\mu g/m^3$ while it was 6.2 (0.3) $\mu g/m^3$ in 2018. Figure 1 depicts 10-year average $PM_{2.5}$ exposure by age and calendar time with one observation per person year. This figure demonstrates clear secular trends in exposure, with individuals in the same age category experiencing dramatically different exposures based on calendar time.

Given these strong temporal trends, we present information on baseline population characteristics stratified by mean-centered 10-year average $PM_{2.5}$ exposure at entry (Table 1). Our total cohort included 4744 individuals; of those, 4166 individuals had non-missing APOE status. Mean age at entry across the entire cohort was 75 years. Most individuals in the cohort were female (59%), white (89%), and had no *APOE* ε4 alleles (65%). Population characteristics were similar across categories of mean-centered baseline $PM_{2.5}$. However, a higher percentage of individuals with elevated mean-centered baseline $PM_{2.5}$ were in the lower categories of census tract median household income.

Mean follow-up time was 9.7 years. Approximately 44% of individuals in our cohort lived at one location throughout the study period. We had exact geocoding matches for 97% of addresses across all person-years in this cohort. Additional exposure coverage and address quality information is provided in the Supplementary Materials.

Inferential Analyses

Our *a priori* primary analysis was based on an analysis of 1134 events over 41,272 person years from individuals with non-missing APOE status. When comparing participants with a 1 ug/m^3 difference in exposure, adjusting for the *a priori* covariates listed above, a higher 10-year average $PM_{2.5}$ was associated with a 1.16 (1.03, 1.31) higher hazard of all-cause dementia diagnosis (Figure 2). Results were similar when using 1-year categories of calendar time, which provided the richest adjustment for temporal confounding. Using crude categories to adjust for calendar time (5-20 year birth cohort categories or 5-year calendar year categories) attenuated the results and indicated an inverse association between $PM_{2.5}$ and dementia onset (birth cohort adjustment: HR: 0.90, 95% CI: 0.84, 0.96; 5-yr calendar year adjustment: HR: 0.94, 95% CI: 0.86, 1.01). Use of the alternative time axis of calendar time provided estimates that were similar to the primary model but slightly attenuated, with the confidence intervals just overlapping the null (birth cohort adjustment: 1.13 (0.99, 1.29); intake age adjustment: 1.14 (0.99, 1.31)). Results using a 20-year exposure period were similar to the primary analysis but those based on shorter term exposures (1-year, 5-year) and well as the 10-year exposure with a 10-year lag suggested elevated HRs but had confidence intervals consistent with a wide range of results ranging from mildly protective effects up to a HR of 1.26 (Figure S5). We did not detect evidence of effect modification by APOE status.

In our secondary analysis of AD-subtype dementia, we estimated that a 1 ug/m^3 increase in 10-year average $PM_{2.5}$ was associated with an 11% greater (1.11 (0.97, 1.27)) increase in the hazard of AD diagnosis, adjusting for the *a priori* covariates listed above (Figure 2). As with the primary dementia analysis, results from shorter term exposures (1-year, 5-year)

and well as the 10-year exposure with a 10-year lag were attenuated compared to the primary averaging period (Figure S6). No effect modification by *APOE* genotype was identified.

Results from additional sensitivity analyses for both all-cause dementia and AD-subtype dementia are presented in Figure S7 and Tables S1 and S2. Estimates were slightly attenuated when IP-weighting was not implemented. Using the diagnosis date procedure conventionally used in ACT cohort survival analyses did not meaningfully alter the effect estimates. Restriction to individuals with high imputation quality decreased the sample size and attenuated the effect estimate, with confidence intervals overlapping the null for both outcomes. Post-hoc analyses suggested possible interaction effects by time period (1994-1999: 1.27 (0.99, 1.62); 2000-2009: 1.23 (1.05, 1.45); 2010-2018: 0.92 (0.74, 1.16).

DISCUSSION

In the first community-based cohort study of men and women in the United States to evaluate the association between long-term exposure to $PM_{2.5}$ and incident late-life dementia, we report that an increase of 1 ug/m^3 in the moving 10-year average $PM_{2.5}$ was associated with a 16% greater hazard of all-cause dementia diagnosis (1.16 (1.03, 1.31). The association with AD-subtype dementia was suggestive of an 11% elevated hazard (1.11 (0.97, 1.27)). HRs using the 20-year exposure period were similar, but results using the 1-year and 5-year exposure periods were attenuated, suggesting that these shorter windows may not capture the relevant etiologic window for dementia development.

Comparison to Prior studies of $PM_{2.5}$ & ADRD

Several prior studies have evaluated the association between $PM_{2.5}$ and incident ADRD (Table S3). Here, we discuss these results with HRs rescaled to a 1 ug/m^3 $PM_{2.5}$ increment for better comparison to our work. Using a primary care practice database for older adults in London (N=~131,000) with mean (SD) $PM_{2.5}$ of 15.7 (0.8) ug/m^3, a 1 ug/m^3 increase in annual average $PM_{2.5}$ was associated with a 1.03 (0.96, 1.12) increase in the hazard of dementia and a 1.11 (1.02, 1.20) increase in the hazard of AD.[222] In a study of administrative data for Ontario, Canada (N=~2.1 million), where mean (SD) was 10.4 (3.6) ug/m^3 – similar to the average exposure over time in our cohort – a 1 ug/m^3 increase in a 2-year lagged 5-year moving average of $PM_{2.5}$ was associated with a 1.008 (1.006, 1.010) increase in the hazard of dementia.[11] Using a female-only research cohort in the United States (N = 3,637) with a mean (SD) of 12.5 (2.7) ug/m^3, Cacciottolo et al., estimated a 1 ug/m^3 increase in 3-yr average $PM_{2.5}$ was associated with 1.07 (1.03, 1.12) increase in the hazard of all-cause dementia.[62] One prior study has evaluated this question among a population exposed to lower average $PM_{2.5}$ than our study population. Using an administrative database for Vancouver, Canada (N=~678,000), where mean (SD) for non-AD dementia cases was 4.12 (1.64) ug/m^3, a 1 ug/m^3 increase in $PM_{2.5}$ over the 4-year study period was associated with a 1.01 (0.99, 1.03) increase in the hazard of dementia.[143] Our results are higher than what has been documented previously – perhaps due to our high quality exposure assessment and outcome ascertainment, further discussed below.

An important difference between our study and prior studies is that we utilized age as the time axis for our survival analysis. Only two prior studies chose to implement the Cox model with age as the time axis;[11,248] all other studies used calendar time or time in study as the time axis.[13,62,143,221,222] As noted above, using age as the time axis allows for non-parametric

specification of the age effect and automatically adjusts for the strong effect of age, which is crucial when evaluating a process highly related to aging, such as late-life dementia.[225-227,230] By contrast, using calendar time as the time-axis could lead to bias when age is an important confounder.[226] This bias may still exist even when the risk model adjusts for baseline age, since this approach imposes a specific functional relationship between age and the hazard rate and ignores the fact the relative change in hazard rate would likely be different at different ages.[227] Because of the strong effect of age on risk of dementia, we believe that using age as the time-axis is the most appropriate approach for these analyses. It also allows for straightforward interpretation of the hazard function as the age-specific incidence function.[226] Yet, it should be noted that using age as the time-axis creates a situation where comparisons are made between individuals of the same age, regardless of the calendar time when exposure occurred. Our exposure of interest – time-varying $PM_{2.5}$ – demonstrates clear secular trends, and therefore our Cox model compares individuals of the same age but who lived at different times and experienced different $PM_{2.5}$ exposures. To adjust for these important secular trends, we initially planned to adjust for 5-year birth cohort categories, with the end categories collapsed to 15 or 20 year groups due to small numbers. Upon further review, however, we realized that this categorization did not provide adequate control of temporal confounding. We saw similar results with crude adjustment for 5-year categories of calendar time. Thus, we updated our primary analysis to use adjustment for 2-year calendar year category instead. Given the very strong decreasing trends in air pollution over time, and the 25+ year duration of the ACT cohort, we believe this provides the best control of temporal confounding when using age as the time axis in the Cox model. Reassuringly, our results using this model are aligned with

results using calendar time as the time axis, where control for temporal confounding is inherent to the model.

Future survival analyses of air pollution and dementia should carefully consider the strong trends in both the exposure and outcome when selecting the time axis and covariates for the Cox model. Our experience suggests that models with differing time axes can provide equivalent results when there is adequate control of confounding; our disparate results using the age axis with an adjustment for crude categories of birth cohort and calendar year demonstrated that we had not properly controlled for temporal confounding in our study.

Strengths & Limitations

Our study has many strengths, making it an important contribution to the growing evidence on the link between air pollution and dementia. First, we utilized a newly developed spatiotemporal exposure prediction model, specifically for the Puget Sound, that provided the potential to generate estimates of residence-based $PM_{2.5}$ for a 40 year period (1978-2018). This is an unprecedentedly long exposure history to leverage in a survival analysis; in prior studies, the longest duration of exposure modeling coverage was 18 years (Table S3).

We complemented this extensive exposure data with detailed address histories available through Group Health/Kaiser Permanente of Washington records, with nearly complete histories since 1989 for the entire cohort and reasonably good coverage prior to 1989. Overall, we were able to estimate 10-year average $PM_{2.5}$ exposures using known address history for 91% of the person-years across the entire study period. Evaluating a long exposure period is crucial for this research question, given the extended period of disease development

in ADRD.[159] In fact, in our dataset, hazard ratios from shorter term averaging periods (1-yr, 5-yr) were attenuated, suggesting that these exposure windows may be inadequate to capture the true effects of $PM_{2.5}$. Most prior have studies focused on exposure periods of five years or less (Table S3). The only previous study to potentially consider a 10-year follow-up period actually only had five years of monitored data and relied on a ratio of $PM_{2.5}/PM_{10}$ to fill in the missing period; moreover, we have concerns with this study's analytical approach with respect to exposure estimation, since exposure was assigned based on length of follow-up.[221] Thus, our study is unique in the ability to estimate 10-year exposures with high coverage and quality across the cohort and over time.

However, using data across such an extended time window also presented some challenges: our study covered a 40-year period exhibiting stark changes in levels and sources of $PM_{2.5}$ exposure. Because of these strong secular trends, we believed it was important to model time-varying exposure to $PM_{2.5.}$ Yet, in our analysis that adjusted for birth cohort category to account for temporal confounding, we observed substantial confounding by time. In our final model, we accounted for this temporal confounding by adjusting for calendar time in 2-year categories. Because of this strong temporal adjustment, our study focused on spatial contrasts within calendar year time periods and ultimately did not leverage this time-varying exposure information. When we decomposed the $PM_{2.5}$ variance, we found that between-year variation (SD: 3.0) was much higher than average within-year variation (SD: 0.5). Thus, our decision to finely control for confounding by calendar year and focus on within-year variation comes at the expense of removing much of the exposure contrast in the inferential analysis.

An additional challenge for our ambitious exposure coverage over time is that there were limited monitoring sites across the region in the early years; as such, we cannot rule out the possibility of higher exposure measurement error in early time periods. However, many of the features that predict spatial contrasts in exposure, such as heavy industry, shipping, and the road network, have been in place for the entire time period, suggesting that our models which leverage more recent spatial information to predict historical spatial contrasts are appropriate. Furthermore, prior work provides some evidence to support this assumption of consistent spatial contrasts over time in this region.[249] Because we incorporated a rich adjustment for calendar time, we are essentially eliminating temporal contrasts and relying entirely on within-year spatial contrasts for the Cox model. Post-hoc analyses suggested that the observed HRs were higher in the earlier time periods compared to the later time period. Unfortunately, we are not able to disentangle whether these results are due to differential toxicity of the exposures, due e.g., to more airborne lead and/or wood-smoke based $PM_{2.5}$ in earlier years, or time-dependent uncertainty or bias in our exposure model.

With respect to outcome assessment, a central strength of this study is that it draws upon 25 years of consistently implemented, research quality biennial assessments of cognitive status and ADRD in the ACT study.[145] Most prior studies of $PM_{2.5}$ and ADRD have utilized administrative data for outcome ascertainment (Table S3); misclassification is a key concern with these approaches. Positive predictive value (PPV) is the probability that individuals with a positive test truly have the condition of interest. Recent data, including from a systematic review, indicate that the PPV for all cause-dementia based on routinely collected health data can be highly variable, ranging from 33%-100%.[224,250,251] This wide range suggests the need for

caution in the interpretation of results when outcome ascertainment is based on administrative records. Our use of high-quality research evaluations to detect ADRD may partially explain the higher effect estimates obtained in our study.

Through the ACT study, we also had access to extensive individual-level covariate information, which allowed for robust control of confounding. While we did not incorporate some potentially relevant covariates such as noise or greenspace,[252] our models did not appear to be sensitive to any additional confounding adjustments added to the *a priori* model. A limitation of our work is that we only adjusted for baseline values of potentially time-varying covariates. While this allows us to maintain temporal structure that preserves our ability to draw causal inference (ie: no possibility that later values of covariates influenced exposure levels), it ignores the possible important effects of late life medical conditions (such as cardiovascular disease and diabetes) that could affect dementia. Future analyses could utilize marginal structural models to incorporate time-varying covariates.

We were only able to include estimates of $PM_{2.5}$ in our models. Evidence suggests that other common air pollutants, such as ozone, nitrogen oxides, and ultrafine particles (UFP), may also play a role in ADRD and related neurodegeneration.[64,221,253-255] Focusing on the single pollutant effect does not fully capture the impact of real-world, multipollutant exposures. Spatiotemporal models for other pollutants were not available at this time; these will be available for analogous future analyses.

A common challenge in cohort studies – particularly those of elderly populations – is selection bias, which occurs with differential enrollment or attrition of study participants. However, the ACT study has an exceptional Completeness of Follow-up Index (95.6%),[218] which

minimizes our concern with bias due to selective attrition. Yet, differential enrollment is a still potential concern: individuals had to have health insurance, survive and be free of dementia to enter the cohort. Eligibility began at age 65, which reduces our concern with selection bias due to insurance coverage because of Medicare eligibility. However, because of the community-based sampling approach, mean age of entry in our cohort was 75 years, with a range of 65-101. Older enrollees had to survive free of dementia for a longer period, and characteristics that contributed to their healthy survival might create bias in our analysis. In the case of smoking and AD, it has been hypothesized that selection bias may account for the apparent "protective" effect of smoking: due to premature mortality and/or early ADRD diagnosis, smokers that are susceptible to dementia are eliminated from the eligible population and only survivors remain to be studied.[256] It is possible that a similar situation could arise with $PM_{2.5}$ exposure, given the well-established link to premature mortality[219] and the growing link to ADRD. In this scenario, our effect estimate would likely be biased to the null. There is also possible bias in our effect estimates because the traditional Cox model approach does not account for competing risk of death.

CONCLUSION

In this community-based prospective cohort study with uniquely extensive exposure data and research quality outcome ascertainment, we report that elevated long-term exposure to $PM_{2.5}$ is associated with an increased hazard of all-cause dementia and a suggestive increase hazard of AD-subtype dementia. Our results also demonstrate that with sufficient control of confounding by time, use of either age or calendar time as the time axis in the Cox model is

appropriate for a survival analysis of air pollution and dementia. These results add to a growing body of both epidemiological and toxicological evidence on the neurodegenerative effects of air pollution and suggest that reducing exposures across the population could contribute to reducing the burden of dementia.

TABLES & FIGURES

	Total	Mean-Centered Baseline 10-yr Avg PM2.5	
		<= Year Mean	> Year Mean
	(n=4744)	(n=2406)	(n=2338)
Intake Age (Years)	75 (± 6.3)	74 (± 6.1)	75 (± 6.5)
Female	1962 (41 %)	1033 (43 %)	929 (40 %)
ACT Cohort			
original	2327 (49 %)	1150 (48 %)	1177 (50 %)
expansion	740 (16 %)	359 (15 %)	381 (16 %)
replacement	1677 (35 %)	897 (37 %)	780 (33 %)
Birth Cohort			
1890 - <1910	177 (4 %)	81 (3 %)	96 (4 %)
1910 - <1915	352 (7 %)	150 (6 %)	202 (9 %)
1915 - <1920	703 (15 %)	352 (15 %)	351 (15 %)
1920 - <1925	965 (20 %)	491 (20 %)	474 (20 %)
1925 - <1930	893 (19 %)	448 (19 %)	445 (19 %)
1930 - <1935	490 (10 %)	245 (10 %)	245 (10 %)
≥1935	1164 (25 %)	639 (27 %)	525 (22 %)
≥1 *APOE* ε4 allele	1103 (23 %)	573 (24 %)	530 (23 %)
Missing	578 (12.2%)	301 (12.5%)	277 (11.8%)
White	4242 (89 %)	2131 (89 %)	2111 (90 %)
Census Tract Median Household Income			
<35,000	433 (9 %)	103 (4 %)	330 (14 %)
35,000- 50,000	1473 (31 %)	616 (26 %)	857 (37 %)
50,000-75,000	2330 (49 %)	1281 (53 %)	1049 (45 %)
>75,000	508 (11 %)	406 (17 %)	102 (4 %)
Degree			
none	404 (9 %)	198 (8 %)	206 (9 %)
GED.HS	1823 (38 %)	881 (37 %)	942 (40 %)
bachelors	1086 (23 %)	575 (24 %)	511 (22 %)
masters	718 (15 %)	388 (16 %)	330 (14 %)
doctorate	281 (6 %)	155 (6 %)	126 (5 %)
other	432 (9 %)	209 (9 %)	223 (10 %)
Marital Status			
never married	192 (4 %)	78 (3 %)	114 (5 %)
married	2647 (56 %)	1468 (61 %)	1179 (50 %)
separated/divorced	684 (14 %)	284 (12 %)	400 (17 %)
widowed	1086 (23 %)	523 (22 %)	563 (24 %)

other	135 (3 %)	53 (2 %)	82 (4 %)
Smoking Status			
never	2317 (49 %)	1193 (50 %)	1124 (48 %)
past	2197 (46 %)	1116 (46 %)	1081 (46 %)
current	230 (5 %)	97 (4 %)	133 (6 %)
Regular Exercise	3420 (72 %)	1745 (73 %)	1675 (72 %)
Body Mass Index (BMI)			
underweight	42 (1 %)	12 (0 %)	30 (1 %)
normal	1499 (32 %)	789 (33 %)	710 (30 %)
overweight	1988 (42 %)	992 (41 %)	996 (43 %)
obese	1215 (26 %)	613 (25 %)	602 (26 %)
Diabetes	509 (11 %)	242 (10 %)	267 (11 %)
Heart Disease	786 (17 %)	360 (15 %)	426 (18 %)
Cardiovascular Disease	420 (9 %)	201 (8 %)	219 (9 %)
Hypertension	1947 (41 %)	989 (41 %)	958 (41 %)
CASI IRT Score	0.34 (± 0.70)	0.37 (± 0.70)	0.32 (± 0.70)
Never Moved	2094 (44 %)	1120 (47 %)	974 (42 %)
Dementia Diagnosis	1267 (27 %)	617 (26 %)	650 (28 %)
AD Diagnosis	1021 (22 %)	492 (20 %)	529 (23 %)

Table 1: Descriptive Statistics on Cohort Based on Baseline Information; Total and Stratified by Above/Below Mean-Centered $PM_{2.5}$. Continuous variables reported as mean (SD); categorical variables reported as N (%).

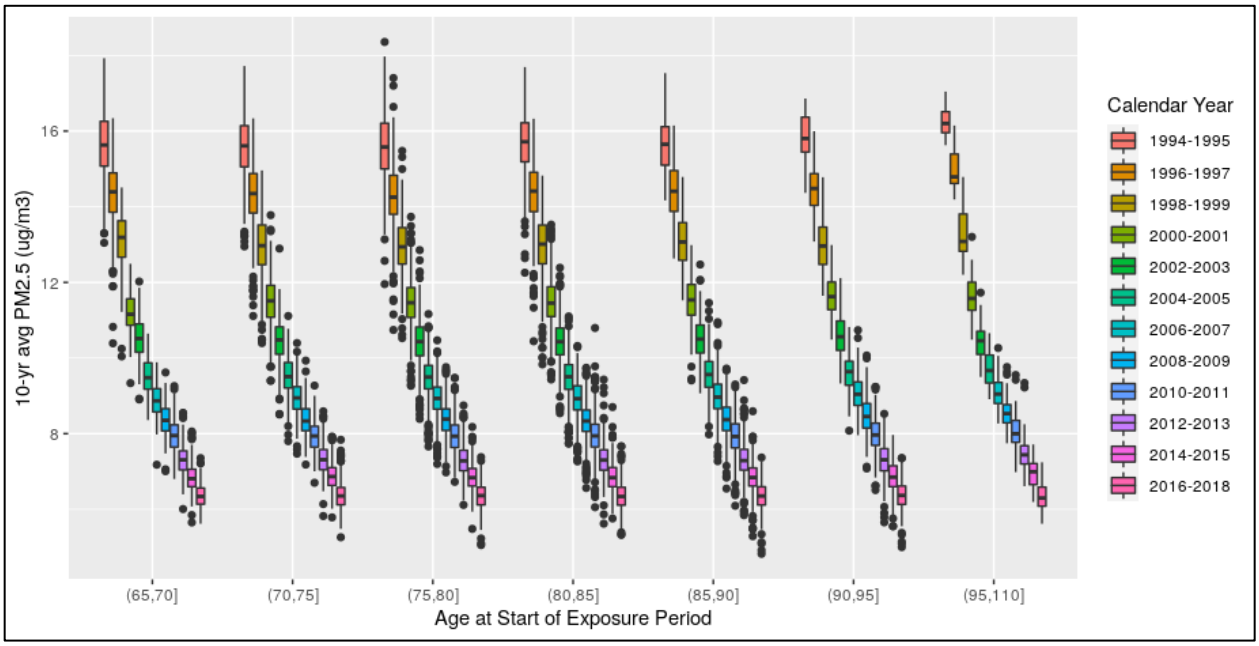

Figure 1: 10-Year Average $PM_{2.5}$ by Age at Start of Exposure Period & Calendar Year. X-axis indicates age by 5-year age groups. Color coding indicates calendar year category of $PM_{2.5}$ exposure. In each boxplot, the middle line represents the median value; the edges of the box represent the 25th and 75th percentiles, and the whiskers extended up to 1.5 times the interquartile range (IQR). Points represent outlier observations outside this range.

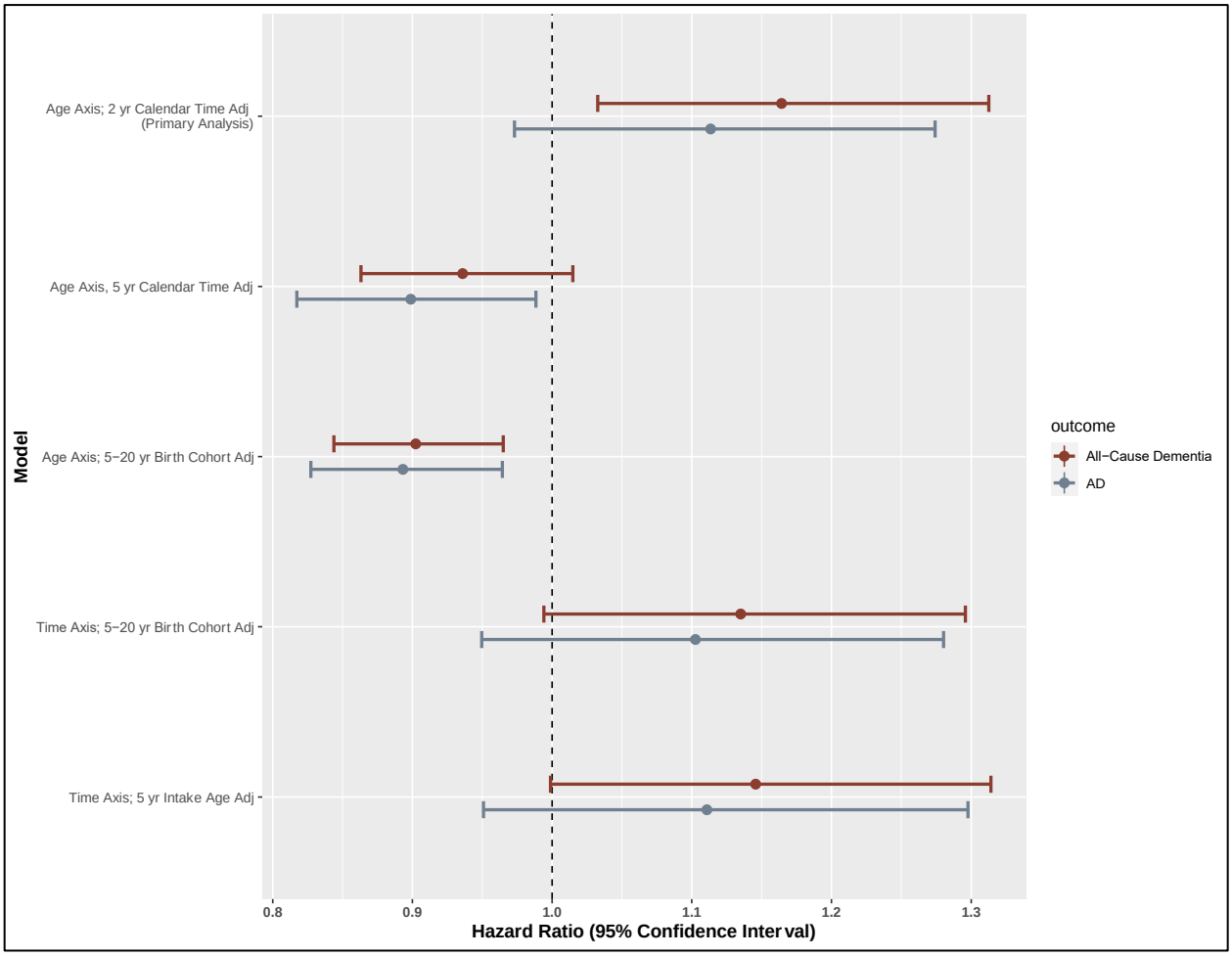

Figure 2: **Hazard Ratios (95% CI) for 10-year $PM_{2.5}$ and All-Cause Dementia or AD**
Results based on an increment of 1 ug/m^3 increase in $PM_{2.5}$. The primary model uses age as the time axis, with APOE stratification and adjustment for *a priori* covariates: gender, educational degree, race, neighborhood median household income, time-varying calendar year category. The birth cohort adjustment model uses age as the time axis, APOE stratification, and adjustment for *a priori* covariates except for the use of birth cohort instead of calendar year. The time axis models use calendar time as the time axis, with APOE stratification and adjustment for *a priori* covariates except for the use of either birth cohort or intake age instead of calendar year as noted.

SUPPLEMENTAL MATERIAL

A: Exposure Coverage & Quality

A.1 Additional details on exposure assessment

We incorporated monitoring data from 35 long-term (>2 years) regulatory monitors at 29 sites, 52 sites from research studies conducted in 2003-4 and 2012, and low-cost sensor measurements from 105 community and ACT participant home sites (collected during 2017-2019) with an additional 5 co-located with regulatory monitors.

To predict $PM_{2.5}$ we used two-week average data from all available monitors and fit the spatio-temporal model originally introduced by Szpiro,[148] Sampson,[147] and Lindstrom,[146] and described in six cities by Keller.[257] This model is comprised of a space-time mean plus residual, where the mean model includes terms that represent a spatially varying long-term average as well as a spatially varying trend. It can be fit to sparse space-time data by leveraging a small number of sites with long-term monitoring to estimate time trends. These trends anchor the seasonal and other short-term variation in order to estimate spatial contrasts using data from all sites, which are particularly informed by multiple short-term monitoring sites. Due to a limited number of monitoring sites prior to 1999 and the absence of any long-term sites that provided data over the bulk of the monitoring period, the Puget Sound model required modifications to the standard modeling framework. Specifically, prior to fitting the spatio-temporal model we subtracted a single smooth long-term trend from log-transformed measurements and later added this back to the predictions.

The fitted model included a single time trend to capture spatially-varying seasonal and other short-term fluctuations. The trend was estimated from a singular value decomposition (SVD) of data providing at least two years of monitoring data followed by smoothing using a spline with eight degrees of freedom per year. The spatially varying long-term mean and trend were fit using separate universal kriging models each with a mean that reflects land use characteristics that was estimated from over 100 geographic covariates reduced to a single partial least squares (PLS) score. Input geographic covariates included proximity variables (such as measured distance in meters to major roads, intersections, truck routes, railways, railyards, coastlines, airports and ports) and buffer variables (such as those based on major road length, truck route length, land-use category percentage, normalized difference vegetation index (NDVI), and year 2000 population density). Kriging was captured using an exponential variogram.

A.2. Imputation rules and classification

We had exact geocoding matches for 97% of addresses across all person-years in this cohort. Address histories since 1978 were obtained from a combination of archived Group Health/Kaiser Permanente administrative records, ACT study records, and a Lexis-Nexis search. There were occasional gaps in some individual administrative records, most likely due to temporary changes in health coverage. We imputed missing address history information for

two types of address coverage gaps: gaps prior to 1989 (when the bulk of the administrative address history data became available) and gaps after the first available address. We imputed missing addresses for individuals based on available information and classified each individual's imputation quality for each year beginning in 1978. We classified individuals with no missing address history information and those with a short gap in administrative address data (up to 2 years) with the same address before and after the gap as having a complete address history (score=1). Individuals with nearly complete address history (score = 2) had address gaps less than two years and a change of address during this time; they were assumed to have moved halfway through the time period. The remaining individuals had a less complete address history (score=3). When there was missing address information prior to the first recorded address, we projected the first address back in time and assigned a score of 2 for the duration up to the time they were known to live at that address and a score of 3 for any duration in excess.

A.3. Descriptive statistics on exposure coverage & quality across the cohort

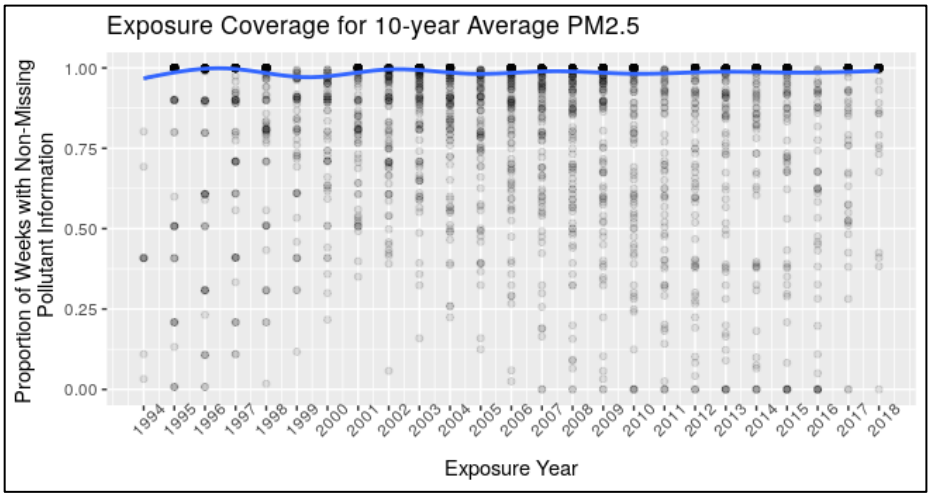

Figure S1: Exposure coverage for 10-year average $PM_{2.5}$; Proportion of weeks with non-missing pollutant information. Pollutant estimates are missing when the participant lived outside of the spatiotemporal modeling region. Individual records appear as gray circles with shading to reflect data density while the blue trend line depicts the average across all individuals in each year.

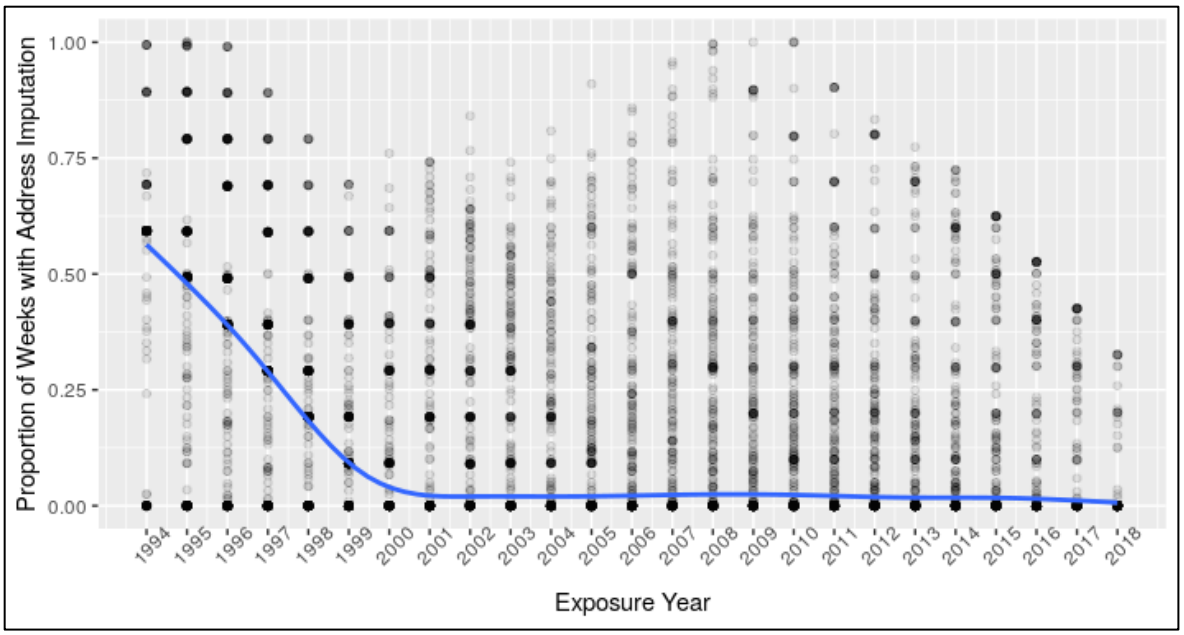

Figure S2: Address history coverage for 10-year average $PM_{2.5}$. Proportion of weeks with address history imputation. Individual records appear as gray circles with shading to reflect data density while the blue trend line depicts the average across all individuals in each year.

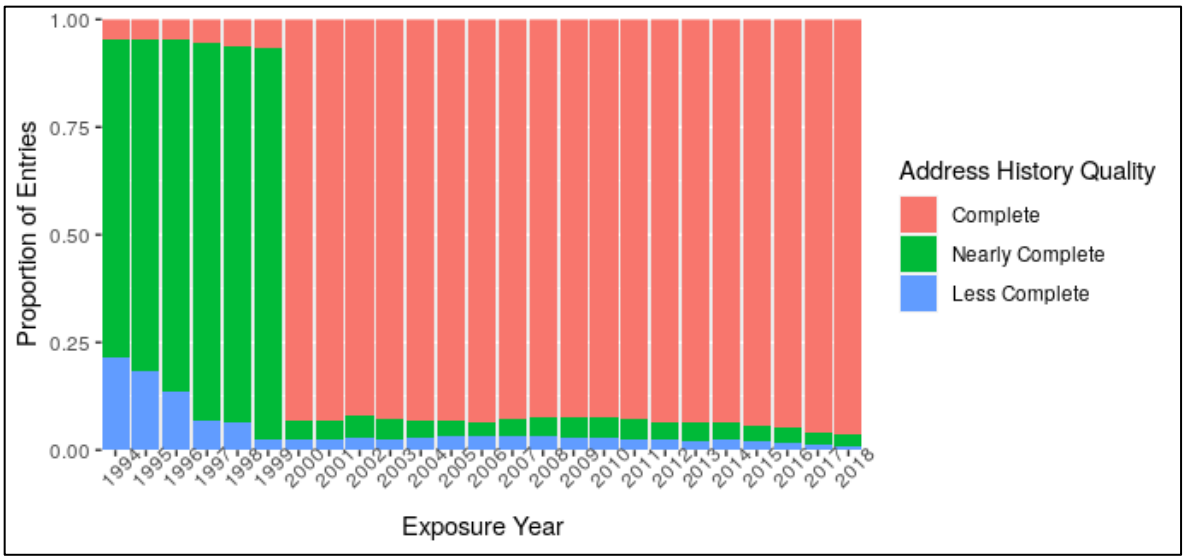

Figure S3: Address history quality for 10-year average $PM_{2.5}$. Proportion of person-time entries corresponding to different levels of imputation quality across the study period.

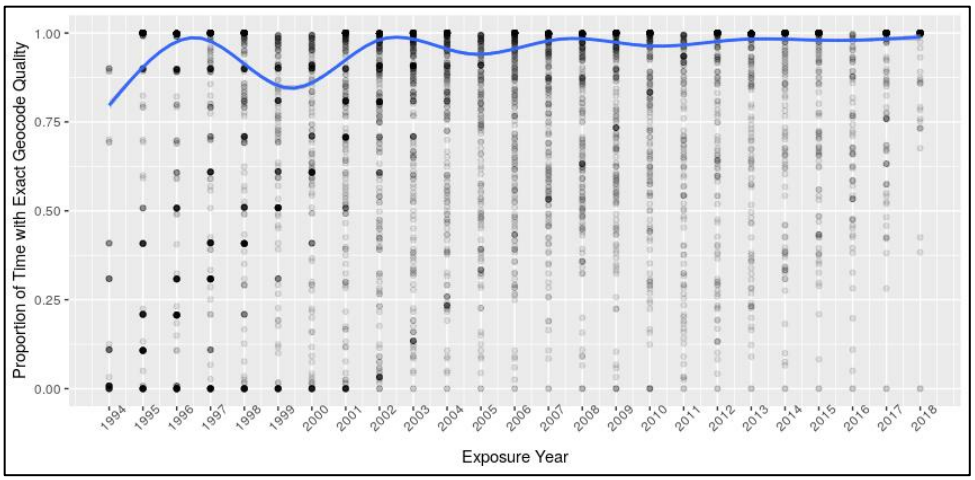

Figure S4: Exact Geocoding Coverage for 10-year Average PM2.5. Proportion of person-time with exact geocode quality. Individual records appear as gray circles with shading to reflect data density while the blue trend line depicts the average across all individuals in each year.

B: Secondary & Sensitivity Analyses

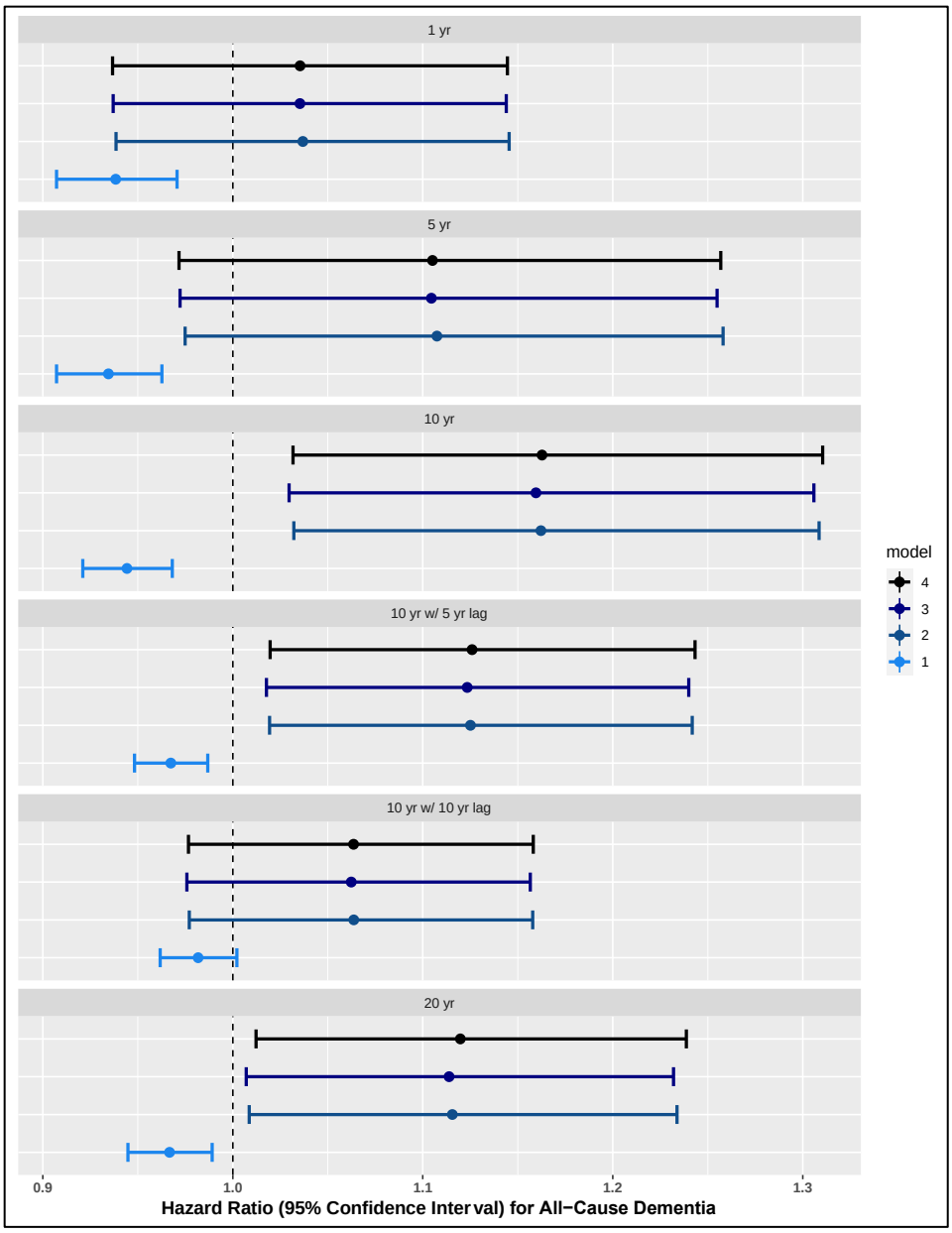

Figure S5: Hazard Ratios (95% CI) for a 1 ug/m^3 difference in $PM_{2.5}$ for Primary Time Period (10-year average) and Alternate Exposure Averaging Periods for All-Cause Dementia. All models include IP-weighting to address APOE missingness. Model 1: unadjusted with APOE stratification of the baseline hazard; Model 2 (*a priori*): Model 1 + gender, educational degree, race, neighborhood median household income, calendar year; Model 3: Model 2 + smoking status, regular exercise; Model 4: Model 3 + BMI, diabetes, heart disease, cardiovascular disease, hypertension.

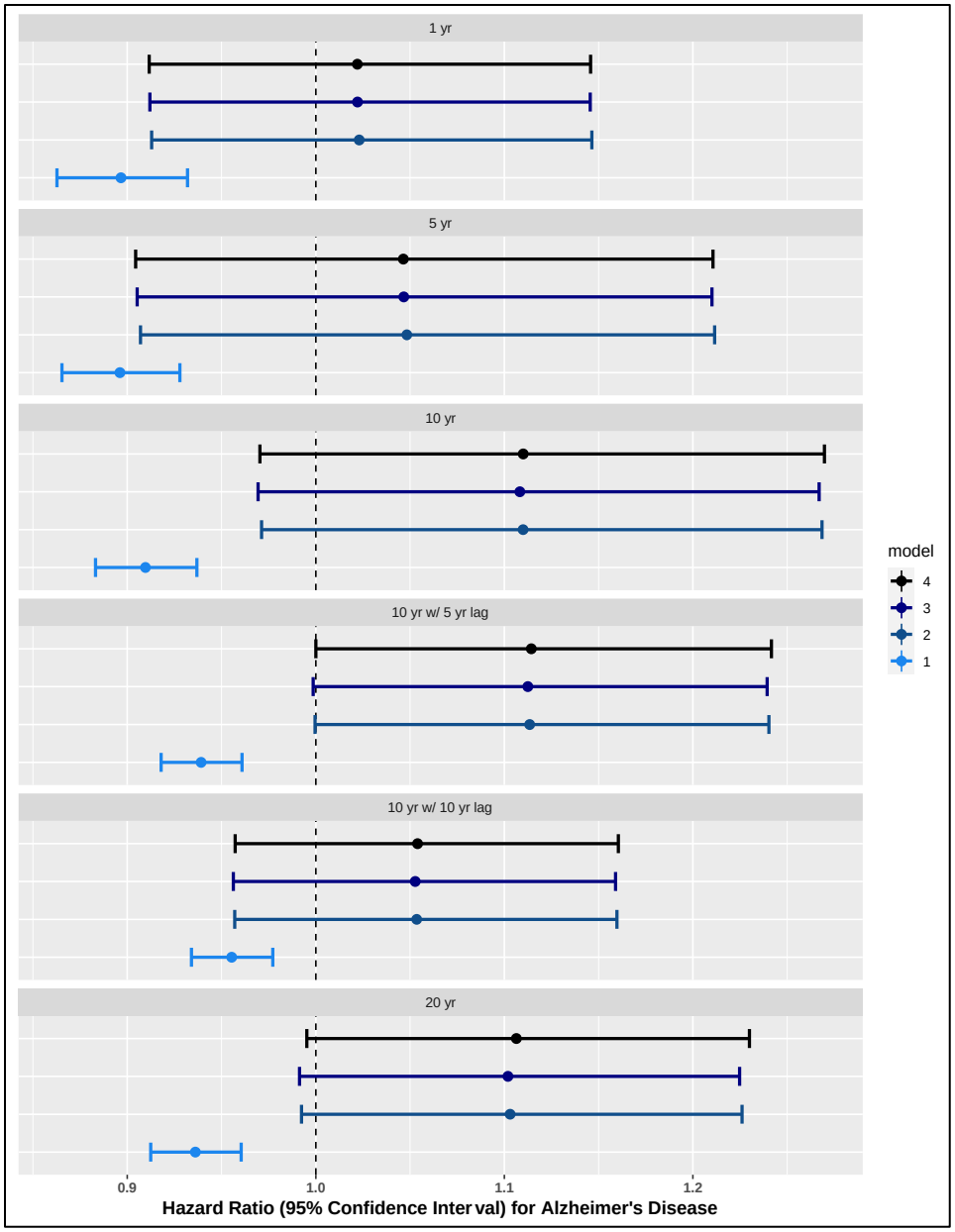

Figure S6: Hazard Ratios (95% CI) for a 1 ug/m^3 difference in $PM_{2.5}$ for Primary Time Period (10-year average) and Alternate Exposure Averaging Periods for AD-subtype Dementia. All models include IP-weighting to address APOE missingness. Model 1: unadjusted with APOE stratification of the baseline hazard; Model 1: unadjusted; Model 2 (*a priori*): gender, educational degree, race, neighborhood median household income, calendar year; Model 3: Model 2 + smoking status, regular exercise; Model 4: Model 3 + BMI, diabetes, heart disease, cardiovascular disease, hypertension.

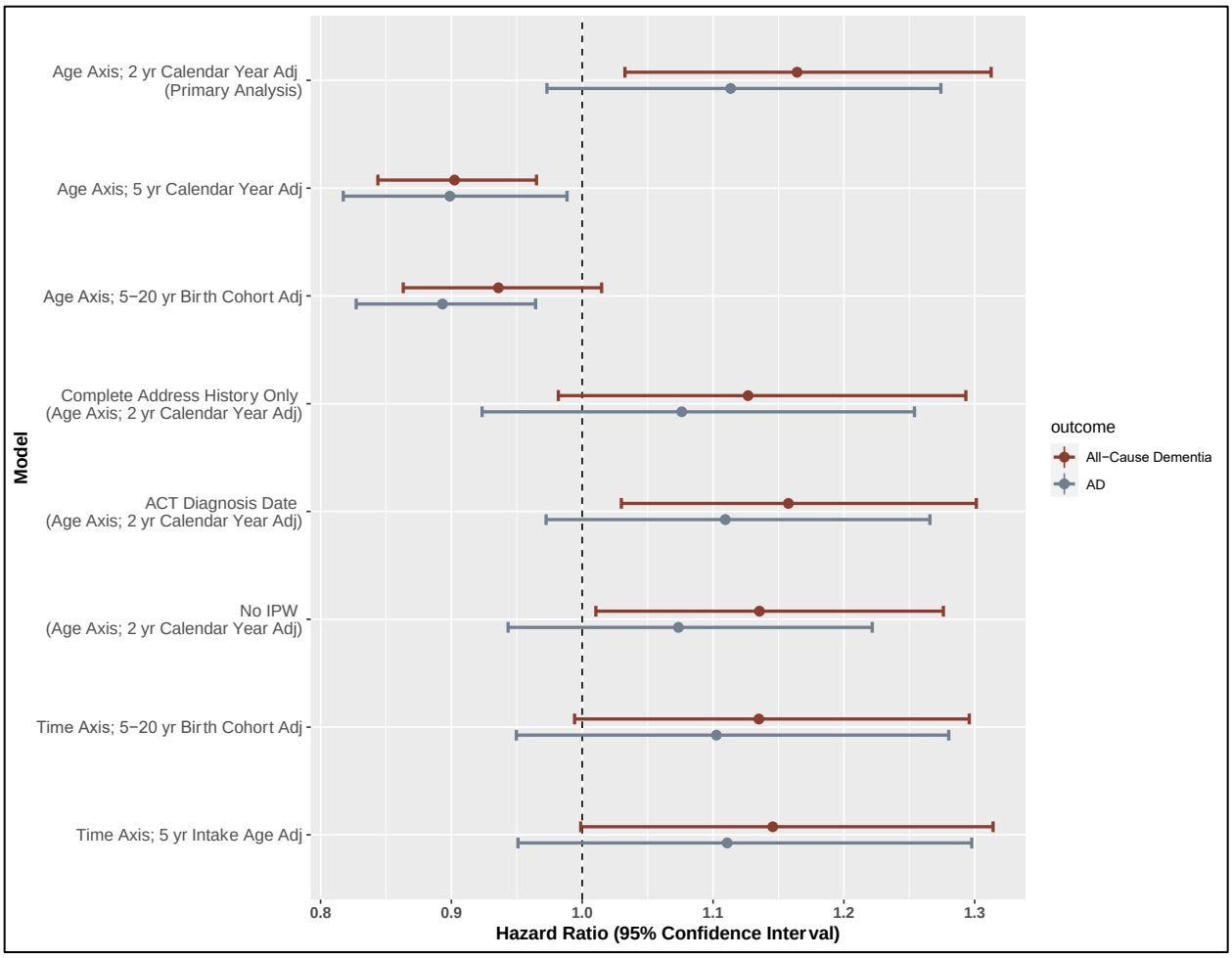

Figure S7: Sensitivity Analyses Hazard Ratios (95% CI) for a 1 ug/m^3 difference in 10-year $PM_{2.5}$ and All Cause Dementia or AD: Investigating the Impact of Different Ways to Adjust for Calendar Time and Age. Unless otherwise noted, all models use age as the time axis, with APOE stratification and adjustment for *a priori* covariates: gender, educational degree, race, neighborhood median household income, calendar year categories.

Model	HR	Robust SE	Lower 95% CI	Upper 95% CI	Person-Years	# Events
Age Axis; 2 yr Calendar Year Adj (Primary Analysis)	1.16	0.06	1.03	1.31	41272	1134
Age Axis; 5 yr Calendar Year Adj	0.90	0.03	0.84	0.97	41272	1134
Age Axis; 5-20 yr Birth Cohort Adj	0.94	0.04	0.86	1.01	41272	1134
Complete Address History Only (Age Axis; 2 yr Calendar Year Adj)	1.13	0.07	0.98	1.29	29356	981
ACT Diagnosis Date (Age Axis; 2 yr Calendar Year Adj)	1.16	0.06	1.03	1.30	41272	1134
No IPW (Age Axis; 2 yr Calendar Year Adj)	1.14	0.06	1.01	1.28	41329	1136
Time Axis; 5-20 yr Birth Cohort Adj	1.14	0.07	0.99	1.30	41270	1134
Time Axis; 5 yr Intake Age Adj	1.15	0.07	1.00	1.31	41270	1134

Note:
HR = Hazard Ratio; SE = Standard Error; CI = Confidence Interval

Table S1: Main Analyses and Sensitivity Analysis Hazard Ratios for 10-year $PM_{2.5}$ and All Cause Dementia. Results based on an increment of 1 ug/m^3 increase in $PM_{2.5}$. Unless otherwise noted, all models use age as the time axis, with APOE stratification and adjustment for *a priori* covariates: gender, educational degree, race, neighborhood median household income, calendar year categories

Model	HR	Robust SE	Lower 95% CI	Upper 95% CI	Person-Years	# Events
Age Axis; 2 yr Calendar Year Adj (Primary Analysis)	1.11	0.07	0.97	1.27	41272	919
Age Axis; 5 yr Calendar Year Adj	0.90	0.05	0.82	0.99	41272	919
Age Axis; 5-20 yr Birth Cohort Adj	0.89	0.04	0.83	0.96	41272	919
Complete Address History Only (Age Axis; 2 yr Calendar Year Adj)	1.08	0.08	0.92	1.25	29356	810
ACT Diagnosis Date (Age Axis; 2 yr Calendar Year Adj)	1.11	0.07	0.97	1.27	41272	919
No IPW (Age Axis; 2 yr Calendar Year Adj)	1.07	0.07	0.94	1.22	41207	916
Time Axis; 5-20 yr Birth Cohort Adj	1.10	0.08	0.95	1.28	41270	919
Time Axis; 5 yr Intake Age Adj	1.11	0.08	0.95	1.30	41270	919

Note:
HR = Hazard Ratio; SE = Standard Error; CI = Confidence Interval

Table S2: Main Analyses and Sensitivity Analysis Hazard Ratios for 10-year $PM_{2.5}$ and AD. Results based on an increment of 1 ug/m^3 increase in $PM_{2.5}$. Unless otherwise noted, all models use age as the time axis, with APOE stratification and adjustment for *a priori* covariates: gender, educational degree, race, neighborhood median household income, calendar year categories.

C: Prior Published Studies

Authors	Location	Cohort Type	Follow-up Period (Years)	N	Baseline Age	Outcome	Outcome Assessment	Exposure Assessment Methods	Exposure Model Coverage (Years)	Avg (SD) ug/m3 PM2.5 for Study Period	Primary Period for Cox Model	Time Varying Exposure?	Time Axis for Cox Model	Original HR (SD) [per xx ug/m3 increment]	Rescaled HR (SD) (per 1 ug/m3 increment)
Jung et al., 2015	Taiwan	Administrative Cohort	10 yrs (2001-2010)	95,690	65+	AD	Administrative data	monitoring data + Inverse Distance Weighting (pre-2006 PM2.5 estimates generated from ratio of PM2.5/PM10 during 2006-2010 period)	5 yrs (2006-2010)[A]	33.6 (9.2)	Change from baseline to end of follow-up period	No	Calendar Time	2.38 (2.21, 2.56) [4.34]	1.22 (1.20, 1.24)
Cacciottolo et al., 2017	USA	Research cohort	16 yrs (1995-2010) (mean: 9.9 yrs)	3,637	65-79	All-cause dementia	Clinical evaluation (annual)	Spatiotemporal model	12 yrs (1999-2010)	12.5 (2.7)	3-yr avg prior to diagnosis	Yes	Time in Study	1.92 (1.32, 2.80) [~9.2][B]	1.07 (1.03, 1.12)
Chen et al., 2017	Ontario, Canada	Administrative Cohort	13 yrs (2001-2013)	~ 2.1 million	65-85	All-cause dementia	Administrative data	Satellite observations, land-use regression (LUR), & interpolation	14 yrs (1998-2012)	10.4 (3.4)[C]	5-yr avg w/ 2 yr lag prior to diagnosis	Yes	Age	1.04 (1.03, 1.05) [4.8]	1.008 (1.006, 1.01)
Carey et al., 2018	United Kingdom	Administrative Cohort	9 yrs (2005-2013) (mean: 6.9 yrs)	130,978	60-79	All-cause dementia & AD	Administrative data	Dispersion model	1 yr (2004)	15.7 (0.8)	1-yr avg prior to baseline (2004)	No	Time in Study	Dementia: 1.03 (0.96, 1.11) [0.95] AD: 1.10 (1.02, 1.18) (0.90)	Dementia: 1.03 (0.96, 1.12) AD: 1.11 (1.02, 1.2)
Oudin et al., 2018	Umea, Sweden	Research Cohort	18 yrs (1993-2010) (mean: 11.4 yrs)	1,806	65+	All-cause dementia	Clinical evaluation (every 5 yrs)	Gaussian disperson model, wind model, & emissions factors from vehicles	18 yrs (1993-2010)	traffic PM2.5: 0.18 (0.17) wood burning PM2.5: 0.77 (0.30)	1-yr avg	No	Calendar Time	traffic PM2.5: 1.14 (0.59, 2.23) [1.0] wood burning PM2.5: 1.55 (1.00, 2.41) [1.0]	traffic PM2.5: 1.14 (0.59, 2.23) wood burning PM2.5: 1.55 (1.00, 2.41)
Yuchi et al., 2020	Vancouver, Canada	Administrative Cohort	5 yrs (1999-2003)	678,000	45-84	non-AD dementia[D]	Administrative data	LUR	5 yrs (1994-1998)	non-cases median (IQR): 4.0 (1.6)	5-yr avg prior to baseline	No	Calendar Time	1.02 (0.98, 1.05) [1.54]	1.01 (0.99, 1.03)
Grande et al., 2020	Stockholm, Sweden	Research Cohort	13 yrs (2001-2013) (mean: 6.0 yrs)	2,927	60+	All-cause dementia	Clinical evaluation (ages 60-77: every 6 yrs; ages 78+: every 3 yrs)	Dispersion model	22 yrs (1990-2011)[E]	8.4[F]	5-yr avg prior to diagnosis	Yes	Age	1.54 (1.33, 1.78) [0.88]	1.63 (1.38, 1.92)
Smargiassi et al., 2020	Quebec, Canada	Administrative Cohort	13 yrs (2000-2012) (mean: 7 yrs)	1,807,133	65+	All-cause dementia	Administrative data	Satellite aerosol optical depth (AOD) converted to surface levels with chemical transport model	13 yrs (2000-2012)	7.6 (2.4)	1-yr avg	Yes	Age	1.02 (1.003, 1.03) [3.9]	1.004 (1.00, 1.007)
Current Study	Seattle, WA	Research Cohort	25 yrs (1994-2018) (mean: 9.7 yrs)	4744 (4166 with non-missing APOE)	65+	All-cause dementia & AD	Clinical evaluation (biennial)	Spatiotemporal model	40 yrs (1978-2018)	10.0 (2.9)	10-yr avg prior to diagnosis	Yes	Age		Dementia: 1.16 (1.03, 1.31) AD: 1.11 (0.97, 1.27)

Notes:
[A] This study included 10 years of exposure data, but the first 6 years were estimated from the ratio of PM2.5/PM10 obtained during the later time period, so this initial period was subtracted off for this cell
[B] This study originally reported HRs based on comparisons between individuals in high PM2.5 (>12mg/u3) vs. low PM2.5 (< = 12 ug/m3); we derived an approximate increment by taking the difference of the average exposures in those two exposure groups
[C] Baseline exposure
[D] This study also reported results for AD, but these were part of a nested case-control study and therefore are not presented for this comparison
[E] Exposures for 2012 and 2013 were set based on 2011 levels
[F] SD not provided

Table S3: Comparison to Prior Published Studies on $PM_{2.5}$ and Dementia

Chapter 5: Conclusion

This dissertation contributes to advancing the state of the science on the relationship between $PM_{2.5}$ and ADRD through two entirely novel analyses (Aim 1 and Aim 2) and one that has substantial methodological advantages compared to prior analogous work (Aim 3).

Results from Aim 1 indicate that both short-term and long-term exposure to $PM_{2.5}$ impact the levels of endothelial injury markers in the CSF among cognitively normal individuals. Prior work had demonstrated the linkage between $PM_{2.5}$ and elevated markers of endothelial injury in blood samples, but this is the first evaluation of CSF, which directly reflects brain pathology. The clinical significance of these changes is unknown. Yet, in the context of the role of vascular injury in neurodegeneration and dementia,[43,83,128] our results support the link between air pollution and ADRD.[12,65,69]

Results from Aim 2 suggest that long-term exposure to $PM_{2.5}$ may impact levels of AD pathology as assessed via categorical stages at autopsy. However, confidence intervals from these analyses included the null, precluding our ability to draw strong conclusions. Given the potential bias due to mediation by age at death, we believe that biostatistical methodological advancements are needed to better address this research question.

Results from Aim 3 corroborate prior studies indicating a link between $PM_{2.5}$ and ADRD incidence. Our analysis had important advantages over prior work, including the use of 40 years of exposure data and research quality outcome ascertainment. Our study also provides comparisons between the use of the age axis and time axis in air pollution survival analyses, indicating that either may be appropriate as long as there is adequate control of confounding of the alternative covariate.

Together, results from these aims contribute to filling in the pieces of our understanding of air pollution's detrimental effects on brain health. The first aim provides evidence of the linkage between $PM_{2.5}$ and biomarkers of cerebrovascular injury. Because cerebrovascular injury is a risk factor for dementia, this work provides preliminary evidence of a mechanistic pathway between $PM_{2.5}$ and dementia. In contrast to the evaluation of early biomarkers in the first aim, the second aim assesses the effects of $PM_{2.5}$ on AD pathology at death. Our results were inconclusive, yet we were constrained by current available biostatistical methods. In the third aim, we build on the biomarker-based investigations of the first two aims to answer the underlying policy-relevant question: does $PM_{2.5}$ contribute to greater hazard of dementia diagnosis? Our results provide strong evidence to support this association. Overall, by spanning mechanistic and population-based questions, this dissertation provides integrative information on the linkage between $PM_{2.5}$ exposure and neurodegeneration.

Given the growing global burden of ADRD and the lack of effective medications, it is becoming increasingly important and urgent to identify potentially modifiable risk factors. The three aims of this dissertation support this goal by contributing to the growing body of evidence on the association between $PM_{2.5}$ and ADRD. In the coming years, there will likely be sufficient data to conduct a formal causal evaluation of this question. Because of the extensive population exposures and changing demographics, the public health and health policy implications of a conclusive linkage between air pollution and dementia would be enormous. For example, it could prompt tighter control of $PM_{2.5}$ through measures such as the Environmental Protection Agency (EPA)'s National Ambient Air Quality Standards (NAAQS), reducing exposures to millions of individuals in the United States. We encourage future policy-

relevant research in this area, with the aim of stemming the projected surge in dementia over the next several decades.

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