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Fine Particulate Matter Exposure and Cerebrospinal Fluid Markers of Vascular Injury

Rachel M. Shaffer^a, Lianne Sheppard^{a,b}, Elaine R. Peskind^{c,d}, Jing Zhang^e, Sara D. Adar^f, Ge Li^{c,d,g,*}

^aDepartment of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA

^bDepartment of Biostatistics, University of Washington, Seattle, WA, USA

^cVA Northwest Network Mental Illness Research, Education, and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, USA

^dDepartment of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA

^eDepartment of Pathology, University of Washington, Seattle, WA, USA

^fDepartment of Environmental Health Sciences, University of Michigan, Ann Arbor, WA, USA

^gGeriatric Research, Education, and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, USA

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.

*Correspondence to: Ge Li, S182 GRECC, VAPSHCS, 1660 S. Columbian Way, Seattle, WA 98108, USA. Tel.: +1 206 764 2485; gli@uw.edu.

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SUPPLEMENTARY MATERIAL

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Results: Among cognitively normal individuals, a 5 $\mu\text{g}/\text{m}^3$ increase in 7-day and 1-year average $\text{PM}_{2.5}$ 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 $\mu\text{g}/\text{m}^3$ increase in 1-year average $\text{PM}_{2.5}$, 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 $\text{PM}_{2.5}$ and CSF biomarkers of vascular damage in cognitively normal adults. These results are aligned with prior research linking $\text{PM}_{2.5}$ to vascular damage in other biofluids as well as emerging evidence of the role of $\text{PM}_{2.5}$ in neurodegeneration.

Keywords

Alzheimer's disease; biomarkers; cellular adhesion molecules; cerebrospinal fluid; cerebrovascular disorders; dementia; particulate matter

INTRODUCTION

Growing evidence suggests that cerebrovascular damage, such as microvascular injury and stroke, may contribute to cognitive impairment and dementia [1, 2]. Specifically, based on the vascular contributions to cognitive impairment and dementia 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 [3].

Vascular disease morbidity and mortality is strongly linked to fine particulate matter air pollution ($\text{PM}_{2.5}$) exposure [4, 5]. There are several plausible mechanisms by which $\text{PM}_{2.5}$ could impact vascular health, including systemic oxidative stress and inflammation leading to endothelial damage [4]. Vascular cell adhesion molecule-1 (VCAM-1) and e-selectin are adhesion molecules expressed by endothelial cells in response to injury and inflammation [6, 7]. Elevations in these markers reflect vascular injury and are associated with hypertension, atherosclerosis, and dysregulation of cerebral blood flow [8, 9]. Prior epidemiological studies indicate associations between exposure to air pollution, such as $\text{PM}_{2.5}$, and these and other biomarkers of vascular damage in plasma and serum [10–21]. $\text{PM}_{2.5}$ has also been linked to cerebrovascular damage, such as stroke [22].

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 [6, 7, 23–29]. Yet, despite the well-recognized link between $\text{PM}_{2.5}$ and vascular injury and the role of vascular injury in dementia, no prior studies have evaluated the association between $\text{PM}_{2.5}$ 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) $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ exposure over days or weeks and changes in these

biomarkers of vascular injury in the blood [10–21]. 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 [20]. Since individuals with mild cognitive impairment (MCI) or AD often also already exhibit vascular pathologies, we stratified our analyses by cognitive status (cognitively normal versus 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 [3, 30], 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 [31–33].

METHODS

The cohort included 133 individuals enrolled in studies at the University of Washington (UW) Alzheimer's Disease Research Center (ADRC) between 2001–2012 (Supplementary Table 1). 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 [34]. 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) [35]. Apolipoprotein (*APOE*) genotype was assessed through a restriction digest method [36]. 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) [37]. 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), 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 [38]. 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 [39]. 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 versus 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 [40, 41] and diabetes e [16, 18, 42–44]; 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-year 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-year, 10-year, 20-year), 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 (years) [27, 45]; smoking status [27]; sex [27, 45]; education (years) [46, 47]; apolipoprotein E4 (*APOE* ε4) status (at least 1 copy of E4 versus no copies of E4) [27, 45], body mass index (BMI) [27], hypertension [45, 48–51], coronary heart disease [45], and diabetes [45, 52, 53]. 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 $\mu\text{g}/\text{m}^3$ 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) (Table 1). 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* ϵ 4 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* ϵ 4. 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 $5 \mu\text{g}/\text{m}^3$ increase in 7-day average $\text{PM}_{2.5}$ was associated with increased CSF VCAM-1 (*a priori* adjusted: 35.4 (9.7, 61.1) ng/ml) (Fig. 1; Supplementary Table 2). 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-year average $\text{PM}_{2.5}$ and CSF VCAM-1 among cognitively normal individuals (Fig. 1; Supplementary Table 2). Based on our *a priori* adjustment model (model 2), a $5 \mu\text{g}/\text{m}^3$ increase in 1-year average $\text{PM}_{2.5}$ 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-year, 10-year, 20-year) 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 $\text{PM}_{2.5}$ 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) (Supplementary Table 4). There was no evidence of effect modification by age. In sensitivity analyses, 2-day average $\text{PM}_{2.5}$ 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-year, 10-year, 20-year), 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 $\text{PM}_{2.5}$ and e-selectin was inconclusive (–1.8 (–27.1, 23.4) pg/ml) in the cognitively normal subgroup (Fig. 2; Supplementary Table 3). We observed similar results in sensitivity analyses. There was no evidence of effect modification by age.

However, we estimated positive associations between 1-year average PM_{2.5} and e-selectin. Based on our *a priori* model, a 5 µg/m³ increase in 1-year average PM_{2.5} was associated with a 53.3 (11.0, 95.5) pg/ml increase in CSF e-selectin (Fig. 2; Supplementary Table 3). In sensitivity analyses evaluating other long-term exposure periods, results from the 5-year and 10-year averages were consistent with results from the 1-year 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) (Supplementary Table 5). 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 [20]; 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 [54]. 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, demonstrating the role of oxidative stress in PM_{2.5}-related endothelial inflammation [55]. Another study using the same cell line yielded inconsistent effects on VCAM-1 but a dose-dependent increase in expression of E-selectin [56].

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 $\mu\text{g}/\text{m}^3$ increase in 1-year $\text{PM}_{2.5}$ (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 [45]. In our own dataset using the *a priori* model among the cognitively normal cohort, a 25-year increase in age was associated with an 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 [27]. This is perhaps counterintuitive given the known links between smoking and endothelial injury [57]. 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 [58, 59], indicating the possibility of different mechanisms of action or the presence of adaptation.

Nevertheless, our results indicating positive associations between $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ is associated with inflammation and endothelial injury [4]. Our novel findings suggest potential cerebrovascular and neuroinflammation effects from $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ is linked to increased cerebrovascular resistance and decreased cerebral blood flow velocity [60]. Given the growing recognition of the role of vascular injury and neuroinflammation in neurodegeneration [3, 30], including recent findings suggesting associations between CSF VCAM-1 and CSF tau [61, 62], these cerebrovascular and inflammation changes may provide evidence to support the link between $\text{PM}_{2.5}$, cognitive decline, and dementia [31–33].

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 [3, 6, 7, 23, 27, 30]. 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 $\text{PM}_{2.5}$ exposure—and thus would obscure any potential $\text{PM}_{2.5}$ effects.

This study has several limitations. First, there is possible exposure misclassification for both long-term and short-term exposures to $\text{PM}_{2.5}$. 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-year 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 [38, 63]; 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 [14, 64–71]. 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 [18] (Table 2), 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 [13, 60, 72–74].

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 [3, 30, 62], our results may provide evidence to support the link between air pollution and cognitive decline or dementia [31–33].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Estimated associations between PM2.5 and VCAM-1 among cognitively normal individuals (*a priori* adjusted model)¹.

¹Model adjusted for age, smoking, and sex.

Fig. 2. Estimated associations between PM2.5 and E-selectin among cognitively normal individuals (*a priori* adjusted model)¹.

¹Model adjusted for age, smoking, and sex.

Table 1

Descriptive statistics on UW ADRC cohort, stratified by cognitive status

<i>Covariates mean (SD)/n(%)</i>	Cognitively Normal (<i>n</i> = 73)	MCI/AD (<i>n</i> = 60)
Age (y)	71.7 (8.0)	69.9 (9.7)
Education (y)	15.9 (2.5)	16.2 (3.0)
Male	37 (50.7)	33 (55.0)
Former smoker	39 (53.4)	26 (43.3)
<i>APOE</i> 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)
<i>Outcome variables (mean (sd))</i>		
VCAM-1 (ng/ml)	126.4 (56.8)	139.2 (57.6)
e-selectin (pg/ml)	62.6 (48.4)	58.9 (44.0)
<i>PM_{2.5} (μg/m³) average (mean (sd))</i>		
<i>Short-term</i> 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)
<i>Long-term</i>		
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)

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

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

Author	Study Cohort/Location	PM _{2.5} increment (µg/m ³)	Blood biomarker	Avg. Period: Effect Estimate (% change (95% CI) or mean change (95% CI))
Bind et al. [10]	Veterans Administration Normative Aging Study / Boston, MA, USA	7.1	Plasma VCAM-1	4-h, 24-h, 3–28 day: 2–5% ¹
Wilker et al. [13]	Veterans Administration Normative Aging Study / Boston, MA, USA	4.3	Serum VCAM-1	7-day: 2.5 (0.6, 4.5)%
Pope et al. [21]	Provo, UT, USA	10	Plasma VCAM-1	24-h: 0.5% ¹ ; (also reported as 2.3 (0.3, 4.3) ng/ml increase)
O'Neill et al. [18]	Boston, MA; diabetics only	7.6	Plasma VCAM-1	All diabetics 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)% Excluding statin users 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. [17]	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. [19]	Shanghai, China	27.4	Serum VCAM-1	24-h: 12% ²
Delfino et al. [14]	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

Author	Study Cohort/Location	PM _{2.5} increment (µg/m ³)	Blood biomarker	Avg. Period: Effect Estimate (% change (95% CI) or mean change (95% CI)
Hajat et al. [20]	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

¹Estimated from figure; exact numbers not provided in manuscript.

²Confidence interval not provided.

³Estimates for this study were based on PM_{0.25-2.5} µg/m³.