

Ambient Fine Particulate Matter Alters Cerebral Hemodynamics in the Elderly

Gregory A. Wellenius, ScD; Luke D. Boyle, MB, BCh, BAO, MSc; Elissa H. Wilker, ScD; Farzaneh A. Sorond, MD, PhD; Brent A. Coull, PhD; Petros Koutrakis, PhD; Murray A. Mittleman, MD, DrPH; Lewis A. Lipsitz, MD

Background and Purpose—Short-term elevations in fine particulate matter air pollution (PM_{2.5}) are associated with increased risk of acute cerebrovascular events. Evidence from the peripheral circulation suggests that vascular dysfunction may be a central mechanism. However, the effects of PM_{2.5} on cerebrovascular function and hemodynamics are unknown.

Methods—We used transcranial Doppler ultrasound to measure beat-to-beat blood flow velocity in the middle cerebral artery at rest and in response to changes in end-tidal CO₂ (cerebral vasoreactivity) and arterial blood pressure (cerebral autoregulation) in 482 participants from the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) of Boston study. We used linear mixed effects models with random subject intercepts to evaluate the association between cerebrovascular hemodynamic parameters and mean PM_{2.5} levels 1 to 28 days earlier adjusting for age, race, medical history, meteorologic covariates, day of week, temporal trends, and season.

Results—An interquartile range increase (3.0 μg/m³) in mean PM_{2.5} levels during the previous 28 days was associated with an 8.6% (95% confidence interval, 3.7%–13.8%; *P*<0.001) higher cerebral vascular resistance and a 7.5% (95% confidence interval, 4.2%–10.6%; *P*<0.001) lower blood flow velocity at rest. Measures of cerebral vasoreactivity and autoregulation were not associated with PM_{2.5} levels.

Conclusions—In this cohort of community-dwelling seniors, exposure to PM_{2.5} was associated with higher resting cerebrovascular resistance and lower cerebral blood flow velocity. If replicated, these findings suggest that alterations in cerebrovascular hemodynamics may underlie the increased risk of particle-related acute cerebrovascular events. (*Stroke*. 2013;44:1532-1536.)

Key Words: air pollution ■ cerebrovascular ■ elderly ■ epidemiology ■ transcranial Doppler

Existing evidence has convincingly shown that short-term elevations in fine particulate matter air pollution (PM_{2.5}) are associated with increased risk of acute cardiovascular events, including stroke.¹ The mechanisms responsible for these effects are not fully understood, but there is substantial evidence suggesting that vascular dysfunction is a central component. Specifically, several observational and controlled exposure studies in people have found an association between short-term changes in PM_{2.5} or its components and increased blood pressure, increased peripheral vascular resistance, decreased brachial artery diameter, and decreased brachial artery flow-mediated dilation.^{2–8} Further evidence of vascular effects of PM_{2.5} is provided by animal toxicological studies.^{9–11}

In healthy individuals, cerebral blood flow is tightly regulated, such that it remains relatively constant over a wide range of arterial pressures. Derangements in cerebral vascular

function have been associated with stroke incidence and poorer prognosis,^{12,13} as well as cognitive impairment, dementia, and depression.^{14,15} Given the documented associations between ambient air pollution and both cerebrovascular events and peripheral vascular function, PM_{2.5} may also affect cerebral vascular function. However, this hypothesis has not been previously investigated. Accordingly, the aim of this study was to evaluate the association between PM_{2.5} and cerebrovascular hemodynamics at rest and during provocative testing in a cohort of community-dwelling older adults.

Methods

Study Design

We evaluated the association between short-term changes in ambient PM_{2.5} and measures of cerebral blood flow velocity among 482

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From the Department of Epidemiology, Brown University, Providence, RI (G.A.W., L.D.B.); Centre for Public Health, Queen's University Belfast, Belfast, UK (L.D.B.); Cardiovascular Epidemiology Research Unit, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA (E.H.W., M.A.M.); Department of Neurology, Brigham and Women's Hospital, Boston, MA (F.A.S.); Institute for Aging Research, Hebrew SeniorLife, Boston, MA (F.A.S., L.A.L.); Departments of Biostatistics (B.A.C.) and Environmental Health (P.K., M.A.M.), Harvard School of Public Health, Boston, MA; and Division of Gerontology, Beth Israel Deaconess Medical Center, Boston, MA (L.A.L.)

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Correspondence to Gregory A. Wellenius, ScD, Brown University Center for Environmental Health and Technology, 121 South Main St, Box G-S121-2, Providence, RI 02912. E-mail Gregory_wellenius@brown.edu

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participants from the MOBILIZE Boston Study (MBS), a prospective, community-based cohort study of novel risk factors for falls in older adults.¹⁶ Briefly, between 2005 and 2008, we recruited 765 non-institutionalized men and women ≥ 65 years of age, able to communicate in English, residing ≤ 5 miles (8.0 km) from the study clinic, and able to walk 20 feet (6.1 m) without personal assistance. Individuals with a Mini-Mental State Examination score < 18 were not eligible to participate. On enrollment, subjects participated in an in-home interview followed within 4 weeks by a clinic examination. Participant characteristics, medical history, medication inventory, smoking history, blood pressure, height, and weight were assessed, as previously described.¹⁷ A second assessment consisting of an in-home interview and clinic examination was performed a median of 16.5 months after the baseline assessment. All subjects provided written informed consent on enrollment. This analysis was approved by the Institutional Review Boards at Hebrew SeniorLife and Brown University.

Cerebrovascular Hemodynamics

During the clinic visit, we used transcranial Doppler ultrasonography (TCD) to noninvasively evaluate cerebrovascular hemodynamics at rest and during provocative stimulation, as previously described.¹⁶ Briefly, we measured cerebral blood flow velocity continuously in the middle cerebral artery (MCA) while subjects sat in a chair. A 2-MHz TCD probe (MultiDop X4, DWL-Transcranial Doppler Systems Inc, Sterling, VA) was placed over the right or left temporal bone with the best signal and held in place during recordings using a Velcro headband. TCD data could not be obtained in some subjects because of the absence of a suitable acoustic window to insonate the MCA. We obtained continuous measures of arterial blood pressure using a Finometer photoplethysmographic system (Finapres Medical Systems, Arnhem, The Netherlands) placed on a finger and held at heart level with a sling. The envelope of the velocity waveform, derived from a fast-Fourier analysis of the Doppler frequency signal, was digitized at 500 Hz, displayed simultaneously with the blood pressure, ECG, and end-tidal CO_2 signals, and stored for later offline analysis.

After a 5-minute resting period, the hemodynamic responses to CO_2 inhalation and posture change were evaluated. We assessed cerebral vasoreactivity by asking participants to breathe room air normally for 2 minutes, inspire a gas mixture of 8% CO_2 , 21% O_2 , and balance nitrogen for 2 minutes, and then mildly hyperventilate to an end-tidal CO_2 of ≈ 25 mmHg for 2 minutes. Cerebral vasoreactivity was calculated as the slope of the linear regression of mean MCA blood flow velocity versus end-tidal CO_2 during the maneuver.

We assessed cerebral autoregulation by asking participants to perform a sit-to-stand maneuver, as previously described.¹⁸ Briefly, participants sat with their legs elevated at 90° in front of them on a stool for 5 minutes before standing for 1 minute. We calculated cerebrovascular resistance with the following equation:

$$\text{CVR} = \frac{\text{MAP}}{\text{BFV}}$$

where CVR, MAP, and BFV denote cerebrovascular resistance, mean arterial blood pressure, and mean MCA blood flow velocity, respectively. The intraclass correlation coefficients for cerebrovascular resistance, mean arterial pressure, and blood flow velocity ranged from 0.81 to 0.84, indicating excellent within-person reproducibility of these measures over time.

Air Pollution and Meteorologic Data

$\text{PM}_{2.5}$ was measured continuously at the Boston/Harvard ambient monitoring station, and daily averages were calculated, as previously described.¹⁹ This monitoring station is located < 10 km from the study clinic site and < 20 km from the residential address of any study participant. We obtained hourly meteorologic data from the National Weather Service station at Boston's Logan Airport.

Statistical Methods

For this analysis, we excluded 76 participants reporting a history of stroke. We used linear mixed models with a random subject intercept

to evaluate the association between each outcome and $\text{PM}_{2.5}$ levels while accounting for repeated measures within participants. In all analyses, we controlled for age (natural cubic spline with 3 degrees of freedom), sex, race (white versus other), smoking status (never versus ever), hypertension status (normotension, controlled hypertension, uncontrolled hypertension), diabetes mellitus, body mass index (natural cubic spline with 3 degrees of freedom), visit number, day of week, mean ambient and mean dew point temperature (natural cubic splines with 3 degrees of freedom each), season (sine and cosine of time with period of 1 year), and long-term temporal trends (time as linear and quadratic functions). We modeled $\text{PM}_{2.5}$ as a continuous variable, and the assumption of a linear exposure-response relationship was confirmed by standard techniques.

Previous studies have reported changes in vascular function associated with $\text{PM}_{2.5}$ levels averaged during 1 to 28 days before assessment of the outcome. Accordingly, in separate models, we considered pollutant levels averaged during the 1, 3, 5, 7, 14, 21, and 28 days before cerebral hemodynamic assessment. We evaluated whether the observed associations with $\text{PM}_{2.5}$ differed according to sex, and the presence or absence of hypertension, diabetes mellitus, and obesity (body mass index ≥ 30 versus < 30), as well as season (warm versus cool with warm defined as April through September) by adding interaction terms to the model. Analyses were performed using SAS (v9.3; SAS Institute Inc, Cary, NC) and R statistical software (R v2.15). A 2-sided P value of < 0.05 was considered statistically significant.

Results

Data on cerebral blood flow velocity were available in 482 participants, with 425 participants completing the cerebral vasoreactivity protocol and 424 participants completing the cerebral autoregulation protocol. Measures of cerebral blood flow velocity were available at both the baseline and follow-up visit in 72% of participants. Participants included in this analysis were predominantly white and women with a mean age of 77.9 (SD, 5.3) years at baseline (Table). Compared with the 765 participants enrolled in the MBS, the subgroup included in this analysis was slightly younger, more likely to be white and men, and relatively healthier.

The mean daily $\text{PM}_{2.5}$ level during the study period was $8.6 \mu\text{g}/\text{m}^3$ (SD, 4.9). Because the most etiologically relevant exposure window is unknown, we assessed the association between measures of cerebral blood flow and $\text{PM}_{2.5}$ levels averaged during the 1, 3, 5, 7, 14, 21, and 28 days before outcome assessment. $\text{PM}_{2.5}$ levels averaged during the previous 3 to 28 days were associated with higher resting cerebrovascular resistance, reaching statistical significance in association with the 21- and 28-day averages of $\text{PM}_{2.5}$ (Figure 1A). Because cerebrovascular resistance is calculated as the ratio of mean arterial pressure to cerebral blood flow velocity, we assessed whether the observed increase in resistance was attributable to decreased blood flow velocity, increased mean arterial pressure, or a combination of both. We found that 21- and 28-day averages of $\text{PM}_{2.5}$ levels were associated with statistically significant decreases in cerebral blood flow velocity (Figure 1B), with little evidence of change in resting mean arterial pressure (Figure 1C). Specifically, we observed an 8.6% (95% confidence interval, 3.7%–13.8%) higher cerebrovascular resistance and a 7.5% (95% confidence interval, 4.2%–10.6%) lower blood flow velocity comparing the 75th with the 25th percentiles of $\text{PM}_{2.5}$ levels averaged during the past 28 days. These results did not differ significantly according to sex, hypertension

Table. Baseline Characteristics of 482 Participants ≥ 65 Years of Age From the MOBILIZE Boston Study With Measurements of MCA Blood Flow During Either the Sit-to-Stand or CO₂ Reactivity Protocols, 2005 to 2009

Characteristics	Cerebral Autoregulation Protocol (n=424)	Cerebral Vasoreactivity Protocol (n=425)
Age, mean \pm SD	77.7 \pm 5.2	77.9 \pm 5.3
Women, n (%)	238 (56.1)	242 (56.9)
White, n (%)	365 (86.1)	366 (86.1)
Hypertension, n (%)		
Normotension	109 (25.8)	106 (25.1)
Controlled hypertension	225 (53.3)	230 (54.5)
Uncontrolled hypertension	89 (21.0)	86 (20.4)
Diabetes mellitus, n (%)	65 (15.3)	65 (15.3)
Hyperlipidemia, n (%)	203 (47.9)	202 (47.5)
Ever smoker, n (%)	243 (57.3)	232 (54.6)
Body mass index, mean \pm SD	26.5 \pm 4.7	26.8 \pm 4.8

status, diabetes mellitus, obesity, or season (Table I in the online-only Data Supplement).

Cerebral vasoreactivity was not associated with PM_{2.5} at any averaging period (Table II in the online-only Data Supplement). Measures of cerebral autoregulation were also not related to PM_{2.5}. On standing from the sitting position, mean arterial pressure decreased by an average of 18.9 \pm 6.4 mmHg and was accompanied by a 0.16 \pm 0.31 mmHg/(cm/s) decrease in cerebrovascular resistance. The magnitude of the changes in cerebrovascular resistance and blood flow velocity on standing were not associated with PM_{2.5} (Figure 2). However, the decrease in mean arterial pressure observed on standing was smaller after 1 to 5 days with higher average PM_{2.5}.

Discussion

The results of this study suggest that exposure to fine particulate matter air pollution may be associated with adverse changes in the cerebral vasculature. Specifically, in this population-based cohort of community-dwelling older adults, we found that PM_{2.5} levels within the past month were

associated with higher cerebrovascular resistance and lower MCA blood flow velocity at rest in the absence of significant changes in resting mean arterial pressure. Our results did not differ significantly among participants with diabetes mellitus, hypertension, smoking, or by sex or season.

Although we are not aware of any previous studies examining this hypothesis, short-term exposure to ambient air pollution has been linked with changes in the peripheral vasculature, including increased arterial blood pressure, increased peripheral vascular resistance, decreased brachial artery diameter, decreased brachial artery flow-mediated dilation, and decreased small-vessel elasticity.²⁻⁸ Additionally, studies in humans and animals have shown that air pollution exposure can attenuate the vascular response to the endothelium-dependent vasodilators acetylcholine and bradykinin, and potentiate the vasoconstriction induced by phenylephrine.^{9,20} These findings support the notion that short-term exposure to ambient air pollution can alter endothelial function in the peripheral vasculature.

The results of the current study extend this previous work and suggest that ambient air pollution may also be detrimental to cerebrovascular endothelial function. Basal resting cerebral blood flow is determined, at least in part, by release of NO from vascular endothelial cells.^{21,22} Moreover, resting cerebral blood flow velocity declines with age, is lower in obese individuals and those with diabetes mellitus with microvascular complications, and is correlated with indices of systemic arterial stiffness.²³⁻²⁵ These observations suggest an important role of endothelium in the maintenance of resting cerebral blood flow, although multiple other factors are also clearly involved.

In healthy participants, cerebral blood flow is altered in response to fluctuations in arterial CO₂ concentrations via a mechanism that also depends on endothelium-derived NO.²⁶ Thus, cerebral vasoreactivity has been proposed as a marker of cerebrovascular endothelial function analogous to brachial artery flow-mediated dilation.²⁶ Contrary to our expectations, we did not find an association between ambient pollution and cerebral vasoreactivity. In this regard, our results seem closest to those of Brook et al,² who observed a reduction in brachial artery diameter but no change in flow-mediated dilation after controlled exposure to PM_{2.5} and ozone. Like flow-mediated dilation, cerebral vasoreactivity represents a dynamic

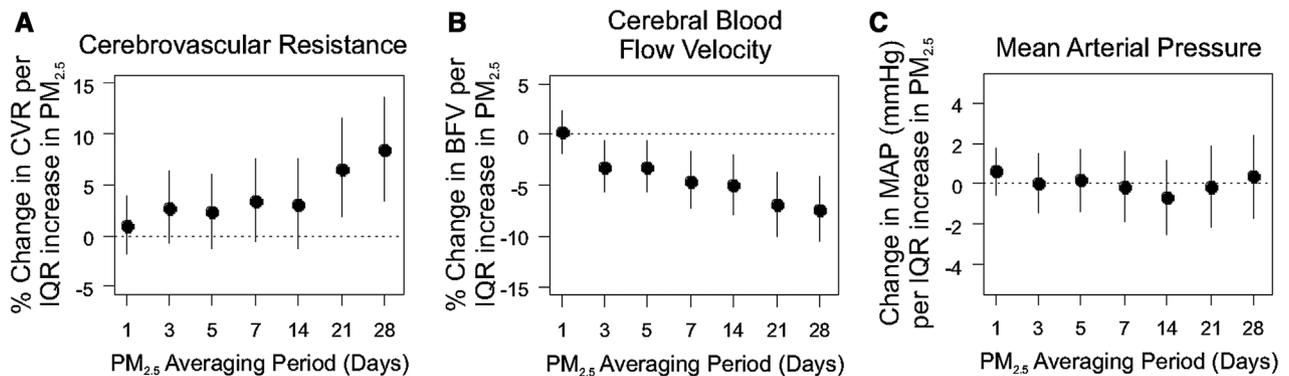


Figure 1. Association between ambient fine particles (PM_{2.5}) and resting cerebrovascular resistance (CVR; **A**), blood flow velocity (BFV; **B**), and mean arterial pressure (MAP; **C**). The y-axis denotes the change in each outcome per interquartile range (IQR) increase in PM_{2.5} averaged during 1 to 28 days before assessment. The x-axis denotes the length of the PM_{2.5} averaging period in days.

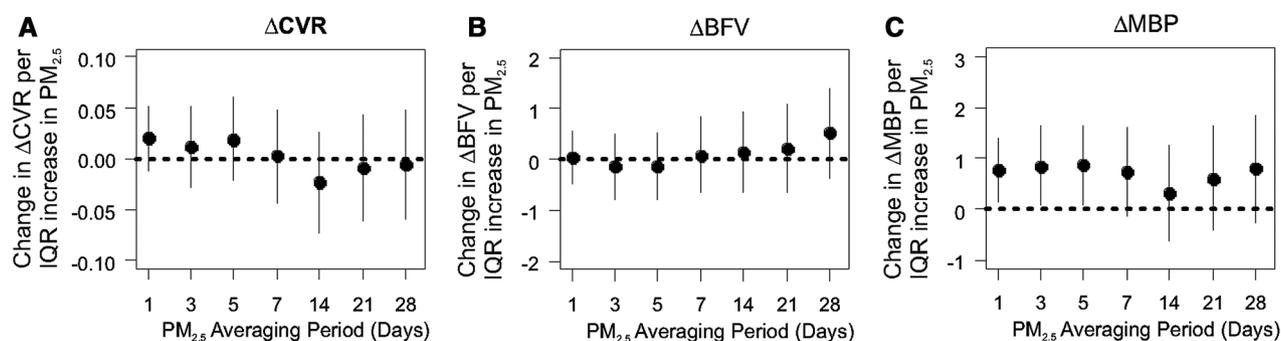


Figure 2. Association between fine particles ($PM_{2.5}$) and Δ cerebrovascular resistance (Δ CVR; **A**), Δ blood flow velocity (Δ BFV; **B**), and Δ mean arterial pressure (Δ MAP; **C**) assessed during the cerebral autoregulation protocol. Δ CVR, Δ BFV, and Δ MAP denote standing minus sitting values for CVR (in units of [cm/s]/mm Hg), BFV (cm/s), and MAP (mm Hg), respectively. The y-axis denotes the change in each outcome per interquartile range (IQR) increase in $PM_{2.5}$ averaged during 1 to 28 days before assessment. The x-axis denotes the length of the $PM_{2.5}$ averaging period in days.

response to an acute stimulus, whereas basal cerebral blood flow represents an assessment of flow under steady-state conditions. Although NO is thought to be involved in both static and dynamic responses, the physiological mechanisms and pathophysiological influences are likely quite different.^{27,28}

We also did not observe an association between $PM_{2.5}$ and cerebral autoregulation as assessed by the change in either MCA blood flow velocity or cerebrovascular resistance on standing from a seated position. This finding is not surprising given that the maintenance of cerebral blood flow in response to acute changes in arterial pressure is largely attributable to a myogenic response (ie, mechanoregulation) without key involvement of either neurogenic or endothelial factors.^{21,26}

Short-term changes in ambient $PM_{2.5}$ levels have been associated with increased risk of ischemic stroke onset,²⁹ and long-term exposure to higher levels of $PM_{2.5}$ has been associated with higher risk of stroke³⁰ and faster cognitive decline.³¹ Indeed, within the MOBILIZE Boston Study cohort, we have found an association between long-term exposure to traffic pollution and lower cognitive function.³² If causal, the results of the current study suggest a potential common mechanism for these observations mediated through alterations in endothelial function, potentially leading to cerebral hypoperfusion.

Our study has some important limitations. First, we were not able to obtain TCD measurements on 37% of participants, and those participants with TCD measurements tended to be healthier than those without measurements. Although a TCD acoustic window is expected to be absent in about one third of elderly participants,³³ the observation that participants with versus without TCD acoustic windows tended to be healthier may limit the generalizability of our results. Second, because it is likely that the effects of $PM_{2.5}$ vary depending on pollution sources, particle constituents, and age or other participant characteristics, our results are not necessarily generalizable to other geographic locations or study populations. Identifying the sources of $PM_{2.5}$ responsible for observed health effects remains a top research priority, and additional analyses using detailed $PM_{2.5}$ speciation data are currently underway. Third, TCD provides a measure of cerebral blood flow velocity rather than absolute flow. However, studies using a variety of techniques have confirmed that MCA blood flow velocity is

correlated with regional cerebral blood flow, and that relative changes in cerebral blood flow velocity are representative of changes in cerebral blood flow.^{34–36} Fourth, use of $PM_{2.5}$ measurements from a single monitoring site is expected to lead to some exposure misclassification, decreasing the precision of our estimates but not otherwise biasing our results.³⁷ However, all participants lived <20 km from the $PM_{2.5}$ monitoring site, limiting the potential for misclassification. Finally, we did not have data on the amount of time participants spent indoors. However, studies suggest that ambient $PM_{2.5}$ is a relatively good surrogate of personal exposure to $PM_{2.5}$ of ambient origin,^{38,39} the metric on which current environmental regulations are based.

Important strengths of our study include detailed assessment of hemodynamic responses in a large, prospective cohort of community-dwelling elderly subjects evaluated repeatedly. Because MOBILIZE Boston Study participants are representative of seniors in the Boston area in terms of age, sex, race, and ethnicity,¹⁶ our results are broadly relevant to elderly individuals rather than a selected patient population. Additionally, these associations were observed at $PM_{2.5}$ levels that are common in urban environments and below the current standards set by the US government.

In conclusion, the current study found that short-term exposure to ambient $PM_{2.5}$ was associated with lower resting cerebrovascular flow velocity and higher resting cerebrovascular resistance in community-dwelling elderly participants. If confirmed in future studies, these findings suggest that ambient air pollution may be detrimental to endothelial function in the cerebral vasculature and suggest a novel mechanism for pollution-related cerebrovascular events.

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Disclosures

None.

References

1. Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Diez-Roux AV, et al; American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121:2331–2378.
2. Brook RD, Brook JR, Urch B, Vincent R, Rajagopalan S, Silverman F. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. *Circulation*. 2002;105:1534–1536.
3. Zanobetti A, Canner MJ, Stone PH, Schwartz J, Sher D, Eagan-Bengston E, et al. Ambient pollution and blood pressure in cardiac rehabilitation patients. *Circulation*. 2004;110:2184–2189.
4. O'Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA, et al. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. *Circulation*. 2005;111:2913–2920.
5. Briet M, Collin C, Laurent S, Tan A, Azizi M, Agharazii M, et al. Endothelial function and chronic exposure to air pollution in normal male subjects. *Hypertension*. 2007;50:970–976.
6. Schneider A, Neas L, Herbst MC, Case M, Williams RW, Cascio W, et al. Endothelial dysfunction: associations with exposure to ambient fine particles in diabetic individuals. *Environ Health Perspect*. 2008;116:1666–1674.
7. Auchincloss AH, Diez Roux AV, Dvonch JT, Brown PL, Barr RG, Daviglius ML, et al. Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect*. 2008;116:486–491.
8. Brook RD, Urch B, Dvonch JT, Bard RL, Speck M, Keeler G, et al. Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans. *Hypertension*. 2009;54:659–667.
9. Sun Q, Yue P, Ying Z, Cardounel AJ, Brook RD, Devlin R, et al. Air pollution exposure potentiates hypertension through reactive oxygen species-mediated activation of Rho/ROCK. *Arterioscler Thromb Vasc Biol*. 2008;28:1760–1766.
10. Bartoli CR, Wellenius GA, Diaz EA, Lawrence J, Coull BA, Akiyama I, et al. Mechanisms of inhaled fine particulate air pollution-induced arterial blood pressure changes. *Environ Health Perspect*. 2009;117:361–366.
11. Ying Z, Yue P, Xu X, Zhong M, Sun Q, Mikolaj M, et al. Air pollution and cardiac remodeling: a role for RhoA/Rho-kinase. *Am J Physiol Heart Circ Physiol*. 2009;296:H1540–H1550.
12. Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *J Am Med Assoc*. 2000;283:2122–2127.
13. Troisi E, Matteis M, Silvestrini M, Paolucci S, Grasso MG, Pasqualetti P, et al. Altered cerebral vasoregulation predicts the outcome of patients with partial anterior circulation stroke. *Eur Neurol*. 2012;67:200–205.
14. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al; American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:2672–2713.
15. Direk N, Koudstaal PJ, Hofman A, Ikram MA, Hoogendijk WJ, Tiemeier H. Cerebral hemodynamics and incident depression: the Rotterdam Study. *Biol Psychiatry*. 2012;72:318–323.
16. Leveille SG, Kiel DP, Jones RN, Roman A, Hannan MT, Sorond FA, et al. The MOBILIZE Boston Study: design and methods of a prospective cohort study of novel risk factors for falls in an older population. *BMC Geriatr*. 2008;8:16.
17. Wellenius GA, Wilhelm-Benartzi CS, Wilker EH, Coull BA, Suh HH, Koutrakis P, et al. Ambient particulate matter and the response to orthostatic challenge in the elderly: the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) of Boston study. *Hypertension*. 2012;59:558–563.
18. Sorond FA, Serrador JM, Jones RN, Shaffer ML, Lipsitz LA. The sit-to-stand technique for the measurement of dynamic cerebral autoregulation. *Ultrasound Med Biol*. 2009;35:21–29.
19. Kang CM, Koutrakis P, Suh HH. Hourly measurements of fine particulate sulfate and carbon aerosols at the Harvard-U.S. Environmental Protection Agency Supersite in Boston. *J Air Waste Manag Assoc*. 2010;60:1327–1334.
20. Törnqvist H, Mills NL, Gonzalez M, Miller MR, Robinson SD, Megson IL, et al. Persistent endothelial dysfunction in humans after diesel exhaust inhalation. *Am J Respir Crit Care Med*. 2007;176:395–400.
21. Lavi S, Egbarya R, Lavi R, Jacob G. Role of nitric oxide in the regulation of cerebral blood flow in humans: chemoregulation versus mechanoregulation. *Circulation*. 2003;107:1901–1905.
22. White RP, Hindley C, Bloomfield PM, Cunningham VJ, Vallance P, Brooks DJ, et al. The effect of the nitric oxide synthase inhibitor L-NMMA on basal CBF and vasoneuronal coupling in man: a PET study. *J Cereb Blood Flow Metab*. 1999;19:673–678.
23. Xu TY, Staessen JA, Wei FF, Xu J, Li FH, Fan WX, et al. Blood flow pattern in the middle cerebral artery in relation to indices of arterial stiffness in the systemic circulation. *Am J Hypertens*. 2012;25:319–324.
24. Selim M, Jones R, Novak P, Zhao P, Novak V. The effects of body mass index on cerebral blood flow velocity. *Clin Auton Res*. 2008;18:331–338.
25. Kim YS, Davis SC, Truijien J, Stok WJ, Secher NH, van Lieshout JJ. Intensive blood pressure control affects cerebral blood flow in type 2 diabetes mellitus patients. *Hypertension*. 2011;57:738–745.
26. Lavi S, Gaitini D, Milloul V, Jacob G. Impaired cerebral CO₂ vasoreactivity: association with endothelial dysfunction. *Am J Physiol Heart Circ Physiol*. 2006;291:H1856–H1861.
27. Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke*. 1995;26:1014–1019.
28. Stoner L, Erickson ML, Young JM, Fryer S, Sabatier MJ, Faulkner J, et al. There's more to flow-mediated dilation than nitric oxide. *J Atheroscler Thromb*. 2012;19:589–600.
29. Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Koutrakis P, et al. Ambient air pollution and the risk of acute ischemic stroke. *Arch Intern Med*. 2012;172:229–234.
30. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007;356:447–458.
31. Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. *Arch Intern Med*. 2012;172:219–227.
32. Wellenius GA, Boyle LD, Coull BA, Milberg WP, Gryparis A, Schwartz J, et al. Residential proximity to nearest major roadway and cognitive function in community-dwelling seniors: results from the MOBILIZE Boston Study. *J Am Geriatr Soc*. 2012;60:2075–2080.
33. Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Transcranial Doppler hemodynamic parameters and risk of stroke: the Rotterdam study. *Stroke*. 2007;38:2453–2458.
34. Dahl A, Russell D, Nyberg-Hansen R, Rootwelt K. A comparison of regional cerebral blood flow and middle cerebral artery blood flow velocities: simultaneous measurements in healthy subjects. *J Cereb Blood Flow Metab*. 1992;12:1049–1054.
35. Larsen FS, Olsen KS, Hansen BA, Paulson OB, Knudsen GM. Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. *Stroke*. 1994;25:1985–1988.
36. Clark JM, Skolnick BE, Gelfand R, Farber RE, Stierheim M, Stevens WC, et al. Relationship of 133Xe cerebral blood flow to middle cerebral arterial flow velocity in men at rest. *J Cereb Blood Flow Metab*. 1996;16:1255–1262.
37. Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, et al. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ Health Perspect*. 2000;108:419–426.
38. Sarnat JA, Koutrakis P, Suh HH. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. *J Air Waste Manag Assoc*. 2000;50:1184–1198.
39. Avery CL, Mills KT, Williams R, McGraw KA, Poole C, Smith RL, et al. Estimating error in using residential outdoor PM_{2.5} concentrations as proxies for personal exposures: a meta-analysis. *Environ Health Perspect*. 2010;118:673–678.

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Supplemental Data for:

Ambient Fine Particulate Matter Alters Cerebral Hemodynamics in the Elderly

Gregory A. Wellenius, ScD,¹ Luke D. Boyle,^{1,2} Elissa H. Wilker, ScD,³ Farzaneh A. Sorond, MD, PhD,^{4,5} Brent A. Coull, PhD⁶ Petros Koutrakis, PhD⁷ Murray A. Mittleman, MD, DrPH^{3,7} Lewis A. Lipsitz, MD^{5,9}

From: ¹Department of Epidemiology, Brown University, Providence, RI; ²Centre for Public Health, Queen's University Belfast, Belfast, UK; ³Cardiovascular Epidemiology Research Unit, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA; ⁴Department of Neurology, Brigham and Women's Hospital, Boston, MA; ⁵Institute for Aging Research, Hebrew SeniorLife, Boston, MA; ⁶Department of Biostatistics, Harvard School of Public Health, Boston, MA; ⁷Department of Environmental Health, Harvard School of Public Health, Boston, MA; and ⁸Division of Gerontology, Beth Israel Deaconess Medical Center, Boston, MA.

Table S1: Association of blood flow velocity and cerebrovascular resistance with PM_{2.5} levels averaged over the 28 days prior to evaluation, overall and stratified by participant characteristics.

Participant Subgroup	% Difference in Flow Velocity* (95% CI)	P _h	% Difference in Resistance* (95% CI)	P _h
Overall	-7.5 (-10.6, -4.2) [†]		8.6 (3.7, 13.8) [†]	
Sex				
Female	-6.2 (-9.7, -2.6)	0.078	7.0 (1.6, 12.6)	0.14
Male	-9.4 (-13.1, -5.6)		11.3 (5.1, 17.8)	
Hypertension Status				
Normotension	-5.4 (-9.6, -1.0)	0.13	5.6 (-0.8, 12.4)	0.40
Controlled Hypertension	-7.6 (-11.2, -3.8)		10.3 (4.5, 16.4)	
Uncontrolled Hypertension	-10.7 (-15.1, -6.0)		9.4 (2.1, 17.3)	
Diabetes				
No	-7.6 (-10.8, -4.2)	0.86	8.4 (3.3, 13.8)	0.75
Yes	-7.1 (-12.0, -1.9)		9.6 (1.8, 18.1)	
Obesity				
BMI<30	-7.5 (-10.8, -4.0)	0.99	9.5 (4.2, 15.1)	0.34
BMI≥30	-7.5 (-11.7, -3.0)		6.3 (-0.4, 13.4)	
Season				
Cool	-10.6 (-14.7, -6.2)	0.084	8.2 (1.3, 15.5)	0.81
Warm	-5.1 (-9.6, -0.4)		9.4 (2.4, 16.9)	

*Estimates represent the percent difference in each outcome per interquartile range increase in PM_{2.5} levels. [†]:p<0.05. BMI: body mass index. IQR: interquartile range. P_h: P-value from test for homogeneity.

Table S2: Association between cerebral vasoreactivity and PM_{2.5} levels averaged 1 to 28 days prior to assessment.

PM _{2.5} Averaging Period (Days)	IQR (µg/m ³)	Difference in Cerebral Vasoreactivity* (95% CI)
1	4.8	3.0 (-0.8, 6.9)
3	4.4	0.9 (-3.7, 5.5)
5	3.9	0.0 (-4.7, 4.7)
7	3.8	-0.3 (-5.5, 4.8)
14	3.4	-0.6 (-6.1, 4.8)
21	3.2	-2.8 (-8.7, 3.1)
28	3.0	-1.5 (-7.7, 4.7)

*Change in cerebral vasoreactivity is expressed in units of (100 cm/s)/mmHg per interquartile range increase in PM_{2.5}. IQR: interquartile range.