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Ambient Fine Particulate Matter Alters Cerebral Hemodynamics in the Elderly

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Abstract

Background—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 CO_2 (cerebral vasoreactivity) and arterial blood pressure (cerebral autoregulation) in 482 participants from the MOBILIZE 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 $\mu g/m^3$) in mean $PM_{2.5}$ levels over the previous 28 days was associated with a 8.6% (95% confidence interval [CI]: 3.7%, 13.8%; $p<0.001$) higher cerebral vascular resistance and a 7.5% (95% CI: 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.

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Keywords

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, a number of 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 toxicologic 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 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 aged ≥65 years, 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. Upon 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, and 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 upon 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 non-invasively 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, electrocardiogram, and end-tidal CO_2 signals, and stored for later off-line analysis.

After a 5-min 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 mm Hg for 2 minutes. Cerebral vasoreacitivty 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 degrees in front of them on a stool for 5 min before standing for 1 min. We calculated cerebrovascular resistance as: ***CVR=MAP/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 Meteorological data

$PM_{2.5}$ was measured continuously at the Boston/Harvard ambient monitoring station and daily averages 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 meteorological 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 $PM_{2.5}$ 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, 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 $PM_{2.5}$ 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 $PM_{2.5}$ levels averaged over 1 to 28 days prior to assessment of the outcome. Accordingly, in separate models we considered pollutant levels averaged over the 1, 3, 5, 7, 14, 21 and 28 days prior to cerebral hemodynamic assessment. We evaluated whether the observed associations with $PM_{2.5}$ differed according to sex, and the presence or absence of hypertension, diabetes, and obesity (BMI ≥ 30 vs < 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 two-sided p value of <0.05 was considered statistically significant.

Results

Data on cerebral blood flow velocity were available in 482 participants, with 425 completing the cerebral vasoreactivity protocol and 424 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 female with a mean age of 77.9 (SD: 5.3) years at baseline (Table 1). In comparison to the 765 participants enrolled in the MBS, the subgroup included in this analysis were slightly younger, more likely to be white and male, and relatively healthier.

The mean daily $PM_{2.5}$ level during the study period was 8.6 $\mu g/m^3$ (SD: 4.9). As the most etiologically relevant exposure window is unknown, we assessed the association between measures of cerebral blood flow and $PM_{2.5}$ levels averaged over the 1, 3, 5, 7, 14, 21, and 28 days prior to outcome assessment. $PM_{2.5}$ levels averaged over the prior 3 to 28 days were associated with higher resting cerebrovascular resistance, reaching statistical significance in association with the 21- and 28-day averages of $PM_{2.5}$ (Fig. 1A). Since 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 due to decreased blood flow velocity, increased mean arterial pressure, or a combination of the two. We found that 21- and 28-day averages of $PM_{2.5}$ levels were associated with statistically significant decreases in cerebral blood flow velocity (Fig. 1B), with little evidence of change in resting mean arterial pressure (Fig 1C). Specifically, we observed an 8.6% (95% CI: 3.7%, 13.8%) higher cerebrovascular resistance and a 7.5% (95% confidence interval [CI]: 4.2%, 10.6%) lower blood flow velocity comparing the 75^{th} to the 25^{th} percentiles of $PM_{2.5}$ levels averaged over the past 28 days. These results did not differ significantly according to sex, hypertension status, diabetes, obesity, or season (Table S1).

Cerebral vasoreactivity was not associated with $PM_{2.5}$ at any averaging period (Table S2). Measures of cerebral autoregulation were also not related to $PM_{2.5}$. Upon standing from the sitting position, mean arterial pressure decreased by an average of 18.9 ± 6.4 mmHg, and was accompanied by a 0.16 ± 0.31 mmHg/(cm/s) decrease in cerebrovascular resistance. The magnitude of the changes in cerebrovascular resistance and blood flow velocity upon standing were not associated with $PM_{2.5}$ (Fig. 2). However, the decrease in mean arterial pressure observed upon standing was smaller following 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, hypertension, smoking, or by sex or season.

Although we are not aware of any prior 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 phenylepherine.[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 prior 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 nitric oxide (NO) from vascular endothelial cells.[21, 22] Moreover, resting cerebral blood flow velocity declines with age, is lower in obese individuals and diabetics 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 CO_2 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 following controlled exposure to $PM_{2.5}$ and ozone. Like flow-mediated dilation, cerebral vasoreactivity represents a dynamic response to an acute stimulus while basal cerebral blood flow represents an assessment of flow under steady-state conditions. While NO is thought to be involved in both static and dynamic responses, the physiologic 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 upon 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 (i.e.: 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 stroke[30] 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.

A limitation of our study is that 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. While 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. In addition, 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 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.

On the other hand, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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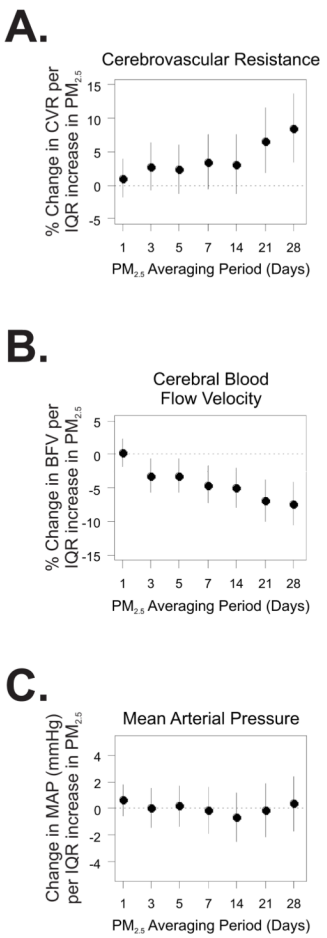

Figure 1.

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

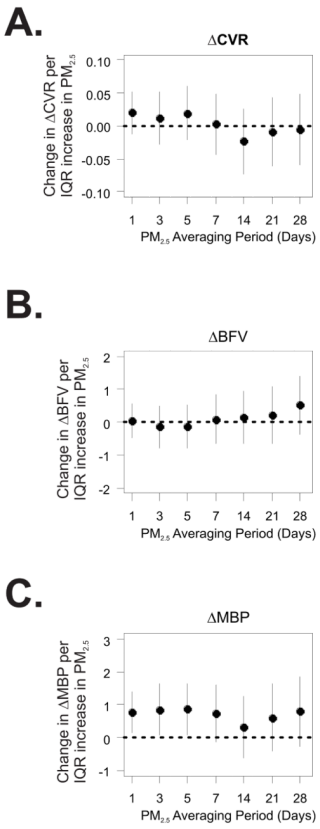

Figure 2.

Association between $PM_{2.5}$ and ΔCVR (A.), ΔBFV (B.), and ΔMAP (C.) assessed during the cerebral autoregulation protocol. ΔCVR, ΔBFV, and ΔMAP denote standing minus sitting values for cerebrovascular resistance (in units of (cm/s)/mmHg), blood flow velocity (cm/s), and mean arterial pressure (mmHg), respectively. The y-axis denotes the change in each outcome per interquartile range (IQR) increase in $PM_{2.5}$ averaged over the 1 to 28 days prior to assessment. The x-axis denotes the length of the $PM_{2.5}$ averaging period in days.

Table 1

Baseline characteristics of 482 participants aged ≥65 years from the MOBILIZE Boston Study with measurements of middle cerebral artery blood flow during either the sit-to-stand or CO_2 reactivity protocols, 2005–2009.

Characteristic	Cerebral Autoregulation Protocol (n=424)	Cerebral Vasoreactivity Protocol (n=425)
Age, Mean ± SD	77.7 ± 5.2	77.9 ± 5.3
Female, 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 ± SD	26.5 ± 4.7	26.8 ± 4.8