Exposure to Particulate Air Pollution and Cognitive Decline in Older Women

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Background: Chronic exposure to particulate air pollution may accelerate cognitive decline in older adults, although data on this association are limited. Our objective was to examine long-term exposure to particulate matter (PM) air pollution, both coarse ([PM 2.5-10 μm in diameter [$PM_{2.5-10}$]) and fine (PM <2.5 μm in diameter [$PM_{2.5}$]), in relation to cognitive decline.

Methods: The study population comprised the Nurses' Health Study Cognitive Cohort, which included 19 409 US women aged 70 to 81 years. We used geographic information system–based spatiotemporal smoothing models to estimate recent (1 month) and long-term (7-14 years) exposures to $PM_{2.5-10}$, and $PM_{2.5}$ preceding baseline cognitive testing (1995-2001) of participants residing in the contiguous United States. We used generalized estimating equation regression to estimate differences in the rate of cognitive decline across levels of $PM_{2.5-10}$ and $PM_{2.5}$ exposures. The main outcome measure was cognition, via validated telephone assessments, administered 3 times at approximately 2-year intervals, including tests of general cognition, verbal memory, category fluency, working memory, and attention.

Results: Higher levels of long-term exposure to both $PM_{2.5-10}$ and $PM_{2.5}$ were associated with significantly faster cognitive decline. Two-year decline on a global score was 0.020 (95% CI, −0.032 to −0.008) standard units worse per 10 μg/m^3 increment in $PM_{2.5-10}$ exposure and 0.018 (95% CI, −0.035 to −0.002) units worse per 10 μg/m^3 increment in $PM_{2.5}$ exposure. These differences in cognitive trajectory were similar to those between women in our cohort who were approximately 2 years apart in age, indicating that the effect of a 10-μg/m^3 increment in long-term PM exposure is cognitively equivalent to aging by approximately 2 years.

Conclusion: Long-term exposure to $PM_{2.5-10}$ and $PM_{2.5}$ at levels typically experienced by many individuals in the United States is associated with significantly worse cognitive decline in older women.

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DESPITE THE TREMENDOUS public health importance of cognitive decline and dementia in older age[1-8] and much effort to develop effective preventive and treatment regimes, few modifiable risk factors have been identified.[9] One model has forecasted that a broadly applied intervention that delays the onset of Alzheimer disease (AD) by 2 years could reduce the number of prevalent cases in the United States by approximately 2 million over a 40-year interval.[7]

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Exposures to environmental toxins are potential risk factors that can be modified. Among the most pervasive environmental toxins is particulate air pollution. Extensive toxicologic and epidemiologic research has documented the relation of exposure to ambient particles with mortality and adverse respiratory and cardiovascular outcomes.[10,11] Regulatory actions have reduced ambient particulate matter (PM), resulting in decreased mortality.[12,13] However, reductions have not occurred uniformly,[14] and health effects remain associated with PM, even at current levels.[15,16]

Very little is known about the role of PM exposure in relation to cognitive decline. Evidence supporting such a relation could implicate exposure reduction as a potential means for reducing the public health burden of cognitive impairment. Yet existing studies in humans are rare,[17-22] few have used measures that account for the exposures' complex spatial and temporal patterns, and none has evaluated the cognitive effects of exposure to fine particulate air pollution (<2.5 μm in diameter [$PM_{2.5}$]). More notably, to our knowledge, no study has evaluated air pollution exposures in relation to longitudinal change in cognition. Therefore, using an established longitudinal study of older women living throughout the contiguous United States, we explored the hypothesis, specified a priori, that higher levels of expo-

sure to PM would correspond to faster subsequent rates of decline in cognitive function.

METHODS

The Nurses' Health Study (NHS) began in 1976 when 121 700 female registered nurses, aged 30 to 55 years and living in 11 US states, returned a mailed questionnaire about their medical history and health-related behaviors.[23] Since then, women have completed questionnaires every 2 years. To date, we have maintained follow-up of more than 90% of the original participants. This study was approved by the institutional review board of Brigham and Women's Hospital, Boston, Massachusetts.

STUDY POPULATION

From 1995 to 2001, we invited participants 70 years and older with no history of stroke to participate in a study of cognition. Of the 22 715 women who were eligible, we were unable to contact 1031 (4.5%). Of those remaining, 7.7% declined participation. Our analyses of exposure to coarse PM (2.5-10 μm in diameter [$PM_{2.5-10}$]) and $PM_{2.5}$ in relation to cognitive decline were based on data from up to 19 409 women with relevant data. Second (1997-2004) and third (2002-2008) cognitive assessments were administered a mean (SD) of 1.9 (0.4) years (n = 17 089) and 4.3 (0.8) years (n = 14204) after initial testing, reflecting at least 83% participation at each follow-up cycle.

EXPOSURE TO COARSE AND FINE PM

We used geographic information system (GIS)-based spatiotemporal smoothing models to estimate exposures to PM_{10} (<10 μm in diameter) and $PM_{2.5}$ for women residing in the contiguous United States. Coarse PM ($PM_{2.5-10}$) was the difference between PM_{10} and $PM_{2.5}$. The methods for estimating these exposures for a 13-state region have been described previously.[24-26] These methods have been extended to estimate PM_{10} and $PM_{2.5}$ for the contiguous United States. Briefly, PM_{10} and $PM_{2.5}$ monitor data were obtained from the US Environmental Protection Agency's (USEPA) Air Quality System (AQS).[26-28] Monitor data on PM_{10} were available nationwide from 1988 through 2007. Monitor data on $PM_{2.5}$ were not widely available before 1999. Thus, separate $PM_{2.5}$ models were developed for the pre-1999 and post-1999 periods, as in previous work.[26] The pre-1999 $PM_{2.5}$ model described seasonal spatial and monthly temporal patterns in the $PM_{2.5}$ to PM_{10} ratio; we multiplied this ratio by PM_{10} to obtain $PM_{2.5}$ predictions during this earlier period. Generalized additive mixed models were constructed to explain variation in measured PM_{10} and $PM_{2.5}$ (post-1999) levels as the sum of effects of GIS-derived covariates (eg, distance to nearest road by road class, urban land use), meteorological data, and smooth spatial terms. These models were used with GIS-derived and meteorological data specific to each geocoded residential location for each nurse, to provide highly spatially resolved estimates of monthly PM_{10} and $PM_{2.5}$ concentrations.

We averaged month-specific exposures to $PM_{2.5-10}$, $PM_{2.5}$, and PM_{10} over several intervals preceding the initial cognitive interview: preceding month, year, 2 years, 5 years, and from 1988 through the preceding month. (See the eFigure and eAppendix 1 for further detail on PM exposure models and exposure estimation, and the timing of exposure and cognitive assessments; http://www.archinternmed.com.)

COGNITIVE ASSESSMENT

Cognitive testing was administered using validated telephone interviews. In the initial interviewing, we administered only the Telephone Interview for Cognitive Status (TICS)[29] and gradually added 5 more tests as high participation in the cognitive testing became apparent. Thus, the sample size differs somewhat across the cognitive tests, although participation rates remained identical for all tests. The TICS (n = 19 409) is modeled on the Mini-Mental State Examination (MMSE), and scores on the 2 tests are strongly correlated (Pearson correlation, 0.94).[29] A test of delayed recall of the 10-word list from the TICS (N = 16 908) was one of the 5 tests added to our battery. We also added the East Boston Memory Test (EBMT)[30,31] to assess immediate (n = 18 662) and delayed (= 18 635) paragraph recall. We administered a test of category fluency in which participants were asked to name as many animals as they could in 1 minute[32] (n = 18 652). Finally, participants were administered the Digit Span Backward test[33] (n = 16 916), measuring working memory and attention. We used the full testing battery in the second and third assessment waves.

Our 2 prespecified primary outcomes were composite measures of cognition.[5,34] Specifically, to summarize the overall association of the air pollution exposure measures with cognitive performance, for women given all 6 tests (n = 16 887), we constructed a global score by averaging *z* scores from all tests. In addition, to assess overall verbal memory, a strong predictor of developing AD,[35] we combined the immediate and delayed recalls of the EBMT and the TICS 10-word list, for women given all 4 tests (n = 16 906), by averaging *z* scores from these tests. We extensively tested the reliability and validity of our telephone procedure for assessing cognition in high functioning, educated women (eAppendix 2).

STATISTICAL ANALYSES

We performed separate analyses for each of the PM measures, evaluating exposures in quintiles and as continuous variables, in relation to each cognitive score, including the verbal and global scores. All individual test scores were expressed as *z* scores, computed from the means and standard deviations in our study population. We compared trajectories in cognitive function over the 3 repeated measures across levels of the exposure measures, using generalized estimating equations regression models,[36] which allowed us to account for the correlations among repeated cognitive scores. In these models, we included terms for time, in years, since baseline cognitive assessment (as a continuous variable), air pollution exposure, and cross-products between the time and air pollution exposure terms. We adjusted these analyses for potential confounding variables, including age at cognitive assessment, education (registered nurse degree, bachelor's degree, or advanced graduate degree), husband's education (high school diploma or less, college degree, advanced graduate degree, or other), energy expended on recreational physical activity[37] (mean of responses to 4-7 questionnaires from 1986 through initial cognitive assessment, in quartiles), and alcohol consumption (mean of responses to 5-8 questionnaires from 1986 through initial cognitive assessment; none, up to 1 drink/wk, 2-6 drinks/wk, or ≥1 drink/d). We also included terms for the cross-products between each covariate and time. Additional adjustment for body mass index, diabetes, smoking (status and pack-years), aspirin use (3 frequency categories), and ibuprofen use (ever/never), did not change our findings. We conducted tests for linear trend across the PM quintiles using an ordinal variable that took on values corresponding to each quintile (1, 2, 3, 4, or 5).

All associations are reported as mean differences in cognitive score change over a 2-year interval, across exposure levels, as 2 years is the approximate interval between the testing cycles. In addition, to help interpret these mean differences, we compared findings on the relation of PM exposure to cognitive decline with age-related differences in cognitive de-

Table 1. Distributions of and Correlations Between the Measures of Exposure to Air Particulate Matter (PM) Pollution

Variable	$PM_{2.5-10}$[a]					$PM_{2.5}$[a]				
	Preceding Month	Preceding Year	Preceding 2 Years	Preceding 5 Years	Since 1988	Preceding Month	Preceding Year	Preceding 2 Years	Preceding 5 Years	Since 1988
Distributions of the Coarse ($PM_{2.5-10}$) and Fine ($PM_{2.5}$) Particulate Matter Exposure Measures, μg/m³										
No.	19 307	19 326	19 395	19 406	19 409	19 307	19 326	19 395	19 406	19 409
Mean (SD)	8.6 (5.2)	8.3 (4.1)	8.2 (3.9)	8.5 (3.8)	9.6 (4.1)	12.5 (3.7)	12.7 (2.8)	13.1 (2.8)	13.1 (2.8)	14.2 (3.0)
Range[b]	−4.0 to 69.0	−0.2 to 56.1	0.1 to 52.2	1.0 to 48.8	1.0 to 50.2	2.1 to 33.7	2.3 to 23.9	2.1 to 24.8	1.9 to 24.0	1.9 to 25.5
Spearman Correlations Between the Coarse ($PM_{2.5-10}$) and Fine ($PM_{2.5}$) Exposure Measures[c]										
$PM_{2.5-10}$										
Preceding month		0.75	0.76	0.74	0.72	0.13	0.16	0.15	0.10	0.07
Preceding year			0.98	0.95	0.91	0.13	0.22	0.22	0.17	0.14
Preceding 2 years				0.98	0.93	0.12	0.20	0.20	0.14	0.11
Preceding 5 years					0.97	0.15	0.26	0.26	0.20	0.17
Since 1988						0.15	0.27	0.27	0.22	0.20
$PM_{2.5}$										
Preceding month							0.67	0.65	0.64	0.60
Preceding year								0.98	0.94	0.89
Preceding 2 years									0.97	0.92
Preceding 5 years										0.97

[a] $PM_{2.5-10}$, particulate matter 2.5 to 10 μm in diameter; $PM_{2.5}$, particulate matter smaller than 2.5 μm in diameter. All measures pertain to intervals prior to the baseline cognitive assessment.

[b] Negative estimates of $PM_{2.5-10}$ exposure are possible if the estimated exposure to $PM_{2.5}$ exceeds exposure to PM_{10} (a possibility at very low exposure levels in the presence of error in the measurement of either of these PM fractions).

[c] All Spearman correlations have *P* values of <.001.

cline, generated from the women in our data set. While our primary focus was on $PM_{2.5-10}$ and $PM_{2.5}$, we also evaluated PM_{10}.

In secondary analyses, we further adjusted our analyses for 3 measures of socioeconomic position in the census tract of residence: percentage of adults who have less than high school education, median home value, and median income. We also evaluated potential mediation of air pollution's association with cognitive decline by respiratory and cardiovascular conditions. In additional analyses, we further adjusted for self-reported emphysema and indicators of cardiovascular and cerebrovascular disease (high blood pressure, coronary heart disease, congestive heart failure, coronary artery bypass graft, transient ischemic attack, and carotid endarterectomy). Finally, we conducted sensitivity analyses restricted to women who did not move between 1988 and their first cognitive assessment (62% of the study population).

RESULTS

Estimated exposures to $PM_{2.5-10}$ and $PM_{2.5}$ varied widely among the women (**Table 1**). Estimated exposures over the month preceding the initial cognitive assessment were significantly correlated with longer-term exposures, but these correlations weakened with increasing measurement interval length (Table 1). For any given interval, estimated exposure to $PM_{2.5-10}$ was significantly correlated with estimated exposure to $PM_{2.5}$ but at magnitudes lower than the correlations between measures of the same PM type.

EXPOSURE TO COARSE PM ($PM_{2.5-10}$)

There were few meaningful differences in characteristics of women across quintiles of long-term $PM_{2.5-10}$ exposure (**Table 2**). From our multivariable-adjusted analyses, we observed rates of change in global cognitive function score that were significantly worse with higher levels of long-term exposure to $PM_{2.5-10}$ (*P* value for trend, .01; **Table 3**) and were significantly worse in the highest vs the lowest quintile of exposure (*P* = .003). Higher estimated $PM_{2.5-10}$ exposures in the 1, 2, and 5 years before the initial cognitive assessment were also associated with significantly worse subsequent decline on the global cognitive score. By contrast, exposure to $PM_{2.5-10}$ in the previous month was weakly and not significantly associated with cognitive decline. This pattern also was apparent in the findings for decline in the TICS and verbal memory scores, while short- and long-term $PM_{2.5-10}$ exposures were associated with comparable increases of rates of decline in digit span backward and verbal fluency scores.

EXPOSURE TO FINE PM ($PM_{2.5}$)

The distributions of key characteristics across quintiles of estimated long-term $PM_{2.5}$ exposure were similar to those for $PM_{2.5-10}$ (**Table 4**), with few notable or consistent differences across quintiles. Similar to $PM_{2.5-10}$,

Table 2. Characteristics of Women by Quintile of Long-term Exposure[a] to Coarse Air Particulate Matter ($PM_{2.5-10}$[b])

Characteristic	Quintile of Exposure to $PM_{2.5-10}$ (1988 to Baseline Cognitive Assessment), Range, μg/m³				
	Lowest, 6.7-19.6 (n = 3881)	Second, 19.7-21.8 (n = 3882)	Third, 21.9-24.2 (n = 3882)	Fourth, 24.3-27.2 (n = 3882)	Highest, 27.3-68.2 (n = 3882)
Age at baseline cognitive assessment, mean (SD), y	74.0 (2.2)	74.0 (2.2)	74.2 (2.3)	74.3 (2.3)	74.6 (2.3)
Education, %					
Registered nurse	80.2	79.0	77.9	78.0	74.3
Bachelor of arts degree	15.0	15.5	15.7	16.8	19.3
≥Master of arts degree	4.8	5.6	6.5	5.2	6.4
Husband's education, %					
≤High school	43.6	40.2	40.4	42.6	38.0
College	19.9	22.8	21.5	20.1	23.7
Graduate school	15.0	15.4	16.7	14.8	17.3
Other[c]	21.5	21.6	21.5	22.5	21.0
Measures of socioeconomic position in census tract, %					
% Of population with <high school education, highest quintile	16.9	17.3	22.2	25.6	26.3
Median household income, lowest quintile	20.0	18.3	22.5	29.5	23.4
Median home value, lowest quintile	24.0	20.8	21.7	30.5	18.6
Smoking status, as of baseline cognitive assessment, %					
Never	46.7	44.8	45.5	45.6	47.9
Past	45.3	46.8	45.8	45.3	44.7
Current	8.0	8.4	8.7	9.2	7.5
Pack-years of smoking, mean (SD)	29 (23)	29 (24)	30 (24)	31 (24)	29 (24)
Long-term average[d] alcohol consumption, mean (SD), g/d	5.1 (8.6)	5.2 (8.4)	5.3 (9.0)	4.9 (8.4)	5.6 (9.0)
Long-term average[d] level of physical activity (MET-h/wk) by quartile, %					
Lowest	24.0	25.7	25.1	24.9	25.4
Second	24.6	25.1	25.6	24.7	25.0
Third	25.9	24.2	24.4	25.6	25.0
Highest	25.5	25.1	24.9	24.7	24.7
Self-reported history of:					
Diabetes, %	11.1	9.7	9.9	10.7	10.1
Coronary heart disease, %	5.2	5.2	5.5	6.2	5.2
Congestive heart failure, %	3.5	2.8	3.2	3.0	3.5
Coronary artery bypass graft surgery, %	5.4	5.1	5.8	5.6	6.1
High blood pressure, %	56.2	56.1	56.3	54.5	56.7
Transient ischemic attack, %	4.0	4.6	4.9	5.4	5.8
Carotid endarterectomy, %	1.1	1.4	1.2	1.6	1.6
Emphysema or chronic bronchitis, %	9.7	10.0	10.0	11.1	11.4
Annual $PM_{2.5}$[b] exposure between 1988 and baseline cognitive assessment, mean (SD), μg/m³	12.8 (2.1)	14.1 (2.0)	14.9 (2.5)	14.3 (3.4)	14.8 (4.1)

Abbreviation: MET, metabolic equivalent task.
[a] Long-term exposure refers to annual exposures averaged from 1988 until the month prior to the baseline cognitive assessment.
[b] $PM_{2.5-10}$, particulate matter 2.5 to 10 μm in diameter; $PM_{2.5}$, particulate matter smaller than 2.5 μm.
[c] Women with "other" marital status were generally widowed, divorced, or separated.
[d] Physical activity was averaged over responses from 4 to 7 questionnaire cycles prior to baseline cognitive assessment, and alcohol intake was averaged over 5 to 8 questionnaire cycles prior to baseline cognitive assessment.

women in the highest quintile of long-term exposure to $PM_{2.5}$ experienced significantly worse rates of change in the global score than did women in the lowest quintile ($P = .03$; **Table 5**). The trend of across quintiles were borderline significant (P value for trend, .11), but, when modeled as continuous variables, higher levels of both long-term $PM_{2.5}$ exposure (since 1988) and $PM_{2.5}$ exposure in the 5 years before the initial cognitive assessment were associated with significantly worse decline in global cognition. Decline in the individual cognitive domains generally was more strongly predicted by long-term than recent exposure to $PM_{2.5}$.

We observed similar differences in rates of global cognitive change per 10 μg/m³ increment in long-term exposure to $PM_{2.5-10}$ and $PM_{2.5}$ (–0.020 [95% CI, –0.032 to –0.008] and –0.018 [–0.035 to –0.002] standard units/2 years, respectively). These differences were similar to the difference in rates of change we observed between women in our data who were 1 to 2 years apart in age. Expressed per SD increment of each PM measure, these dif-

Table 3. Adjusted[a] Difference (95% CI) in Cognitive Score Change per 2 Years by Level of Exposure to Coarse Particulate Matter ($PM_{2.5-10}$[b])

Variable	No.	Adjusted Difference (95% CI)
Quintile of long-term exposure[c]		Difference in 2-y change in global cognitive score
Highest, 11.9-50.2 μg/m^3	3323	−0.024 (−0.040 to −0.008)
Fourth, 9.6-11.8 μg/m^3	3400	−0.004 (−0.020 to 0.012)
Third, 7.9-9.5 μg/m^3	3339	−0.013 (−0.030 to 0.003)
Second, 6.7-7.8 μg/m^3	3408	−0.006 (−0.022 to 0.010)
Lowest, 1.1-6.6 μg/m^3	3417	0.000 [Referent]
P value for trend		.01
Measurement period		Difference in 2-y change in global cognitive score per 10 μg/m^3 increment in $PM_{2.5-10}$
Preceding month	16 801	−0.007 (−0.017 to 0.003)
Preceding year	16 808	−0.017 (−0.029 to −0.005)
Preceding 2 years	16 873	−0.016 (−0.029 to −0.003)
Preceding 5 years	16 883	−0.019 (−0.032 to −0.006)
Since 1988	16 887	−0.020 (−0.032 to −0.008)
Cognitive test, measurement period		Difference in 2-y change in cognitive score per 10 μg/m^3 increment in $PM_{2.5-10}$
Telephone Interview for Cognitive Status		
Preceding month	19 307	−0.006 (−0.023 to 0.011)
Since 1988	19 409	−0.016 (−0.036 to 0.004)
Digit Span Backward		
Preceding month	16 830	−0.024 (−0.039 to −0.010)
Since 1988	16 916	−0.024 (−0.042 to −0.006)
Verbal Fluency, Animal Naming		
Preceding month	18 552	−0.045 (−0.079 to −0.011)
Since 1988	18 652	−0.041 (−0.084 to 0.001)
Verbal Memory Composite		
Preceding month	16 820	−0.004 (−0.017 to 0.008)
Since 1988	16 906	−0.025 (−0.040 to −0.010)

[a] Adjusted for age, education, husband's education, long-term physical activity, and long-term alcohol consumption.
[b] $PM_{2.5-10}$, particulate matter 2.5 to 10 μm in diameter.
[c] Long-term exposure refers to annual exposures averaged from 1988 up through the month prior to the baseline cognitive assessment.

ferences were −0.008 (95% CI, −0.013 to −0.003) and −0.006 (95% CI, −0.011 to −0.001) standard units/2 years.

Results from analyses of thoracic PM (PM_{10}) indicated generally faster rates of cognitive decline with higher level of long-term exposure (*P* value for trend, .<.001; eTable).

SECONDARY ANALYSES

The associations of $PM_{2.5-10}$ and $PM_{2.5}$ with cognitive decline remained nearly identical when we adjusted our analyses for area socioeconomic position measures and for potential respiratory and cardiovascular intermediates. Analyses restricted to women who did not move yielded modestly stronger associations than those in our primary analyses. For example, 10-μg/m^3 increments in long-term exposure to $PM_{2.5-10}$ and $PM_{2.5}$ corresponded to 2-year rates of decline in the global cognitive score that were worse by 0.025 (95% CI, −0.040 to −0.009) and 0.021 (95% CI, −0.043 to −0.000) standard units, respectively.

COMMENT

In this large, prospective study of older women, higher levels of long-term exposure to both $PM_{2.5-10}$ and $PM_{2.5}$ were associated with significantly faster cognitive decline. Placing these results in context, the differences in cognitive trajectory per 10-μg/m^3 increment in long-term exposure to $PM_{2.5-10}$ and $PM_{2.5}$ were similar to the differences in trajectories between women in our study who were 1 to 2 years apart in age; that is, 10-μg/m^3 higher exposure to PM was cognitively equivalent to aging by up to 2 years.

Several lines of indirect evidence indicate that PM may cause cognitive decline. Results from animal studies indicate that PM may access the brain either via circulation, or intranasally by direct translocation through the olfactory bulb.[38-40] Once in the central nervous system, fine particles appear to exert adverse effects. Several animal studies have shown increased brain inflammation in response to air particulate exposures.[41-44] In one experiment, mice were exposed either to filtered air, ambient ultrafine particles, or a mixture of fine and ultrafine particles sampled from Los Angeles, California, air. Two weeks after exposure, the brains of mice in both exposed groups contained higher levels of inflammatory markers, as compared with the mice in the control group.[41] In dogs, signs of blood-brain barrier dysfunction, neural degeneration, cerebrovascular pathologic signs, and apoptosis in glial cells were present more often in those who had lived in Mexico City, Mexico, an area of high air pollution, than in dogs from less polluted cities.[44] In a postmortem study of 19 humans aged 34 to 83 years, who had died of nonneurologic causes, brain levels of cyclooxygenase-2, an inflammatory mediator, in the frontal cortex and hippocampus were higher among those who had lived in highly polluted cities than among those who had lived in less polluted cities. Importantly, brain lev-

Table 4. Characteristics of Women, by Quintile of Long-term Exposure[a] to Fine Particulate Matter ($PM_{2.5}$[b])

Characteristic	Quintile of Exposure to $PM_{2.5}$ (1988 to Baseline Cognitive Assessment[a]), Range, μg/m³				
	Lowest, 1.9-11.5 (n = 3881)	Second, 11.6-13.2 (n = 3882)	Third, 13.3-15.0 (n = 3882)	Fourth, 15.1-16.8 (n = 3882)	Highest, 16.9-25.5 (n = 3882)
Age at baseline cognitive assessment, mean (SD), y	74.5 (2.3)	74.1 (2.3)	74.1 (2.2)	74.2 (2.3)	74.3 (2.3)
Education, %					
Registered nurse	77.4	77.8	77.8	77.9	78.4
Bachelor of arts degree	16.9	16.9	16.3	16.0	16.2
≥Master of arts degree	5.6	5.4	5.9	6.2	5.4
Husband's education, %					
≤High school	40.8	40.0	41.4	39.8	42.9
College	22.1	22.1	21.5	21.7	20.5
Graduate school	16.8	15.5	15.2	16.6	15.2
Other[c]	20.3	22.4	22.0	22.0	21.4
Measures of socioeconomic position in census tract, %					
% Of population with <high school education, highest quintile	24.8	19.3	18.3	19.5	26.4
Median household income, lowest quintile	33.2	20.3	20.5	16.8	23.0
Median home value, lowest quintile	29.0	21.4	21.7	19.6	23.7
Smoking status, as of baseline cognitive assessment, %					
Never	45.7	44.3	44.8	47.4	48.2
Past	46.9	47.2	47.2	44.0	42.5
Current	7.4	8.5	8.0	8.6	9.3
Pack-years of smoking, mean (SD)	29 (24)	30 (24)	30 (24)	28 (24)	30 (24)
Long-term average[d] alcohol consumption, mean (SD), g/d	5.9 (9.2)	5.7 (9.0)	5.3 (8.6)	4.6 (8.1)	4.4 (8.3)
Long-term average[d] level of physical activity (MET-h/wk), quartile, %					
Lowest	21.5	24.9	25.6	25.2	27.9
Second	25.0	23.6	24.2	26.9	25.3
Third	25.4	25.6	24.5	24.5	25.2
Highest	28.1	25.9	25.8	23.5	21.6
% Self-reported history of:					
Diabetes	10.0	10.1	10.1	10.7	10.6
Coronary heart disease	5.8	5.0	5.3	5.2	5.9
Congestive heart failure	3.5	3.1	3.3	2.6	3.5
Coronary artery bypass graft surgery	5.9	5.2	4.9	5.7	6.4
High blood pressure	55.7	55.0	56.8	56.1	56.2
Transient ischemic attack	5.7	4.6	4.6	4.6	5.2
Carotid endarterectomy	1.7	1.2	1.6	1.4	1.1
Emphysema or chronic bronchitis	10.6	10.1	10.4	10.0	11.0
Annual $PM_{2.5\text{-}10}$[b] exposure between 1988 and baseline cognitive assessment, mean (SD), μg/m³	10.0 (4.3)	8.5 (3.7)	8.1 (3.1)	9.0 (2.8)	12.3 (5.0)

Abbreviation: MET, metabolic equivalent task.
[a] Long-term exposure refers to average annual exposures averaged from 1988 up until month prior to the baseline cognitive assessment.
[b] $PM_{2.5}$, particulate matter smaller than 2.5 μm in diameter; $PM_{2.5\text{-}10}$, particulate matter 2.5 to 10 μm in diameter.
[c] Women with "other" marital status were generally widowed, divorced, or separated.
[d] Physical activity was averaged over responses from 4 to 7 questionnaire cycles prior to baseline cognitive assessment, and alcohol intake was averaged over 5 to 8 questionnaire cycles prior to baseline cognitive assessment.

els of amyloid-β42, a pathologic hallmark of AD, were also higher among residents of the polluted cities.[45]

The relation of PM exposure to cognitive decline may also be mediated through cardiovascular mechanisms. Extensive experimental and epidemiologic data indicate an association between exposure to air pollution and cardiovascular diseases and risk factors.[10,11,46,47] This link is important because vascular factors have also been found to predict cognitive decline and dementia.[48,49] In our data, however, adjustment for vascular factors did not change our findings, indicating that this is not likely a key pathway by which PM influences cognition.

Several limitations of our study warrant consideration. First, our estimates of PM exposure were indirect, based on spatiotemporal modeling of measurements from air pollution monitors located near each woman's residence. Measurement via personal air monitoring devices is not practical for long-term exposures in large-scale epidemiologic studies. Yet, exposure measurement errors in our study were likely to be nondifferential with respect to degree of cognitive decline, resulting in attenuated estimates of association. In addition, our PM exposure estimation[50,51] features GIS-based spatiotemporal statistical models with little bias and high precision—particularly relative to other modeling approaches[24,26]—accounting for small-scale variations in exposure at each participant's residential address using GIS-based covariates. This enabled us to assign estimated PM exposure levels to each address for each participant throughout the study period. Therefore, expo-

Table 5. Adjusted[a] Difference (95% CI) in Cognitive Score Change per 2 Years by Level of Exposure to Fine Particulate Matter ($PM_{2.5}$[b])

Variable	No.	Adjusted Difference (95% CI)
Quintile of long-term exposure[c]		Difference in 2-year change in global cognitive score
Highest, 16.9-25.5 μg/m^3	3348	−0.018 (−0.034 to −0.002)
Fourth, 15.1-16.8 μg/m^3	3422	0.003 (−0.013 to 0.019)
Third, 13.3-15.0 μg/m^3	3401	−0.006 (−0.022 to 0.010)
Second, 11.6-13.2 μg/m^3	3351	−0.004 (−0.020 to 0.012)
Lowest, 1.9-11.5 μg/m^3	3365	0.000 [Referent]
P value for trend,		.11
Measurement period		Difference in 2-y change in global cognitive score per 10-μg/m^3 increment in $PM_{2.5}$
Preceding month	16 801	−0.002 (−0.016 to 0.012)
Preceding year	16 808	−0.016 (−0.034 to 0.003)
Preceding 2 years	16 873	−0.015 (−0.034 to 0.003)
Preceding 5 years	16 883	−0.020 (−0.038 to 0.002)
Since 1988	16 887	−0.018 (−0.035 to −0.002)
Cognitive test, measurement period		Difference in 2-y change in cognitive score per 10-μg/m^3 increment in $PM_{2.5}$
Telephone Interview for Cognitive Status		
Preceding month	19 307	−0.015 (−0.047 to 0.017)
Since 1988	19 409	−0.049 (−0.088 to −0.010)
Digit Span Backward		
Preceding month	16 830	−0.010 (−0.031 to 0.010)
Since 1988	16 916	−0.032 (−0.056 to −0.007)
Verbal Fluency, Animal Naming		
Preceding month	18 552	−0.025 (−0.045 to −0.004)
Since 1988	18 652	−0.002 (−0.027 to 0.023)
Verbal Memory Composite		
Preceding month	16 820	0.009 (−0.008 to 0.025)
Since 1988	16 906	−0.014 (−0.035 to 0.007)

[a] Adjusted for age, education, husband's education, long-term physical activity, and long-term alcohol consumption.
[b] $PM_{2.5}$, particulate matter smaller than 2.5 μm in diameter.
[c] Long-term exposure refers to annual exposures from 1988 up through the month prior to the baseline cognitive assessment.

sure estimates should be more accurate over time than estimates from initial addresses only. If chronic PM exposure particularly affects cognitive aging or if the biologic response occurs over longer than 1 month, this improved accuracy over time may explain, in part, why many associations corresponding to recent PM exposure were weaker than associations corresponding to long-term PM exposures, although it is also plausible that recent PM exposure is less biologically relevant.

It is possible that our results from this observational study are due to confounding. However, we did not find meaningful differences in numerous potential confounding variables across levels of PM exposure, and adjustment for a variety of known confounding variables—some of them measured repeatedly over several study cycles—did not eliminate the observed associations.

Although ours is the first study, to our knowledge, to investigate $PM_{2.5-10}$ and $PM_{2.5}$ in relation to cognitive aging, previous epidemiologic studies of adults generally suggest an adverse association between exposure to other forms of ambient particulates and cognition.[19-22] In a study of 399 older women residing in urban and rural areas of Germany, residential proximity to busy road, a source of exposure to ultrafine particles, was associated with performance on several tests of cognition and olfaction, but higher PM_{10} exposure in the previous 5 years was not.[20] Another study of 671 older men measured exposure to black carbon, a marker of traffic-related particles, and observed that higher level of exposure over the previous 1 to 11 years was associated with worse cognitive function.[22] In the largest study to date, among 15 973 older adults in China, residents of areas with poorer air quality over the previous 7 to 10 years, measured by an index of ambient particulate and gas concentrations, were more likely to have poor cognitive function.[21] Finally, in a study of 1764 adults aged 20 to 59 years living throughout the contiguous United States, higher exposure to ozone over the previous year was associated with worse performance on several cognitive and motor tests, but exposure to PM_{10} was not. Neither of the 2 studies that examined PM_{10} observed an association with cognitive function, yet the range of PM_{10} exposure in the German study may have been too narrow (eg, 39.3-53.6 μg/m^3 from 1980-1993) to observe a measureable effect,[20] and the 1-year measurement interval for PM_{10} exposure used in the study of younger adults may have been too brief.[19] These previous findings also suggest that traffic-related exposures may be important contributors to cognitive aging. Our findings complement and extend these previous findings not only by directly examining cognitive decline in a large population, but also by using detailed modeling of short- and long-term $PM_{2.5-10}$ and $PM_{2.5}$ exposures.

In conclusion, we found that higher levels of exposure to ambient PM are associated with worse cognitive decline. Importantly, these associations were present at levels of PM exposure typical in many areas of the United States. Therefore, if our findings are confirmed in other research, air pollution reduction is a potential means for reducing the future population burden of age-related cognitive decline, and eventually, dementia.

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INVITED COMMENTARY

Policy and Regulatory Action Can Reduce Harms From Particulate Pollution

Particulate matter (PM), a heterogeneous mixture that includes chemicals, metals, and soils, is an air pollutant that contributes to multiple poor health outcomes; small particles, which are able to reach deep into the lungs, cause the greatest harm. Sources of fine PM emissions into the air include motorized vehicles, diesel-powered equipment, industrial and residential fuel combustion, and other industrial processes. Reviews of the health effects of $PM_{2.5}$, which is the fraction of airborne particles less than 2.5 μm in diameter, have established that short- and long-term exposure has causal effects on cardiovascular outcomes such as ischemic heart disease and premature mortality and likely has effects on respiratory morbidity.[1] Toxicological evidence from animal and human studies supports this epidemiologic evidence, demonstrating the physiological effects of $PM_{2.5}$ on the cardiovascular system. The association between ambient $PM_{2.5}$ concentration and ischemic stroke reported in this issue adds to the already strong evidence linking $PM_{2.5}$ to cardiovascular effects (Wellenius et al[2]), and the analysis on cognitive function shows that we may not fully understand the breadth of PM health burdens (Weuve et al[3]). The strong and growing evidence on the harms of $PM_{2.5}$ demands scrutiny of societal efforts to reduce exposure.

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Particulates have been a target for environmental regulation since notorious smog events, such as the one in London, England, in 1952 that resulted in thousands of untimely deaths. Today in the United States, under the Clean Air Act (42 USC §7401 et seq), the US Environmental Protection Agency (EPA) is required to establish air quality standards for PM adequate to protect public health. Since 1997, the primary federal standard for $PM_{2.5}$ as an annual average has been 15 μg/m^3. To achieve the standards, the EPA adopts regulations to restrict emissions from major sources. For example, federal fuel economy standards and rules for diesel engines and equipment will reduce particle emissions from engines. In addition, the EPA requires individual states to develop plans (State Implementation Plans) to achieve compliance with ambient air quality standards.

The EPA's implementation of the Clean Air Act has resulted in progress in reducing $PM_{2.5}$ at an aggregate, nationwide level. On average, the concentration of $PM_{2.5}$ has fallen since 1999, and reported levels at the majority of monitoring sites are below the federal standard. Although this is a significant achievement, evidence also suggests that exposure to $PM_{2.5}$ still contributes to a substantial population health burden as well as to health disparities. Ambient concentrations of $PM_{2.5}$ vary greatly among regions with levels exceeding the current national standard in several major population centers.

An issue deserving close public health attention is the adequacy of the current federal $PM_{2.5}$ annual standard. Evidence demonstrates that negative health effects occur at current levels of exposure including at levels below ambient air quality standards[4] (Wellenius et al[2]). The state of California adopted the more protective standard (12 μg/m^3) in 2002, and at the last federal regulatory review, completed in 2006, the EPA Clean Air Scientific Advisory Committee concluded that that the existing federal standard was not protective of public health, yet the EPA administrator retained that standard. The EPA's own risk assessment conducted for the 2006 review concluded that lowering the proposed $PM_{2.5}$ standard just by 1 μg/m^3 (to 14 μg /m^3) would have resulted in 1900