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Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women

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ABSTRACT

BACKGROUND

Fine particulate air pollution has been linked to cardiovascular disease, but previous studies have assessed only mortality and differences in exposure between cities. We examined the association of long-term exposure to particulate matter of less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) with cardiovascular events.

METHODS

We studied 65,893 postmenopausal women without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998, with a median follow-up of 6 years. We assessed the women's exposure to air pollutants using the monitor located nearest to each woman's residence. Hazard ratios were estimated for the first cardiovascular event, adjusting for age, race or ethnic group, smoking status, educational level, household income, body-mass index, and presence or absence of diabetes, hypertension, or hypercholesterolemia.

RESULTS

A total of 1816 women had one or more fatal or nonfatal cardiovascular events, as confirmed by a review of medical records, including death from coronary heart disease or cerebrovascular disease, coronary revascularization, myocardial infarction, and stroke. In 2000, levels of $PM_{2.5}$ exposure varied from 3.4 to 28.3 μg per cubic meter (mean, 13.5). Each increase of 10 μg per cubic meter was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio, 1.24; 95% confidence interval [CI], 1.09 to 1.41) and a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76; 95% CI, 1.25 to 2.47). For cardiovascular events, the between-city effect appeared to be smaller than the within-city effect. The risk of cerebrovascular events was also associated with increased levels of $PM_{2.5}$ (hazard ratio, 1.35; 95% CI, 1.08 to 1.68).

CONCLUSIONS

Long-term exposure to fine particulate air pollution is associated with the incidence of cardiovascular disease and death among postmenopausal women. Exposure differences within cities are associated with the risk of cardiovascular disease.

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Exposure to air pollution has been associated with death and hospitalization from cardiovascular causes.[1] Uncertainty remains about the magnitude of these associations, the mechanisms, and the effects of long-term exposure to pollutants, as compared with short-term exposure. Although previous studies of daily increases in exposure to pollution have assessed both fatal and nonfatal events,[2] studies investigating long-term exposure — estimating average exposure during years of follow-up — have evaluated mortality only on the basis of death certificates.[3-8] The increase in mortality associated with long-term exposure to air pollution is larger than that seen in studies of short-term exposure, and long-term effects on death rates serve as the current basis for fiercely challenged environmental regulations in this country.[9-13]

In previous studies of the long-term effect of air pollution on cardiovascular disease, investigators have averaged exposures across a city and then compared health effects between cities.[3-5,14] However, gradients of exposure to pollutants within cities also affect the risk of death from cardiovascular causes[8,15] and may be associated with subclinical atherosclerosis.[16]

We evaluated long-term exposure to air pollution and the incidence of cardiovascular disease in the Women's Health Initiative (WHI) Observational Study, a prospective cohort study with medical-record review and classification procedures designed to document specific first cardiovascular events. We also examined how between-city and within-city gradients of exposure to particulate matter of less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) are associated with first cardiovascular events.

METHODS

STUDY SUBJECTS

The WHI enrolled postmenopausal women between the ages of 50 and 79 years in the study from 1994 to 1998. The study design and characteristics of the subjects have been described in detail elsewhere.[17,18] All subjects lived within commuting distance of one of 49 WHI clinical centers and satellite clinics in 36 U.S. Metropolitan Statistical Areas (referred to throughout as "cities"). Eligible subjects were those who planned to remain in the area and were free from conditions (including alcoholism, mental illness, and dementia) that might have precluded their participation in follow-up surveys. Baseline questionnaires assessed demographic and lifestyle characteristics, cardiovascular risk factors, medical history, diet, and medications. Written informed consent was obtained from all subjects. Anthropometric and blood-pressure measurements were performed at baseline.[18]

We restricted our study population to subjects without a history of physician-diagnosed cardiovascular disease, including previous myocardial infarction, congestive heart failure, coronary revascularization, and stroke. To establish a stable primary residence during follow-up, we included women who lived within 150 mi (241 km) of a clinic (and had not changed clinics) before either death or the year 2002. Institutional review boards at the University of Washington and the Fred Hutchinson Cancer Research Center approved the study.

DATA ON AIR POLLUTION EXPOSURE

We obtained data on the monitoring of air pollution from the Environmental Protection Agency's Aerometric Information Retrieval System with the use of AirData (www.epa.gov/oar/data). Such data are recorded for $PM_{2.5}$ and particulate matter of less than 10 μm in aerodynamic diameter (PM_{10}), sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone. We selected monitors on the basis of monitoring objectives and scale to represent ambient community-scale exposure and excluded those with data available from less than 50% of intended samples (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). On the basis of a five-digit ZIP Code centroid, the nearest monitor to the location of each residence was identified and used to assign an average of annual pollutant concentrations to each study subject. Only women linked to a monitor within 30 mi (48 km) of their residence were included. The long-term average $PM_{2.5}$ concentration was the exposure of interest, and the annual average concentration in the year 2000 was the primary exposure measure, owing to the substantially increased network of monitors in place in that year, as compared with previous years.

CARDIOVASCULAR OUTCOMES

The WHI determined events on the basis of subjects' responses on annual questionnaires and

review of medical records (including hospital discharge summaries and diagnostic codes, results of electrocardiography, and reports on diagnostic tests and procedures) by physician adjudicators, following an established protocol.[19] Deaths were identified by proxy reports or by a review of the National Death Index. For deaths, WHI adjudicators reviewed all available records, including those from emergency, outpatient, and inpatient departments, and emergency medical services; autopsy and coroner records; and death certificates. We included outcomes adjudicated through August 2003.

The first cardiovascular event was the first occurrence of any of the following: myocardial infarction, coronary revascularization, stroke, and death from either coronary heart disease (categorized as "definite" or "possible") or cerebrovascular disease. These events were considered to be most consistent with an atherosclerotic disease process and most reliably verified by the WHI protocol.[20] Death from coronary heart disease (both definite and possible diagnoses) required documented myocardial infarction or angina or an antecedent procedure related to coronary artery disease during the follow-up period. Possible deaths from coronary heart disease were those consistent with the condition but without an identifiable nonatherosclerotic cause. Definite deaths from coronary heart disease were those with chest pain within the previous 72 hours or a history of chronic ischemic heart disease, without valvular disease or nonischemic cardiomyopathy. For some analyses, events were classified as coronary events (myocardial infarction, revascularization, and death from coronary heart disease) or cerebrovascular events (stroke and death from cerebrovascular causes). Although some women had more than one type of event, no analysis included multiple events per subject.

Our principal hypothesis concerned levels of $PM_{2.5}$. Single-pollutant and multipollutant models were fit to investigate possible independent or joint effects of other pollutants (see the Supplementary Appendix).

SENSITIVITY ANALYSES

We performed sensitivity analyses that excluded subjects living more than 10 mi (16 km) from a monitor or residing for fewer than 20 years in their current state. Other sensitivity analyses included and excluded coronary revascularization and other outcomes; examined a larger group of cardiovascular events, with the addition of angina pectoris, congestive heart failure, transient ischemic attack, other carotid artery disease, and deaths from all cardiovascular causes; and excluded cities with the highest variation of within-city exposure or the lowest exposure concentration (see the Supplementary Appendix).

STATISTICAL ANALYSIS

We used Cox proportional-hazards regression to estimate hazard ratios and 95% confidence intervals (CIs) for the time to the first cardiovascular event associated with an elevation of 10 μg per cubic meter in the level of long-term exposure to $PM_{2.5}$. In all models, we included factors that we hypothesized a priori could potentially confound the relationship between air pollution and cardiovascular disease. These factors included age, body-mass index (BMI), smoking status, the number of cigarettes smoked per day, the number of years of smoking, systolic blood pressure, educational level, household income, race or ethnic group, and presence or absence of diabetes, hypertension, or hypercholesterolemia. Models were stratified with use of separate baseline hazards according to current treatment for diabetes, age, and BMI. We also evaluated other characteristics previously associated with the risk of cardiovascular disease — including presence or absence of environmental tobacco smoke, occupation, physical activity, diet, alcohol consumption, waist circumference, waist-to-hip ratio, medical history, medications, and presence or absence of a family history of cardiovascular disease — as possible confounders in extended models.

Interactions between exposure and factors that could modify the association between air pollution and the incidence of cardiovascular disease were evaluated with partial-likelihood ratio tests. For tests of linear trend using the partial-likelihood method, potential effect modifiers measured as continuous variables (such as BMI, waist-to-hip ratio, and waist circumference) or as ordered categorical variables (such as household income, educational level, and years lived in state) were grouped into quintiles.

We created exposure variables to estimate between-city and within-city effects. Exposures for all women in a metropolitan area were averaged into a weighted citywide exposure. Two approaches were used to estimate the within-city effects as part of the overall exposure–effect relationship.

One approach fit indicator variables for each metropolitan area, which we term "city-adjusted." The other approach subtracted the weighted citywide mean exposure, which we termed "within-city" (see the Supplementary Appendix for details). Data were analyzed with the use of SAS software (version 8.0, SAS Institute) and Stata software (version 8.0, Stata).

RESULTS

STUDY SUBJECTS

Of the 93,676 subjects, 72,569 had no cardiovascular disease at baseline. Of those women, 65,893 (90.8%) returned a follow-up questionnaire, met our residence criteria, and were assigned $PM_{2.5}$ exposure data. We recorded 349,643 women-years of follow-up for the 58,610 women with complete information for the main analytical variables (88.9% of those who were eligible).

Most of the subjects were white (83.1%), and the median age at enrollment was 63 years. The characteristics of the subjects were similar in most respects across categories of $PM_{2.5}$ exposure (Table 1). Race and ethnic group and socioeconomic measures were distributed somewhat unevenly across exposure categories. Current smoking was rare (reported by 6.1% of the subjects), and half of the cohort reported never having smoked. Stable long-term residential location was typical; 85.7% of the subjects had lived for 20 years or more in their current state.

EXPOSURE TO POLLUTION

We linked each woman in the study to one of 573 $PM_{2.5}$ monitors operating in the year 2000, with

Table 1. Characteristics of Study Subjects and Events, According to the Quintile of Exposure to Fine Particulate Matter ($PM_{2.5}$).*

Characteristic	Quintile of Level of $PM_{2.5}$				
	3.4–10.9 $\mu g/m^3$ (N=12,906)	11.0–12.4 $\mu g/m^3$ (N=13,139)	12.5–14.2 $\mu g/m^3$ (N=13,568)	14.3–16.4 $\mu g/m^3$ (N=13,035)	16.5–28.3 $\mu g/m^3$ (N=13,245)
Cardiovascular and cerebrovascular events†	353	424	453	460	423
Age — yr	63.1±7.3	63.9±7.2	63.1±7.2	62.8±7.3	62.9±7.4
Race or ethnic group — %‡					
American Indian	0.6	0.5	0.2	0.3	0.2
Asian or Pacific Islander	10.4	1.1	1.9	1.2	2.3
Black	2.1	2.5	5.9	15.2	14.9
Hispanic	8.1	3.4	3.8	2.1	2.9
White	77.4	91.4	87.4	80.5	78.6
Other	1.5	1.1	0.8	0.8	1.2
Education — %					
Not high-school graduate	5.6	4.5	3.9	4.6	4.9
Graduate of high school or trade school or GED	27.8	27.4	24.4	24.5	23.3
Some college or associate degree	28.0	28.2	24.3	24.4	27.0
Bachelor's degree or higher	38.5	40.0	47.4	46.6	44.9
Household income — %					
<$20,000	15.2	13.4	11.5	14.6	14.4
$20,000–49,999	43.2	45.7	39.8	39.4	40.2
≥$50,000	38.5	37.9	46.0	43.4	42.0
Respondent did not know	3.2	3.1	2.8	2.7	3.4
Married — %	65.8	65.1	64.2	60.3	59.8
BMI	26.9±5.6	27.1±5.5	26.9±5.7	27.2±6.0	27.1±6.0
Smoking history — %					
Former smoker	40.9	43.6	44.0	42.3	41.4
Current smoker	5.7	5.6	5.5	7.0	6.7

a median of 20 monitors per city (range, 4 to 78) (Table 2). Most women lived within 6 mi (10 km) of a monitor. The overall median concentration of fine particle pollution was 13.4 μg per cubic meter (interquartile range, 11.6 to 18.3). The minimum concentration (3.4 μg per cubic meter) was observed in Honolulu, and the maximum (28.3 μg per cubic meter) in Riverside, California.

CARDIOVASCULAR EVENTS

A total of 1816 women had one or more cardiovascular events during the study (Table 3). An increase in exposure of 10 μg per cubic meter in the level of $PM_{2.5}$ was associated with an adjusted hazard ratio of 1.24 (95% CI, 1.09 to 1.41) for the time to the first cardiovascular event. Within-city estimates tended to be larger than between-city estimates, but the differences were not significant (P=0.07); the city-adjusted approach and the estimate of within-city effects yielded similar results (1.69 and 1.64, respectively). A similar pattern emerged for coronary heart disease and cerebrovascular events.

The magnitude of effects observed was largest for mortality end points (Table 3). The strongest overall association was with death definitely associated with coronary heart disease (hazard ratio, 2.21; 95% CI, 1.17 to 4.16), the fatal event characterized by greatest diagnostic certainty. The effect size increased across the range of exposure concentrations that were measured (Fig. 1). We did not observe associations between other pollutants and cardiovascular disease in single-pollutant models, and adjustment for other mea-

Table 1. (Continued.)

Characteristic	Quintile of Level of $PM_{2.5}$				
	3.4–10.9 μg/m^3 (N=12,906)	11.0–12.4 μg/m^3 (N=13,139)	12.5–14.2 μg/m^3 (N=13,568)	14.3–16.4 μg/m^3 (N=13,035)	16.5–28.3 μg/m^3 (N=13,245)
Physical activity — MET/wk	14.3±14.9	14.3±14.6	14.6±14.5	14.0±14.6	13.5±14.4
Hypertension — %	29.8	29.3	28.1	30.0	30.8
Diabetes mellitus — %	5.0	3.8	3.7	4.9	4.8
Hypercholesterolemia — %	13.3	12.7	12.1	12.4	13.1
Waist circumference — cm	83.9±13.3	84.5±13.1	84.0±13.2	84.2±13.5	84.5±13.7
Hormone-replacement therapy — %					
Past use	19.8	20.5	20.0	19.4	20.1
Current use	53.2	49.6	43.4	48.8	51.1
Alcohol consumption — no. of drinks/wk	2.5±5.0	2.9±5.7	2.7±5.2	2.5±5.0	2.4±5.1
Time lived in current state — %					
≤9 yr	9.6	7.4	4.1	6.8	5.3
10–19 yr	10.0	7.6	5.7	7.9	7.3
≥20 yr	80.4	85.0	90.2	85.3	87.3
Time spent outdoors (summer) — %					
<30 min/day	31.7	30.8	30.2	31.5	33.7
30 min to 2 hr/day	49.0	49.8	49.6	49.6	49.6
>2 hr/day	19.4	19.5	20.2	18.9	16.7
Time spent outdoors (nonsummer) — %					
<30 min/day	37.2	37.8	38.2	37.9	38.2
30 min to 2 hr/day	50.4	50.0	50.8	51.0	50.7
>2 hr/day	12.5	12.2	11.0	11.1	11.0

* A total of 2113 events are listed for the 65,893 women in the study, even though 7283 of the women had missing data for at least one covariate. Therefore, the main analyses were conducted on data for only 1816 events among 58,610 women. Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. GED denotes general equivalency diploma, BMI body-mass index (the weight in kilograms divided by the square of the height in meters), and MET metabolic equivalent.
† Events include myocardial infarction, revascularization, stroke, and death from coronary heart disease or cerebrovascular disease.
‡ Race or ethnic group was reported by the subjects.

Table 2. Average Concentrations of Fine Particulate Matter ($PM_{2.5}$) Measured near the Homes of 65,893 Subjects (Year 2000).*

$PM_{2.5}$ Exposure	Concentration		
	Mean	10th and 90th Percentiles	Range
		$\mu g/m^3$	
Individual exposure	13.5±3.7	9.1 to 18.3	3.4 to 28.3
Citywide average exposure	13.5±3.3	9.3 to 17.8	4.0 to 19.3
Difference between individual exposure and citywide average exposure	0±1.6	−1.6 to 1.7	−11.5 to 11.7

* Plus–minus values are means ±SD. The median distance between the location of monitors and the residences of subjects was 5.6 mi (9.0 km). A total of 573 monitors were used, with a median of 20 (range, 4 to 78) per city.

Table 3. Estimated Hazard Ratios for the Time to the First Cardiovascular Event or Death Associated with an Exposure Increase of 10 μg per Cubic Meter in the Level of Fine Particulate Matter ($PM_{2.5}$).*

Outcome	No. of Events	Hazard Ratio (95% CI)		
		Overall	Between Cities	Within Cities
First cardiovascular event				
Any cardiovascular event†	1816	1.24 (1.09–1.41)	1.15 (0.99–1.32)	1.64 (1.24–2.18)
Coronary heart disease‡	1268	1.21 (1.04–1.42)	1.13 (0.95–1.35)	1.56 (1.11–2.19)
Cerebrovascular disease§	600	1.35 (1.08–1.68)	1.20 (0.94–1.54)	2.08 (1.28–3.40)
Myocardial infarction	584	1.06 (0.85–1.34)	0.97 (0.75–1.25)	1.52 (0.91–2.51)
Coronary revascularization	949	1.20 (1.00–1.43)	1.14 (0.93–1.39)	1.45 (0.98–2.16)
Stroke	554	1.28 (1.02–1.61)	1.12 (0.87–1.45)	2.08 (1.25–3.48)
Death from cardiovascular cause				
Any death from cardiovascular cause	261	1.76 (1.25–2.47)	1.63 (1.10–2.40)	2.28 (1.10–4.75)
Coronary heart disease				
Definite diagnosis	80	2.21 (1.17–4.16)	2.22 (1.06–4.62)	2.17 (0.60–7.89)
Possible diagnosis	59	1.26 (0.62–2.56)	1.20 (0.54–2.63)	1.57 (0.29–8.51)
Cerebrovascular disease	122	1.83 (1.11–3.00)	1.58 (0.90–2.78)	2.93 (1.03–8.38)

* All analyses evaluated the time until the first event in the category. All estimates were adjusted for age, race or ethnic group, educational level, household income, smoking status, systolic blood pressure, body-mass index, and presence or absence of diabetes, hypertension, or hypercholesterolemia.
† Events include myocardial infarction, coronary revascularization, stroke, death from coronary heart disease (both definite and possible diagnosis), and cerebrovascular disease. The sum of events in each category may be greater than the total number of events, since some subjects had both coronary and cerebrovascular events.
‡ Events include myocardial infarction, coronary revascularization, and death from coronary heart disease.
§ Events include stroke and death from cerebrovascular disease.

sured pollutants did not attenuate the findings for $PM_{2.5}$.

SENSITIVITY ANALYSES

A sensitivity analysis incorporating a random-effect term for each city allowed for the possibility that effects might vary from city to city in the estimation of the main effect and its variance for each of the overall, between-city, and within-city effects. Results from this sensitivity analysis were consistent with the primary analysis. The effect estimates were not diminished, and in all cases, the lower confidence limits above 1 did not decrease (see the Supplementary Appendix). Adjustment for additional covariates (i.e., presence or absence of environmental tobacco smoke, occu-

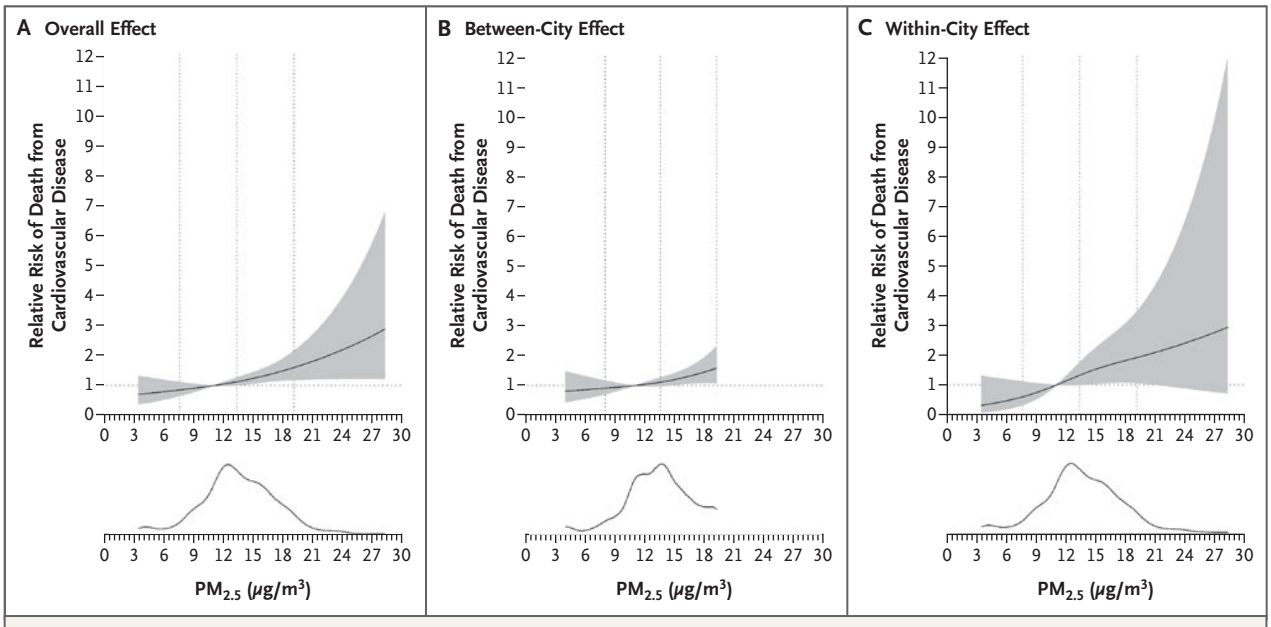

Figure 1. Level of Exposure to Fine Particulate Matter and the Risk of Death from Cardiovascular Causes in Women.

The graphs demonstrate the observed relationship between the risk of death from cardiovascular disease and the level of particulate matter of less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), including both definite and possible deaths from coronary heart disease or cerebrovascular disease. Panel A shows the overall relationship between the $PM_{2.5}$ level and death, Panel B the effects between metropolitan areas, and Panel C the effects within metropolitan areas, with an indicator variable used to adjust for each city. These results suggest a generally linear relationship between exposure and risk, though the 95% confidence intervals (shaded areas) are wide at the extremes of exposure. Risk is depicted in comparison with a reference value of 11 μg per cubic meter. The histogram in each panel illustrates the density of exposure distribution for air pollution. All estimates are adjusted for age, race or ethnic group, educational level, household income, smoking status, systolic blood pressure, body-mass index, and presence or absence of a history of diabetes, hypertension, or hypercholesterolemia.

pation, physical activity, diet, the use or nonuse of dietary supplements, use or nonuse of alcohol, household income, waist circumference, waist-to-hip ratio, medical history, medications, and presence or absence of a family history of cardiovascular disease) did not substantially change the risk estimates.

SUSCEPTIBILITY TO EFFECTS OF AIR POLLUTION

Differences in the relationship between $PM_{2.5}$ and cardiovascular disease according to the characteristics of the subjects are summarized in Table 4. The association between cardiovascular events and the level of $PM_{2.5}$ increased with increasing categories of BMI and waist-to-hip ratio and with a shorter duration of residence in the current state.

DISCUSSION

In a large, prospective cohort of postmenopausal women, long-term (annual average) exposure to increased concentrations of fine particulate air pollution was associated with an increased risk of first cardiovascular events. The increased risk applied to nonfatal and fatal cardiovascular events, including both coronary and cerebrovascular events. We found that estimates of effects within cities were often larger than those of effects between cities; the latter had been the primary measure in previous U.S. studies of long-term exposure to pollutants.

The risk of death associated with higher levels of $PM_{2.5}$ was generally larger than the risk of all first events; it was also larger than mortality estimates reported in previous U.S. cohort studies that used only death certificates. For death from cardiovascular causes (including coronary heart disease and cerebrovascular disease), we estimated an overall 76% increase in risk with each increase of 10 μg per cubic meter in long-term $PM_{2.5}$ exposure — accounting for subjects in approximately the 10th to 90th percentiles for exposure.

Our measurement of the between-city effect is similar to that in the American Cancer Society's

Table 4. Estimated Hazard Ratios for Cardiovascular Events Associated with an Increase of 10 μg per Cubic Meter in the Level of Fine Particulate Matter ($PM_{2.5}$), According to Selected Characteristics.*

Characteristic	No. of Subjects with Event	Hazard Ratio (95% CI)	P Value	Hazard Ratio Adjusted for City (95% CI)†	P Value
Subjects with any cardiovascular event	1816	1.24 (1.09–1.41)		1.69 (1.26–2.27)	
Household income			0.64		0.81
<$20,000	388	1.30 (1.10–1.53)		1.75 (1.28–2.40)	
$20,000–49,999	886	1.23 (1.08–1.41)		1.69 (1.25–2.27)	
≥$50,000	542	1.20 (1.02–1.40)		1.66 (1.22–2.26)	
P for trend		0.34		0.54	
Education			0.22		0.31
Not high-school graduate	112	1.40 (1.11–1.75)		1.88 (1.32–2.67)	
Graduate of high school or trade school or GED	575	1.33 (1.14– 1.55)		1.79 (1.32–2.44)	
Some college or associate degree	514	1.26 (1.09–1.44)		1.74 (1.29–2.34)	
Bachelor's degree or higher	615	1.11 (0.94–1.31)		1.54 (1.13–2.10)	
P for trend		0.07		0.15	
Age			0.50		0.42
<60 yr	234	1.21 (0.84–1.73)		1.66 (1.05–2.61)	
60–69 yr	785	1.14 (0.93–1.39)		1.53 (1.09–2.14)	
≥70 yr	797	1.34 (1.11–1.63)		1.85 (1.34–2.56)	
P for trend		0.20		0.20	
Smoking status			0.36		0.38
Current smoker	150	1.68 (1.06–2.66)		2.28 (1.33–3.92)	
Former smoker	750	1.24 (1.01–1.52)		1.71 (1.23–2.39)	
Never smoked	916	1.18 (0.99–1.40)		1.60 (1.16–2.21)	
Living with smoker			0.55		0.51
Currently	158	1.28 (0.84–1.97)		1.65 (0.99–2.76)	
Formerly	1206	1.18 (1.00–1.38)		1.59 (1.16–2.16)	
Never	436	1.39 (1.07–1.80)		1.90 (1.31–2.78)	
Body-mass index			0.02		0.02
<22.5	227	0.99 (0.80–1.21)		1.35 (0.96–1.88)	
22.5–24.7	337	1.16 (0.96–1.40)		1.58 (1.14–2.19)	
24.8–27.2	359	1.24 (1.05–1.45)		1.69 (1.24–2.30)	
27.3–30.9	439	1.38 (1.18–1.61)		1.88 (1.38–2.56)	
>30.9	454	1.35 (1.12–1.64)		1.84 (1.33–2.55)	
P for trend		0.003		0.004	
Waist-to-hip ratio			0.05		0.04
<0.74	199	1.07 (0.90–1.29)		1.45 (1.05–2.00)	
0.74–0.77	272	1.12 (0.95–1.31)		1.51 (1.11–2.06)	
0.78–0.80	305	1.24 (1.07–1.44)		1.68 (1.23–2.27)	
0.81–0.86	482	1.30 (1.13–1.50)		1.76 (1.30–2.38)	
>0.86	558	1.29 (1.11–1.50)		1.75 (1.29–2.37)	
P for trend		0.008		0.007	

Table 4. (Continued.)

Characteristic	No. of Subjects with Event	Hazard Ratio (95% CI)	P Value	Hazard Ratio Adjusted for City (95% CI)†	P Value
Waist circumference			0.09		0.11
<73 cm	203	1.05 (0.86–1.27)		1.43 (1.02–1.99)	
73–78 cm	295	1.20 (1.02–1.41)		1.63 (1.19–2.23)	
79–85 cm	373	1.22 (1.05–1.41)		1.66 (1.22–2.24)	
86–95 cm	452	1.33 (1.15–1.53)		1.80 (1.33–2.43)	
>95 cm	493	1.27 (1.07–1.51)		1.73 (1.26–2.36)	
P for trend		0.06		0.07	
Hormone-replacement therapy			0.32		0.25
Current use	704	1.33 (1.09–1.61)		1.85 (1.32–2.58)	
No current use	1077	1.16 (0.98–1.39)		1.57 (1.14–2.17)	
Diabetes			0.13		0.08
Yes	219	0.96 (0.67–1.37)		1.24 (0.78–1.96)	
No	1597	1.28 (1.12–1.47)		1.75 (1.30–2.36)	
Hypertension			0.79		0.69
Yes	935	1.22 (1.02–1.45)		1.65 (1.09–2.27)	
No	881	1.26 (1.05–1.51)		1.74 (1.25–2.40)	
Hypercholesterolemia			0.92		0.94
Yes	333	1.25 (0.94–1.67)		1.71 (1.15–2.54)	
No	1483	1.23 (1.07–1.42)		1.69 (1.25–2.28)	
Family history of cardiovascular disease			0.19		0.19
Yes	1359	1.30 (1.12–1.51)		1.80 (1.32–2.44)	
No	436	1.07 (0.83–1.37)		1.46 (1.00–2.12)	
Time lived in current state			0.39		0.23
≥20 yr	1585	1.21 (1.06–1.39)		1.66 (1.23–2.23)	
10–19 yr	114	1.39 (1.12–1.72)		1.97 (1.40–2.79)	
≤9 yr	108	1.54 (1.06–2.26)		2.24 (1.39–3.59)	
P for trend		0.05		0.02	
Health insurance coverage			0.33		0.30
Yes	1763	1.22 (1.07–1.39)		1.71 (1.27–2.30)	
No	42	1.82 (0.81–4.10)		2.65 (1.12–6.28)	
Time spent outdoors			0.35		0.33
<30 min	510	1.09 (0.86–1.39)		1.56 (1.05–2.31)	
≥30 min	945	1.26 (1.05–1.50)		1.82 (1.29–2.57)	

* All estimates were adjusted for age, race or ethnic group, educational level, household income, smoking status, systolic blood pressure, body-mass index, and presence or absence of a history of diabetes, hypertension, or hypercholesterolemia. Data were missing for some subjects, so the number of subjects in each category may not total 1816.
† The city-adjusted models included an indicator variable for each metropolitan area.

Cancer Prevention Study II[4] and the Harvard Six Cities Study.[3] The between-city hazard ratio was 1.63 for death from cardiovascular causes as defined in our study and 1.42 for the broader definition similar to that used in the other two studies. In the independent reanalysis,[6] the estimated hazard ratio for death from all cardiovascular causes associated with an increase of 10 μg per cubic meter in long-term $PM_{2.5}$ exposure was 1.19 (95% CI, 1.05 to 1.34) in the Six Cities Study and

1.13 (95% CI, 1.08 to 1.18) in the American Cancer Society's study. However, subjects in those cohorts differed substantially from ours, especially by the inclusion of men and persons with previous cardiovascular disease. The larger effect sizes observed for levels of $PM_{2.5}$ in our study may be due to these factors or to our efforts to reduce misclassification of outcomes and exposures. However, other studies have suggested greater effects of particulate air pollution in women than in men.[16,21] The increased association we observed between the $PM_{2.5}$ level and death from cardiovascular causes, as compared with all cardiovascular events, could be related to methodologic considerations, such as a reduced misclassification of fatal events. Alternatively, fine particulate exposures could exert effects that disproportionately result in fatal events (such as arrhythmic events or hemorrhagic stroke), as compared with nonfatal cardiovascular events.

In addition to the increased risk of coronary heart disease, we identified an association between long-term exposure to air pollution and the incidence of cerebrovascular disease. For each increase of 10 μg per cubic meter of exposure, there was a 35% increase in the risk of cerebrovascular events and an 83% increase in the risk of death from cerebrovascular causes. Previous evidence in this area included ecologic studies suggesting that the rate of death from stroke may be elevated in areas near main roads or with increased pollution,[22,23] and short-term exposure has been linked to stroke, for example.[24]

We observed a stronger association between the $PM_{2.5}$ level and cardiovascular disease with increasing obesity, as measured by either the BMI or the waist-to-hip ratio. These findings require replication. In contrast to the findings in the American Cancer Society's study,[4,6] we observed a uniform pollution-related risk of cardiovascular events across age groups, possibly because of the greater homogeneity of subjects in our study.

Our study benefited from well-defined outcomes, extensive data regarding risk factors for cardiovascular disease, and long-term geographic stability of a cohort without previous cardiovascular disease. Critics of earlier studies have suggested that poorly measured or unmeasured confounding factors may vary from city to city and account, at least in part, for the observed city-to-city differences in death rates associated with air pollution.[25] We ascertained key characteristics of subjects that might confound the relationship with exposure, and study results were not sensitive to adjustment for these characteristics, although some residual confounding cannot be excluded. Aspects of our analytic approach also reduce the concern over confounding, such as our examination of the between-city and within-city components of exposure. We controlled for the factors that vary from city to city (e.g., imperfectly measured subject characteristics, the composition or toxicity of particulate matter, and particle infiltration) in the analysis, which included a city indicator variable. By investigating many potential covariates, and by including both within-city and between-city exposures, we provided confirmation of the observed association between long-term exposure to air pollution and cardiovascular disease.

The role of socioeconomic status has received attention in air-pollution epidemiology. Beyond controlling for educational level and household income, our results were not sensitive to further adjustment for occupation or Census-derived measures of income, wealth, or poverty on the basis of ZIP Code. Neither educational level nor household income significantly modified the relationship between air pollution and cardiovascular disease, although there was a trend toward greater effects among those with less education.

Since our study included a large number of women who lived in many locales, regional or smaller-scale differences in medical practice might have influenced our findings, particularly regarding coronary revascularization. However, the results did not change when revascularization procedures were not included in the analysis. Furthermore, it is possible that women living close to one another may be more similar than those living farther apart, which could affect the variance estimation. However, we found no evidence that such a bias influenced our results.

Our assessment of exposure remains necessarily limited, since exposure levels were assigned from one monitor with the use of the subjects' primary residential ZIP Codes, which could potentially introduce some inaccuracy. The degree to which ambient pollution monitors represent the exposures of the subjects is imperfect, though we took measures to exclude nonrepresentative monitors. We were unable to assess microclimate differences in exposure, whether some participants may have moved, or details regarding the

subjects' activity and location, such as time spent in traffic and indoors. These factors contribute to errors in measurement and misclassification of exposure but are unlikely to have introduced a bias that would explain the study's findings.

We used data regarding $PM_{2.5}$ levels from a single year at the midpoint of follow-up, rather than a baseline or multiyear average, because of the presence of a much greater number of measuring stations in the year 2000 than at other times. Concentrations of particulate pollution were stable during the period under study; year-to-year $PM_{2.5}$ values were very highly correlated during years available (Pearson's correlation, ≥0.92). Analysis in the American Cancer Society's study showed a strong correlation between the sites at a 20-year interval and no time dependence of the hazard function, indicating that fine particulate pollution measured at any time during follow-up is a reasonable surrogate for the relevant exposure (long-term exposure to particulate matter).[26]

The mechanism by which long-term exposure to fine particulate air pollution may increase the risk of cardiovascular disease remains uncertain and the subject of intensive speculation and investigation.[1,14,27] Accelerated atherosclerosis and vulnerability to plaque rupture have been documented in an experimental model,[28] and ambient pollution has been correlated with carotid intima–media thickness in humans.[16]

Our results were specific to fine particulate pollution; we did not observe robust effects with other sizes of particulate matter or with other measured air pollutants (see the Supplementary Appendix). Finally, since we investigated long-term exposure and first cardiovascular events, the results in this cohort cannot be ascribed primarily to the short-term effects of increases in levels of pollution occurring on a day-to-day basis or to effects of pollution limited to those who were already ill.

Our study provides evidence of the association between long-term exposure to air pollution and the incidence of cardiovascular disease. Our study confirms previous reports and indicates that the magnitude of health effects may be larger than previously recognized. These results suggest that efforts to limit long-term exposure to fine particulate pollution are warranted.

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