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Air Pollution

$PM_{2.5}$ air pollution and cause-specific cardiovascular disease mortality

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Abstract

Background: Ambient air pollution is a modifiable risk factor for cardiovascular disease, yet uncertainty remains about the size of risks at lower levels of fine particulate matter ($PM_{2.5}$) exposure which now occur in the USA and elsewhere.

Methods: We investigated the relationship of ambient $PM_{2.5}$ exposure with cause-specific cardiovascular disease mortality in 565 477 men and women, aged 50 to 71 years, from the National Institutes of Health-AARP Diet and Health Study. During 7.5 x 10^6 person-years of follow up, 41 286 cardiovascular disease deaths, including 23 328 ischaemic heart disease (IHD) and 5894 stroke deaths, were ascertained using the National Death Index. $PM_{2.5}$ was estimated using a hybrid land use regression (LUR) geo-statistical model. Multivariate Cox regression models were used to estimate relative risks (RRs) and 95% confidence intervals (CI).

Results: Each increase of 10 $\mu g/m^3$ $PM_{2.5}$ (overall range, 2.9–28.0 $\mu g/m^3$) was associated, in fully adjusted models, with a 16% increase in mortality from ischaemic heart disease [hazard ratio (HR) 1.16; 95% CI 1.09-1.22] and a 14% increase in mortality from stroke (HR 1.14; CI 1.02-1.27). Compared with $PM_{2.5}$ exposure <8 $\mu g/m^3$ (referent), risks for CVD were increased in relation to $PM_{2.5}$ exposures in the range of 8–12 $\mu g/m^3$ (CVD: HR 1.04; 95% CI 1.00-1.08), in the range 12–20 $\mu g/m^3$ (CVD: HR 1.08; 95% CI 1.03-1.13) and in the range 20+ $\mu g/m^3$ (CVD: HR 1.19; 95% CI 1.10-1.28). Results were robust to alternative approaches to $PM_{2.5}$ exposure assessment and statistical analysis.

Conclusions: Long-term exposure to fine particulate air pollution is associated with ischaemic heart disease and stroke mortality, with excess risks occurring in the range of and below the present US long-term standard for ambient exposure to $PM_{2.5}$ (12 $\mu g/m^3$), indicating the need for continued improvements in air pollution abatement for CVD prevention.

Key words: Air pollution, cardiovascular disease, mortality

Key Messages

- Long-term exposure to fine particulate air pollution is associated with ischaemic heart disease and stroke mortality, with excess CVD risks occurring in the range of and below the present US long-term standard for ambient exposure to $PM_{2.5}$ (12 $\mu g/m^3$).
- Inclusion of data on region, sex, race or ethnic group, education, body mass index, smoking, alcohol use and ecological characteristics of residence census tracts showed that the air pollution associations were independent of these.
- The results, particularly at the lower ranges of exposure experienced in the USA, have implications for air pollution abatement needs internationally.

Introduction

Evaluations developed in the Global Burden of Disease initiative indicate that ambient air pollution has a greater impact on mortality than other major modifiable risk factors, including low physical activity, high sodium diet and high cholesterol.[1] Of all US federal regulatory standards, compliance with the air quality standard for fine particulate matter ($PM_{2.5}$, particles or droplets in the air that are 2.5 microns or less in width) avoids the greatest number of premature deaths, primarily from cardiovascular disease.[2,3] The primary health information for setting regulatory standards for $PM_{2.5}$ comes from observational studies comparing the health outcomes of people exposed to different levels of air pollution, showing particularly important effects of long-term $PM_{2.5}$ exposure on cardiovascular disease mortality.[4] As levels of $PM_{2.5}$ decrease, the nature of the exposure-response relationship at these lower levels becomes more relevant, as it is this relationship that will predict the benefits of future reductions and the hazards of future increases in exposure. As there have been few studies conducted in this lower PM environment, there is a lack of information on the exposure-response relationship.

We evaluated risks for cause-specific cardiovascular disease (CVD) mortality in a cohort of members of the NIH (National Institutes of Health)-AARP (American Association of Retired Persons) Diet and Health Study, with annual average $PM_{2.5}$ exposure of 13.3 $\mu g/m^3$. Having previously established that long-term exposure to $PM_{2.5}$ is associated with increased risk of total and CVD mortality in this cohort,[2] we report here specifically on risks for ischaemic heart disease and stroke, with particular attention to risks in dose ranges currently experienced by large segments of the US population, approaching the present 12 $\mu g/m^3$ annual average standard of the U.S. Environmental Protection Agency for the USA for $PM_{2.5}$.[5]

Methods

Study population

We analysed data from the National Institutes of Health NIH-AARP Diet and Health Study.[6] Between the years 1995 and 1996, members of the American Association of Retired Persons residing in six US states (California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania) and two urban areas (Atlanta, GA, and Detroit, MI,) were recruited to the study. These regions were selected for study because they were areas with large AARP membership, had well-performing cancer registries and, in sum, maximized the minority composition of the cohort. A baseline questionnaire to assess diet, physical activity and medical history was mailed to 3.5 million American Association of Retired Persons members and was satisfactorily completed by 566 398 individuals aged 50 to 71 years. The study, including questionnaire collection and linkage to national databases for mortality follow-up, was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute and completion of the questionnaires was considered to imply informed consent. Among 566 398 participants enrolled in the NIH-AARP cohort and available for analysis in 2014, we excluded subjects who lived in locations without census tract information ($n = 690$), missing $PM_{2.5}$ data ($n = 182$) or who exited from the study on the study entry date ($n = 49$). After accounting for overlapping

exclusions, the analytical cohort included 565 477 (99.9%) participants for whom matching $PM_{2.5}$ air pollution data were available.

Cohort follow-up and mortality ascertainment

Vital status was determined by annual linkage to the Social Security Administration Death Master File, linkage to cancer registries, and by responses to follow-up questionnaires and other mailings to study participants. We used the *International Statistical Classification of Diseases, 10th Revision*, to define deaths due to cardiovascular disease (CVD: ICD-10 I00-I99), including the major cardiovascular diseases of ischaemic heart disease (IHD: ICD-10 I20-I25) and stroke (ICD-10 I60-I69), as well other CVD (i.e. not IHD or stroke). Institutional Review Board approvals for this research were obtained from the National Cancer Institute and New York University School of Medicine.

$PM_{2.5}$ exposure assessment

$PM_{2.5}$ exposure estimates were based on a spatio-temporal prediction model recently developed by Kim *et al.*[7] for the continental USA, 1980–2010. This model provides mean annual estimates of ambient $PM_{2.5}$ for each census tract in the contiguous USA over the time period of our study, allowing for air pollution exposure estimation on an annual basis for relatively small geographical areas that included study residences of cohort study members. For the period from 1999, reliable long-term regulatory monitoring data from spatially distributed monitoring networks began to become available for $PM_{2.5}$. For the period 1999 through 2010, Kim *et al.*[7] used annual average $PM_{2.5}$ data from the U.S. Environmental Protection Agency (EPA) Federal Reference Method (FRM) network, the Interagency Monitoring of Protected Visual Environments (IMPROVE) network and >800 geographical adjustment variables, to derive complete surface estimates of annual average levels of $PM_{2.5}$ for the contiguous USA. Because regulatory monitoring data were not collected in this fashion before 1999, temporal trends before 1999 were estimated using: (i) extrapolation based on $PM_{2.5}$ data in FRM/IMPROVE; (ii) $PM_{2.5}$ sulphate data in the Clean Air Status and Trends Network; and (iii) visibility data across the Weather-Bureau-Army-Navy network. The modelling approach was validated using $PM_{2.5}$ data collected before 1999 from IMPROVE, California Air Resources Board dichotomous sampler monitoring (CARB dichot), the Children's Health Study (CHS) and the Inhalable Particulate Network (IPN). Data for this study were accessed[7] as annual averages of $PM_{2.5}$ for census tracts of the contiguous USA.

Statistical methods

We used descriptive statistics to summarize $PM_{2.5}$ exposures and population characteristics. Person-years of follow-up were calculated from study entry (the return date of the questionnaire) to date of death, loss to follow-up, date of moving from the enrolment residence region or 31 December 2011, whichever occurred first. Cox regression modelling with time-dependent covariates[8] was used to model the hazard ratio (HR) and 95% confidence intervals (CIs) for CVD mortality in relation to ambient $PM_{2.5}$. The Cox regression models were fitted with annual average exposure assignment at the census tract level, lagged by 1 year in a time-dependent fashion and scaled per 10 $\mu g/m^3$ $PM_{2.5}$. Models were also fitted in relation to selected categories of exposure [<8 $\mu g/m^3$ (referent), 8 -<12 $\mu g/m^3$, 12-<20 $\mu g/m^3$, 20+ $\mu g/m^3$].

In Cox regression base models, we treated sex and region (six US states and two municipalities of residence, at study entry) as strata and adjusted for age and race or ethnic group (Non-Hispanic White; Non-Hispanic Black; Hispanic; Asian, Pacific Islander or American Indian/Alaskan Native; unknown). We then included additional personal factors that we a priori hypothesized could potentially confound the relationship between air pollution and cardiovascular disease, including level of education (less than high school, some high school, high school completed, post-high school or some college, college and postgraduate, unknown); marital status (married or living as married, never married, other, unknown); body mass index (BMI) (<18.5 kg/m^2, 18.5-<25.0, 25.0-<30.0, 30-<35, 35+, unknown); alcohol (none, <1, 1-<2, 2-<3, 3-<5 and 5+ drinks per day); and smoking status (never smoker, former smoker of <= 1 pack/day, former smoker of >1 pack/day, current smoker of <= 1 pack/day, current smoker of >1 pack/day, unknown). In addition, from U.S. Census summary data, we evaluated characteristics of the census tract of residence at enrolment (median income, percentage not completing high school, percentage unemployed, percentage in poverty, percentage Black) as categorical covariates, by quartiles, in Cox regression models. After inclusion of median income and the percentage not completing high school in the models, each of the other contextual variables considered individually (percentage unemployed, percentage in poverty, percentage Black) did not contribute to changes in HR related to $PM_{2.5}$ exposure (<10% change). Therefore, median income and the percentage not completing high school were the two census-based variables included as contextual covariates in specified Cox regression models.

In sensitivity analyses, we evaluated risks when incorporating random effects in models for the six US States and two municipalities of residence at study entry. We also

compared risks with respect to distance of residence from AQS $PM_{2.5}$ monitoring sites. We carried out sensitivity analyses with the follow-up risk period starting in 2000 and 2005, instead of 1995–96, because prediction for the model for years before 1999 was derived from multiple sources.[7] We also derived $PM_{2.5}$ estimates for 2000 at the census tract centroids by geospatial interpolation (Empirical Bayesian Kriging), using the AQS data and the ArcGIS Geospatial Analyst module (ESRI, Redlands, CA, USA) and applied these estimates for risk estimation, as an additional sensitivity analysis. Because the largest number of study participants were from California and this region exhibited the greatest exposure variability, we also describe hazard ratios for five regions in this state (Bay Area, Farm Belt, Los Angeles, North and Mountain, Other Southern California). Data analyses were carried out with SAS (SAS 9.3, SAS Institute Inc., Cary, NC) and R statistical software (R 3.4.2, R Foundation for Statistical Computing).

Results

Among the 565 477 participants in our study, the median age at entry was 62.8 years. Of participants, 60.0% were men, 91.2% were Non-Hispanic Whites, more than half of the participants came from either California (30.9%) or Florida (21.5%), and few (7.3%) were resident 50 to 100 km from AQS monitoring sites (Table 1). The median household income in 2000 in census tracts where participants resided was $48 550, somewhat higher than the US average of $40 703 for that year. The median percentage of residents not completing high school in census tracts where participants resided was 13.5%, somewhat lower than the US average of 19.6% in 2000.

Summarizing $PM_{2.5}$ exposure for the year 2000, levels varied in the study census tracts from 2.9 to 28.0 $\mu g/m^3$. Median $PM_{2.5}$ exposure was 13.3 $\mu g/m^3$, with an interquartile range of 4.0 $\mu g/m^3$ and an interquartile range percent [IQR% = (IQR/median $PM_{2.5}$) x 100] of 30.3% (Table 1). Median exposures tended to be higher for Non-Hispanic Blacks (15.0 $\mu g/m^3$), but little difference in exposures was found for other individual factors of sex, education, marital status, body mass index and alcohol or tobacco use. The greatest annual average exposures were in Atlanta (18.0 $\mu g/m^3$), an urban area, and the least in Florida (10.3 $\mu g/m^3$). The range of individual exposures was greatest in California (IQR% = 49.0%); residents in other geographical regions showed limited intraregional variation in $PM_{2.5}$ (ranging from IQR%: 17.3% for Florida, to 5.7% for Atlanta). $PM_{2.5}$ exposures varied moderately with respect to residence census tract income and education characteristics, and tended to be lower with greater distance from AQS measurement sites.

During 7.5 x 10^6 person-years of follow-up (average 13.3 years per person), a total of 135 289 participants died, including 41 286 (30.5%) from CVD, 29 222 (21.6%) due to the major cardiovascular diseases of ischaemic heart disease (IHD, $n = 23\,328$, 17.2%) and stroke ($n = 5894$, 4.4%), and 12 064 (8.9%) from other forms of CVD (Table 2). When adjusted for personal factors, risks for the major cardiovascular disease deaths were elevated (HR 1.19; 95% CI 1.13-1.25), including for IHD (HR 1.20; 95% CI 1.14-1.27) and stroke (HR 1.16; 95% CI 1.05-1.30). Additional adjustment for census tract characteristics moderately altered these risks, for IHD (HR 1.16; 95% CI 1.09-1.22) and stroke deaths (HR 1.14; 95% CI 1.02-1.27). Compared with $PM_{2.5}$ exposure <8 $\mu g/m^3$ (referent), risks for CVD deaths were increased in relation to $PM_{2.5}$ exposures in the range of 8–12 $\mu g/m^3$ (CVD: HR 1.04; 95% CI 1.00-1.08), in the range 12–20 $\mu g/m^3$ (CVD: HR 1.08; 95% CI 1.03-1.13) and in the range 20+ $\mu g/m^3$ (CVD: HR 1.19; 95% CI 1.10-1.28) (Figure 1; Supplementary S1 Appendix, available as Supplementary data at *IJE* online).

The risk relationships for IHD and stroke mortality, per 10 $\mu g/m^3$ $PM_{2.5}$, were similar with respect to sex, age at study entry and race; furthermore, no clear differentials were observed in risk with respect to average income or educational levels associated with the residence census tracts of study participants (Table 3). The relationship between $PM_{2.5}$ and mortality due to the major cardiovascular diseases (IHD and stroke) exhibited some variability between regions (Figure 2, Supplementary S2 Appendix, available as Supplementary data at *IJE* online), although heterogeneity was not strongly evident ($P = 0.26$). Within California, the state with the largest representation and the greatest variation in PM, $PM_{2.5}$-associated risks also exhibited some variability, but these differentials may also have been due to chance ($P = 0.27$).

We conducted several sensitivity analyses to determine the robustness of our findings. First, we evaluated models that included random effects for each of the eight regions and found no differences in major cardiovascular disease hazard for IHD or stroke death (HR 1.14; 95% CI 1.10-1.19), compared with when these regions were treated as strata in Cox regression models (see Table 2). Second, we estimated these major cardiovascular disease risks for IHD or stroke death with respect to distance from AQS $PM_{2.5}$ measurement sites and found that risks were consistently elevated at least up to distances of 50 km from these locations (including 92.7% of the study population); we also found that risks were generally elevated with respect to study follow-up period and calendar period (Table 4). Finally, we compared our risk estimates based on combined geographical predictors and annual average $PM_{2.5}$ data with risks when $PM_{2.5}$ was estimated by Empirical Bayesian Kriging from $PM_{2.5}$ data for the year 2000. We found that fully

Table 1. NIH-AARP participants and $PM_{2.5}$ exposure characteristics

	Participants		PM2.5 Exposure (year 2000)		
Participant category	*n*	%	Median	IQR	**IQR%**[a]
Total	565 477	100	13.3	4.0	30.3
Age at entry (years)					
<57.90	141 370	25	13.5	3.9	28.6
57.90-<62.79	141 369	25	13.4	4.0	29.6
62.79-<66.73	141 369	25	13.3	4.1	30.9
66.73-<72.00	141 369	25	13.1	4.2	32.1
Sex					
Male	339 133	60	13.3	4.0	30.0
Female	226 344	40	13.4	4.1	30.6
Race/ethnicity					
Non-Hispanic White	516 052	91.2	13.2	4.0	30.2
Non-Hispanic Black	21 970	3.9	15.0	3.1	20.9
Hispanic	10 549	1.9	13.2	6.4	48.5
Asian/Pacific Islander/Native	9137	1.6	14.0	5.8	41.3
Unknown	7769	1.4	13.6	4.2	30.8
Education					
<12 years	36 001	6.4	13.3	4.1	30.4
High school	111 368	19.7	13.4	3.9	29.4
Some college	55 560	9.8	13.2	4.3	32.6
Other post-high school	130 135	23	13.2	4.1	31.1
College graduate	215 464	38.1	13.4	3.9	29.2
Unknown	16 949	3	13.3	4.2	31.5
Marital status					
Married	389 195	68.8	13.2	4.0	30.1
Never married	144 824	25.6	13.5	4.2	31.0
Other	26 739	4.7	14.0	4.0	28.7
Unknown	4719	0.8	13.4	4.1	30.7
Body mass index (kg/m^2)					
<18.5	4776	0.8	13.4	4.1	30.8
18.5-<25.0	189 353	33.5	13.3	4.1	30.7
25.0-<30.0	234 380	41.4	13.3	4.0	30.2
30-<35	86 874	15.4	13.4	4.0	29.9
35+	34 737	6.1	13.6	3.9	29.0
Unknown	15 357	2.7	13.4	4.1	30.4
Alcohol (drinks per day)					
None	140 621	24.9	13.5	4.0	29.8
<1	294 102	52	13.4	4.0	29.4
1-<2	63 840	11.3	13.0	4.1	31.7
2-<3	21 389	3.8	12.9	4.2	32.4
3-<5	20 821	3.7	12.8	4.2	32.9
5+	24 704	4.4	12.8	4.3	33.5
Smoking status					
Never	196 171	34.7	13.5	3.9	28.9
Former, ≤1 pack/day	150 486	26.6	13.3	4.0	30.3
Former, >1 pack/day	118 803	21	13.1	4.1	31.6
Current, ≤1 pack/day	50 393	8.9	13.4	4.2	31.0
Current, >1 pack/day	27 871	4.9	13.1	4.2	32.3
Unknown	21 753	3.8	13.4	4.0	30.1
State/city					
California	174 860	30.9	13.8	6.8	49.0
Florida	121 593	21.5	10.3	1.8	17.3
Pennsylvania	84 979	15	14.8	1.8	12.2

(Continued)

Table 1. Continued

Participant category	Participants		PM2.5 Exposure (year 2000)		
	n	%	Median	IQR	IQR%[a]
New Jersey	71 014	12.6	13.0	2.0	15.8
North Carolina	46 937	8.3	14.4	2.3	15.7
Louisiana	21 710	3.8	12.8	2.4	18.7
Detroit	28 573	5.1	14.7	1.9	12.6
Atlanta	15 811	2.8	18.0	1.6	9.0
Median income ($1000) in census tract					
Quartile 1 (<37.07)	141 370	25.0	12.5	4.7	37.4
Quartile 2 (≥37.07 and <48.55)	141 369	25.0	13.5	4.5	33.5
Quartile 3 (≥48.55 and <65.35)	141 369	25.0	13.7	3.7	27.3
Quartile 4 (≥65.35)	141 369	25.0	13.4	3.2	23.7
Percentage not completing high school in census tract					
Quartile 1 (<7.8%)	141 370	25.0	13.4	3.6	27.1
Quartile 2 (≥7.8% and <13.5%)	141 369	25.0	13.1	3.8	29.0
Quartile 3 (≥13.5% and <21.2%)	141 369	25.0	13.2	4.2	31.7
Quartile 4 (≥21.2%)	141 369	25.0	13.8	4.5	32.6
Distance to AQS sites					
< 25 km	432 610	76.5	14.0	3.8	27.5
≥25 and <50 km	88 414	15.6	11.5	3.4	29.7
≥50 and 100 km	41 206	7.3	10.8	2.7	24.8

[a]IQR%: (interquartile range/median $PM_{2.5}$) x 100.

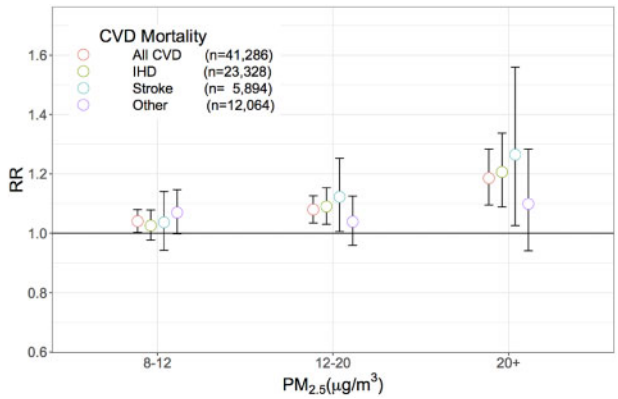

Figure 1. Hazard ratios (HR), for overall and cause-specific CVD mortality, by level of fine particulate matter ($PM_{2.5}$), NIH-AARP. Hazard ratios are adjusted in Cox regression models for sex and region (six US states and two municipalities of residence, at study entry) as strata, and adjusted for age, race or ethnic group, education, marital status, body mass index (BMI), alcohol use, smoking, median income and percenage not completing high school in the census tract of residence at enrolment.

adjusted risks for death due to the major cardiovascular diseases of IHD and stroke were similar by the combined prediction (see Table 2; HR 1.15; 95% CI 1.10-1.21) and by Empirical Bayesian Kriging (HR 1.15; 95% CI 1.11-1.19).

Discussion

In this large cohort, we showed that greater exposure to ambient $PM_{2.5,}$ is associated with increased mortality due to ischaemic heart disease (IHD: 16% increase per 10 $\mu g/m^3$ $PM_{2.5}$) and stroke (14% increase), consistent with our previous report on all-cause and total CVD mortality in this cohort.[2] Furthermore, a meta-analysis[9] of 10 cohort studies[10–19] showed a 15% increase (95% CI 1.04-1.27) in CVD mortality per 10-$\mu g/m^3$ increase in $PM_{2.5}$. In addition to modelling exposure-response as a continuous variable, we also identified excesses of CVD mortality below the range of the current regulatory standard of the U.S. Environmental Protection Agency, consistent with the recent identification of excess total mortality in Medicare beneficiaries exposed to $PM_{2.5}$ at <12 $\mu g/m^3$ [20] and excess IHD mortality in low-exposure residents of Iowa and North Carolina[21] and Canada.[12,22,23] These findings indicate a need for continued air pollution abatement efforts.

The risks we identified for IHD mortality were similar to those reported in most previous studies. The increase in IHD mortality risk per 10 $\mu g/m^3$ $PM_{2.5}$ was about 18% in the American Cancer Society (ACS) cohort of 319 000 participants,[24] about 31% in the Canadian national cohort of 2 145 000 participants exposed on average to 8.7 $\mu g/m^3$ $PM_{2.5}$[12] and about 10% in the Rome longitudinal study of 1 265 000 persons.[11] An estimated 5-$\mu g/m^3$ increase in estimated annual mean $PM_{2.5}$ was associated with a 13% increase in coronary events, in 100 000 Europeans in the ESCAPE study.[25] Most[17,24,26–28] but not all other studies[19,29] show similar associations of $PM_{2.5}$ with IHD.

Table 2. Hazard ratios (HR) for cardiovascular disease (CVD) mortality associated with an exposure increase of 10 $\mu g/m^3$ in the level of fine particulate matter ($PM_{2.5}$)

			Hazard ratio (95% CI)					
			Base model[a]		Adjusted for personal characteristics[b]		Adjusted for personal and census tract characteristics[c]	
Cause of death	Deaths	Cumulative mortality (%)[d]	HR	95% CI	HR	95% CI	HR	95% CI
All CVD[e]	41 286	5.2	1.22	1.17-1.28	1.15	1.10-1.20	1.12	1.07-1.17
Major CVD[f]	29 222	3.8	1.27	1.21-1.33	1.19	1.13-1.25	1.15	1.10-1.21
IHD[g]	23 328	3.0	1.28	1.21-1.35	1.20	1.14-1.27	1.16	1.09-1.22
Stroke	5894	0.8	1.21	1.09-1.35	1.16	1.05-1.30	1.14	1.02-1.27
Other CVD	12 064	1.5	1.12	1.04-1.21	1.05	0.97-1.14	1.03	0.95-1.12

[a]All analyses evaluated the time until death in the category. All estimates were adjusted for sex and region (as strata), age and race or ethnic group.

[b]All analyses were evaluated as above, with additional adjustment for level of education, marital status, body mass index (BMI), alcohol and tobacco use.

[c]All analyses were evaluated as above, with additional adjustment for percentage not completing high school and median income of residents of the census tract of residence at study entry, based on data from the 2000 census.

[d]Cumulative mortality (%, per 10 years) = 1-e($^{(-\text{Deaths/PY})*10}$), where 'e' = 2.718 and 'PY' = 7.74 x 10^6 person-years.

[e]CVD, all cardiovascular disease.

[f]Major CVD deaths are deaths due to ischaemic heart disease or stroke.

[g]IHD, ischaemic heart disease specifically.

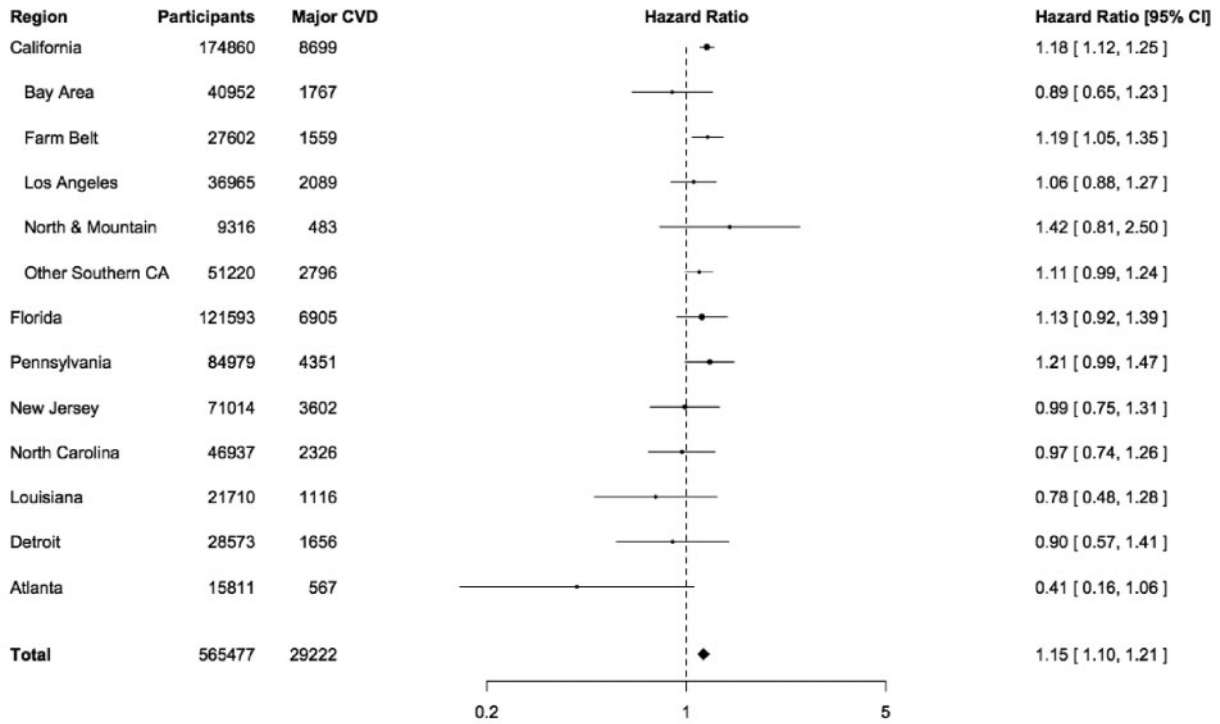

Figure 2. Hazard ratios (HR) for major cardiovascular diseases per 10 $\mu g/m^3$ level of exposure to fine particulate matter ($PM_{2.5}$), NIH-AARP. Major cardiovascular diseases (CVD) include ischaemic heart disease and stroke. Hazard ratios (HR) are adjusted in Cox regression models for sex and region (six US states and two municipalities of residence, at study entry) as strata, and adjusted for age, race or ethnic group, education, marital status, bodymass index (BMI), alcohol use, smoking, median income and percentage not completing high school in the census tract of residence at enrolment.

There is also evidence from previous cohort studies for an association between particulate matter and stroke,[30] although risk estimates are more variable, with some evidence indicating a greater role in ischaemic than in haemorrhagic stroke.[31–33] An 8% excess in stroke mortality per 10 $\mu g/m^3$ $PM_{2.5}$ was found in the Rome longitudinal study[11] and a 19% excess per 5 $\mu g/m^3$ $PM_{2.5}$ was observed in ESCAPE,[34] whereas no association was found

Table 3. Hazard ratios (HR) for ischaemic heart disease and stroke (major CVD) mortality associated with an exposure increase of 10 $\mu g/m^3$ in the level of fine particulate matter ($PM_{2.5}$)

	Major CVD Deaths[a]	HR[b]	95% CI	*P* for interaction
Sex				
Male	21 337	1.12	1.06–1.19	
Female	7885	1.23	1.12–1.34	0.23
Age (years)				
Below median (<62.79 years)	8512	1.12	1.03–1.23	
Above median	20 710	1.16	1.10–1.23	0.12
Race[c]				
Black	1139	0.98	0.73–1.32	
White	26 681	1.15	1.09–1.21	0.63
Census tract: income				
Below median (<48.55, $1000s)	16 834	1.13	1.07–1.21	
Above median	12 388	1.17	1.08–1.27	0.29
Census tract: not completing high school				
Below median (<13.5%)	12 463	1.19	1.09–1.29	
Above median	16 759	1.15	1.08–1.22	0.95

[a]Major CVD deaths are deaths due to ischaemic heart disease or stroke.

[b]Analyses evaluated the time until death in the category. Hazard ratios (HR) are adjusted in Cox regression models for sex and region (six US states and two municipalities of residence, at study entry) as strata, and adjusted for age, race or ethnic group, education, marital status, body mass index (BMI), alcohol use, smoking, median income and percentage not completing high school in the census tract of residence at enrolment.

[c]Presented for Blacks and Whites only, due to small numbers for other groups.

Table 4. Hazard ratios (HR) for ischaemic heart disease and stroke (major CVD) mortality associated with an exposure increase of 10 $\mu g/m^3$ in the level of fine particulate matter ($PM_{2.5}$)

	Major CVD deaths[a]	HR[b]	95% CI
Distance from AQS sites			
0-25km	21 933	1.14	1.07–1.21
25-50km	4783	1.31	1.11–1.54
50-100km	2346	0.81	0.59–1.11
Time on study (days)			
Q1: ≤1460	3192	1.04	0.91–1.20
Q2: 1460-2921	6572	1.20	1.10–1.31
Q3: 2921-4747	9864	1.19	1.10–1.29
Q4:>4747	9594	1.09	0.99–1.21
Risk entry period			
1995-96 (all subjects)	29 222	1.15	1.10–1.21
2000	24 385	1.17	1.11–1.23
2005	15 652	1.14	1.07–1.21

[a]Major CVD deaths are deaths due to ischaemic heart disease or stroke.

[b]Analyses evaluated the time until death in the category. Hazard ratios (HR) are adjusted in Cox regression models for sex and region (six US states and two municipalities of residence, at study entry) as strata, and adjusted for age, race or ethnic group, education, marital status, body mass index (BMI), alcohol use, smoking, median income and percentage not completing high school in the census tract of residence at enrolment.

in the ACS cohort.[24] Other generally smaller studies tended to show non-significant excesses,[12,16] as reviewed by Hoek *et al.*[9] Specific details on stroke due to haemorrhage or infarction were generally not available from death certificates in our and most other large cohort studies, limiting our understanding of the role of air pollution in these specific stroke types. Also in our study, the number of stroke deaths was far lower than for IHD, somewhat limiting our ability to assess stroke risks. We found no association of $PM_{2.5}$ exposure with other causes of cardiovascular death, similar to results from the ACS,[24] although there is some evidence from other studies of a role for particulate matter in peripheral arterial and venous diseases.[35,36]

Based on our models, we can expect approximately 570 fewer CVD deaths per 100 000 persons for 5 years associated with a reduction of 10 ug/m^3 of the annual average $PM_{2.5}$ level for Black men in California who are current or recent smokers, at reference values for other covariates, whereas for White women in Florida who are non-smokers, absolute CVD mortality reduction would be approximately 80 deaths per 100 000 persons. Considering a 1-ug/m^3 reduction in $PM_{2.5}$, a more relevant target given current lower exposure levels, the model predicts reductions of 57 and eight deaths, respectively, per 100 000 persons. Although individual risks are modest, $PM_{2.5}$ exposure is ubiquitous and even small reductions in these exposures could lead to many thousands of deaths averted globally.[37]

The National Institutes of Health NIH-AARP Diet and Health Study[6] includes members of a national organization who volunteered for participation in this study and, therefore are not entirely representative of the population in the regions studied. Given this important caveat, however, our overall findings are robust. Analyses stratified by personal

(sex, age, race) or census tract characteristics (income and education) generally revealed similar $PM_{2.5}$-associated IHD and stroke mortality risks, lessening concerns that observed associations of mortality with $PM_{2.5}$ might be due to confounding. We observed some degree of variation in risk by geographical area, but these differentials could be due to chance, indicating within the limits of our study that the effects of $PM_{2.5}$ air pollution are not regionally limited. We demonstrated robustness of our findings for $PM_{2.5}$-associated IHD mortality, whether risk estimates were based on a hybrid land use regression-geostatistical interpolation or Empirical Bayesian Kriging. Since our study lacked a complete history of moving during the follow-up period, we ended follow-up time when participants moved from the enrolment residence region. Ascertaining detailed within-region moving history and identification of specific $PM_{2.5}$ chemical constituents[38] could be important improvements over our necessarily limited approach. We found that risks were consistently elevated for subjects resident up to 50 km from stationary monitoring sites (including 92.7% of the study population), indicating the robustness of exposure estimation to at least this distance. We found no remarkable variation in risk by time since study entry, indicating that risk patterns were similar over follow-up time, consistent with the proportional hazards assumption of Cox regression analysis.[8] Finally, we found that risk estimates were not biased by inclusion of follow-up time and related exposure estimates for earlier time periods, when direct data on $PM_{2.5}$ were unavailable nationally.[7]

Although associations of $PM_{2.5}$ with cardiovascular mortality could partially be related to unmeasured confounding, there is substantial biological support for the observed relations between $PM_{2.5}$ and cardiovascular disease mortality.[28,39] Inhaled particulate matter has extrapulmonary effects on the cardiovascular system, through release from lung-based cells of pro-inflammatory mediators and vasculo-active molecules, through autonomic nervous system imbalance due to particle interactions with lung receptors or nerves, through predisposition to heart rhythm disturbances and potentially through increased platelet activation and translocation of particulate matter into the systemic circulation. Animal models point to acceleration of vascular inflammation and atherosclerosis related to long-term air pollution exposure,[40] and long-term $PM_{2.5}$ exposure has been related in epidemiological study to early-stage progression of intima-media thickness[41] and coronary calcification.[42] The evidence is strongest for ischaemic disease and a central role of fine particulate matter in the atherothrombotic process,[17,24,43,44] but air pollution may also be involved in heart failure and haemorrhagic stroke.[45]

The large size of the AARP cohort allowed us to address $PM_{2.5}$–related IHD and stroke mortality in detail across the broad spectrum of exposures experienced in the USA, represented by six states and two cities. Further studies are needed to clarify the hazards associated with specific sources and constituents of particulate matter, with interrelationships with other environmental pollutants and other factors unexamined in our study. Nevertheless, these results on $PM_{2.5}$-related IHD and stroke mortality could contribute to the discussion of appropriate measures to reduce the mortality burden of cardiovascular disease.

In summary, with more than 560 000 participants examined for air pollution-related mortality, our study showed that $PM_{2.5}$ is associated with increased risk for IHD and stroke mortality, with excess CVD risks occurring in the range of and below the present 12 $\mu g/m^3$ annual average standard for the USA for $PM_{2.5}$.[5]

Supplementary data

Supplementary data are available at *IJE* online.

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Author Contributions

R.B.H., J.A. and G.D.T. conceived of and designed the study. R.B.H., Y.S., C.L. and Y.Z. conducted statistical analyses. R.B.H. drafted the manuscript. R.B.H., J.A., G.D.T., H.R.R., D.T.S., R.J. and M.J. interpreted the data and provided critical revision of the manuscript. R.B.H., J.A. and G.D.T. obtained funding. R.B.H. supervised the study.

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