

# Association of air particulate pollution with bone loss over time and bone fracture risk: analysis of data from two independent studies



Didier Prada, Jia Zhong, Elena Colicino, Antonella Zanobetti, Joel Schwartz, Nicholas Dagincourt, Shona C Fang, Itai Kloog, Joseph M Zmuda, Michael Holick, Luis A Herrera, Lifang Hou, Francesca Dominici, Benedetta Bartali, Andrea A Baccarelli



## Summary

**Background** Air particulate matter is a ubiquitous environmental exposure associated with oxidation, inflammation, and age-related chronic disease. Whether particulate matter is associated with loss of bone mineral density and risk of bone fractures is undetermined. We did two independent studies with complementary designs, objectives, and measures to determine the relationship between ambient concentrations of particulate matter and bone health.

**Methods** In the first study, we examined the association of long-term concentrations of particulate matter less than  $2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ ) and osteoporosis-related fracture hospital admissions among 9.2 million Medicare enrollees (aged  $\geq 65$  years) of the northeast-mid-Atlantic USA between January, 2003, and December, 2010. In the second study, we examined the association of long-term black carbon and  $\text{PM}_{2.5}$  concentrations with serum calcium homeostasis biomarkers (parathyroid hormone, calcium, and 25-hydroxyvitamin [25(OH)D]) and annualised bone mineral density over 8 years (baseline, November, 2002–July, 2005; follow-up, June, 2010–October, 2012) of 692 middle-aged ( $46.7$  years [ $\text{SD}12.3$ ]), low-income men from the Boston Area Community Health/Bone Survey (BACH/Bone study) cohort.  $\text{PM}_{2.5}$  concentrations were estimated using spatiotemporal hybrid modelling including Aerosol Optical Depth data, spatial smoothing, and local predictors. Black carbon concentrations were estimated using spatiotemporal land-use regression models.

**Findings** In the Medicare analysis, risk of bone fracture admissions at osteoporosis-related sites was greater in areas with higher  $\text{PM}_{2.5}$  concentrations (risk ratio [RR]  $1.041$ , 95% CI  $1.030$  to  $1.051$ ). This risk was particularly high among low-income communities (RR  $1.076$ , 95% CI  $1.052$  to  $1.100$ ). In the longitudinal BACH/Bone study, baseline black carbon and  $\text{PM}_{2.5}$  concentrations were associated with lower serum parathyroid hormone ( $\beta=-1.16$ , 95% CI  $-1.93$  to  $-0.38$ ,  $p=0.004$ , for 1 IQR increase [ $0.106 \mu\text{g}/\text{m}^3$ ] in the 1-year average of black carbon concentrations;  $\beta=-7.39$ , 95% CI  $-14.17$  to  $-0.61$ ,  $p=0.03$ , for 1 IQR increase [ $2.18 \mu\text{g}/\text{m}^3$ ] in the 1-year average of  $\text{PM}_{2.5}$  concentrations). Black carbon concentration was associated with higher bone mineral density loss over time at multiple anatomical sites, including femoral neck ( $-0.08\%$  per year for 1 IQR increase, 95% CI  $-0.14$  to  $-0.02$ ) and ultradistal radius ( $-0.06\%$  per year for 1 IQR increase,  $-0.12$  to  $-0.01$ ). Black carbon and  $\text{PM}_{2.5}$  concentrations were not associated with serum calcium or serum 25(OH)D concentrations.

**Interpretation** Our results suggest that poor air quality is a modifiable risk factor for bone fractures and osteoporosis, especially in low-income communities.

**Funding** National Institutes of Health, Institute on Aging, National Institute of Environmental Health, the US Environmental Protection Agency, Consejo Nacional de Ciencia y Tecnología, and the Fundación México en Harvard.

**Copyright** © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

## Introduction

In the USA, about 2.1 million osteoporosis-related bone fractures are reported each year, resulting in as much as US\$20.3 billion in annual direct health costs.<sup>1</sup> Within 1 year of a bone fracture, death risks for older individuals increase by 10–20%<sup>2</sup> with only 40% regaining full pre-fracture independence.<sup>1,3</sup> Identification of novel, preventable risk factors for bone loss and fractures is an urgent global priority.<sup>4,5</sup>

Ambient concentrations of particulate matter air pollution have been associated with increased morbidity, hospitalisation, and mortality from cardiovascular<sup>6–8</sup> and

respiratory diseases,<sup>9,10</sup> as well as with cancer<sup>11,12</sup> and impaired cognition.<sup>13–15</sup> Particulate matter causes systemic oxidative damage<sup>16</sup> and inflammation,<sup>17</sup> which can result in accelerated bone loss and increased risk of bone fractures in older individuals. Tobacco smoke, which contains several toxic components also found in particulate matter, has been repeatedly associated with decreased bone mineral density<sup>18</sup> and increased risk of bone fractures.<sup>19</sup> However, evidence on whether individuals living in areas with higher concentrations of particulate matter have higher risk of bone fractures is inconclusive. No longitudinal study has investigated

Lancet Planet Health 2017;

1: e337–47

See Comment page e311

Department of Environmental Health (D Prada PhD, J Zhong ScD, E Colicino PhD, A Zanobetti PhD, Prof J Schwartz PhD, Prof A A Baccarelli PhD) and Department of Biostatistics (Prof F Dominici PhD), Harvard TH Chan School of Public Health, Harvard University, Boston, MA, USA; Unidad de Investigación Biomédica en Cáncer, Instituto Nacional de Cancerología—Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Mexico City, Mexico (D Prada, Prof L A Herrera PhD); Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA (J Zhong, E Colicino, Prof A A Baccarelli); New England Research Institute, Watertown, MA, USA (N Dagincourt MSc, S C Fang PhD, Prof B Bartali PhD); Department of Geography and Environmental Development, Ben-Gurion University of the Negev, Beer Sheva, Israel (I Kloog PhD); Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA (J M Zmuda PhD); School of Medicine Endocrinology, Diabetes, and Nutrition, Boston University, Boston, MA, USA (Prof M Holick PhD); and Institute for Public Health and Medicine, Northwestern University, Chicago, IL, USA (Prof L Hou PhD)

Correspondence to:  
 Prof Andrea A Baccarelli,  
 Columbia University Mailman  
 School of Public Health,  
 ARB 11th Floor 1105E,  
 722 West 168th Street,  
 New York, NY 10032, USA  
 ab4303@cumc.columbia.edu  
 or  
 Prof Benedette Bartali,  
 New England Research Institute,  
 480 Pleasant Street, Watertown,  
 MA 02472, USA  
 bbartali@neriscience.com

### Research in context

#### Evidence before this study

Exposure to particulate matter induces oxidative damage and inflammation, which might affect bone health, particularly of older populations. Smoking, which contains several components of particulate matter, has been consistently associated with bone damage. However, whether ambient particulate matter concentrations affect calcium metabolism, bone damage, and risk of fractures is uncertain.

#### Added value of this study

We demonstrate for the first time higher rates of hospital admissions for bone fractures in communities with higher ambient concentrations of particulate matter less than 2.5 µm in aerodynamic diameter. Participants living at addresses with higher concentrations of traffic-derived particulate matter exhibit lower serum parathyroid hormone

concentrations and higher decreases in bone mineral density over an 8-year follow-up.

#### Implications of all the available evidence

This study provides evidence that long-term exposure to particulate matter—a persistent environmental issue in Europe and globally—is an independent risk factor for bone fractures, possibly involving changes in parathyroid hormone concentrations. These associations might disproportionately affect under-privileged communities. We found the association of particulate matter well below the annual average limits set by the US Environmental Protection Agency and the European Union. Improvements in particulate air pollution concentrations might ameliorate bone health, prevent bone fractures, and reduce the health cost burden associated with fractures in older individuals.

See Online for appendix

ambient particulate matter in relation to bone mineral loss over time, and there is no available data on particulate matter and calcium homeostasis in adults.

To determine the relationship between ambient concentrations of particulate matter and bone health, we did two independent studies with complementary designs, objectives, and measures: using data on 763 630 hospital admissions from 9.2 million Medicare enrollees in the northeast-mid-Atlantic USA from 2003 to 2010, we determined whether communities with higher concentrations of particulate matter less than 2.5 µm in aerodynamic diameter (PM<sub>2.5</sub>) had higher rates of hospital admissions for osteoporosis-related bone fractures among older persons (≥65 years old); in a longitudinal study of 692 middle-aged (mean age 47.5 years [SD 12.8]), low-income men from the Boston Area Community Health/Bone Survey cohort (BACH/Bone study), we determined whether PM<sub>2.5</sub> concentrations and traffic-derived ambient particulate matter—as traced through ambient concentrations of black carbon—were associated with altered markers of calcium homeostasis, including serum parathyroid hormone, 25-hydroxyvitamin D (25(OH)D), and calcium, as well as changes in bone mineral density over approximately 8 years of follow-up.

## Methods

### Medicare analysis

#### Study design and data sources

We obtained 2003–10 hospital admission data for osteoporosis-related bone fractures from approximately 9.2 million beneficiaries of Medicare, aged 65 years or older, who lived in 3974 zip codes of 13 northeast-mid-Atlantic US states located east of the 81° W meridian, for which we recently developed a high-resolution hybrid model for estimating PM<sub>2.5</sub> concentrations (figure 1).<sup>20</sup> We identified primary hospital admissions for osteoporotic-related fractures using the International Classification of

Diseases, 9th revision (appendix pp 2–5) and compiled data on number of admissions per year per zip code. Covariate data at the zip code level were collected from various sources (eg, 2000 Census, Centers for Disease Control and Prevention; appendix p 6) and presented in their original unit to ensure accuracy. Medicare data are previously collected administrative data and, therefore, did not require individual patient consent.

#### Procedures

Annual PM<sub>2.5</sub> concentrations between 2003 and 2010 were estimated using a recently developed and validated (mean out-of-sample R<sup>2</sup>=0.88) spatio-temporal prediction model that incorporates satellite aerosol optical depth data, spatial smoothing, and local predictors.<sup>21</sup> We generated daily PM<sub>2.5</sub> predictions at 1×1 km spatial resolution, as previously described<sup>20</sup> and calculated 1-year averages of PM<sub>2.5</sub> concentrations specific to each zip code for each calendar year. The exposure dataset with yearly averages of PM<sub>2.5</sub> concentrations at a 1×1 km spatial resolution was matched to zip codes using ArcGIS (a geographic information system) and SAS based on spatial location and date. For zip codes that covered several grids, a weighted exposure average was calculated for each zip code based on all covered 1×1 km grid cells.

#### Statistical analysis

We estimated the association of 1-year PM<sub>2.5</sub> averages with annual rates of bone fracture hospital admissions using generalised linear mixed models (PROC GLIMMIX; SAS Institute, Cary, NC, USA) with Poisson distribution and random intercepts for zip code. We considered the Akaike information criterion and residuals' plots to evaluate goodness-of-fit. We adjusted the final model for the multiple zip code-level confounders described in the appendix (p 6). We used Medicare data on age that provides per each zip code the

percentage of the population aged between 65 and 74 years and the percentage older than 75 years. We also adjusted for number of days below 0°C to minimise the potential impact of fall risk due to freezing weather. Urban and rural areas were classified according to the Rural–Urban commuting area from the US Department of Agriculture, which classifies US census tracts using measures of population density, urbanisation, and daily commuting. In separate models, we tested interaction terms between zip code characteristics and  $PM_{2.5}$  concentrations.  $p < 0.05$  was considered significant.

### BACH/Bone study

#### Study design and participants

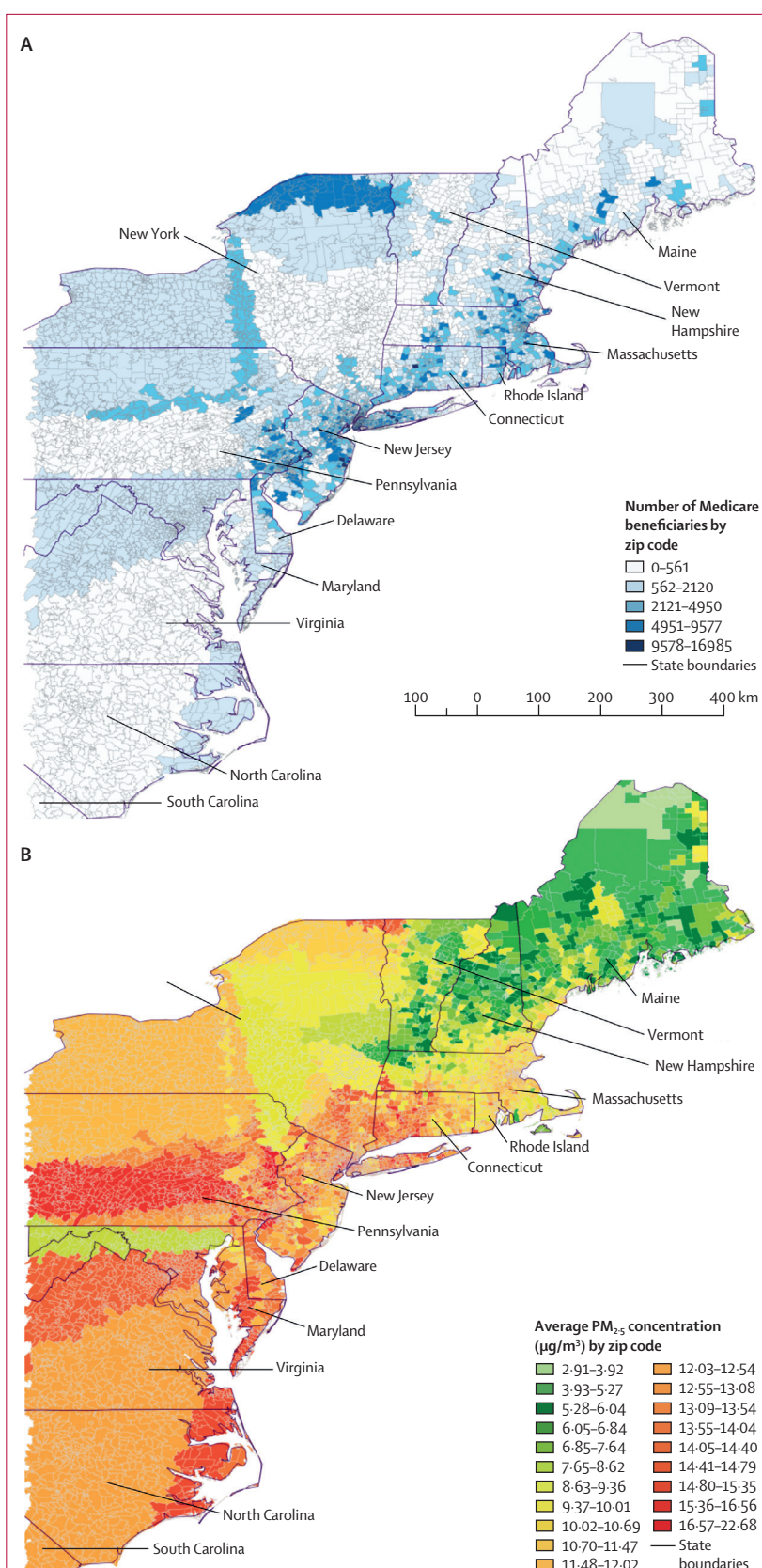
The BACH/Bone study is a population-based longitudinal study of musculoskeletal health, including 1219 low-income black, Hispanic, and white male residents of Greater Boston, MA, USA, aged 30–79 years.<sup>22</sup> Data were collected at baseline (November, 2002–July, 2005) and follow-up (June, 2010–October, 2012) examinations from a total of 692 participants, who completed follow-up assessments.

The institutional review boards at the New England Research Institute and Boston University School of Medicine (BUSM) approved the protocols. Each participant provided written informed consent.

#### Procedures

Physical activity level was measured using the Physical Activity Scale for the Elderly (PASE).<sup>23</sup> Frequency and duration of leisure activities, work (hours per week), and housework and similar duties (yes or no) over the previous week were recorded for each participant. The PASE score was computed by multiplying the amount of time spent in each activity (hours per week) in each activity by empirical item weights and summing over all activities. PASE measurements were categorised as low (0–99), middle (100–249), and high ( $\geq 250$ ). Measurements of participants' height and weight were obtained using a stadiometer (Seca Corporation, Hanover, MD, USA) and digital scale (Tanita, Arlington Heights, IL, USA), respectively. Body-mass index (BMI) was calculated by dividing measured weight (kg) by the square of measured height ( $m^2$ ). Information about dietary habits was obtained by survey in participants' homes using the Block food frequency questionnaire.<sup>24</sup>

Smoking was determined using data from in-person interviews; the questionnaires assessed whether men had smoked at least 100 cigarettes in their lifetime and whether they were currently smoking. Smoking status was defined as current smoker (smoked  $>100$  cigarettes and currently a smoker), never smokers (smoked



**Figure 1: Population and concentrations of fine air particulate pollution in the northeast-mid-Atlantic USA**

Medicare population by zip code (A) and average  $PM_{2.5}$  concentrations per zip code between 2003 and 2010 (B).  $PM_{2.5}$ =fine particulate matter less than 2.5  $\mu m$ .



	Total	Women	Men
Number of Medicare beneficiaries	9 271 035	5 192 340	4 079 695
Number of hospital admissions, 2003–10	763 630	449 105	314 525
Risk ratio (95% CI)			
PM <sub>2.5</sub>	1.041 (1.030 to 1.051)	1.046 (1.036 to 1.056)	1.037 (1.027 to 1.047)
Percentage white, non-Hispanic	1.045 (1.038 to 1.052)	1.044 (1.037 to 1.051)	1.045 (1.036 to 1.054)
Percentage high school graduate	1.035 (0.998 to 1.072)	1.037 (0.998 to 1.076)	1.033 (0.996 to 1.070)
Median income	0.998 (0.992 to 1.004)	0.997 (0.995 to 0.999)	0.996 (0.991 to 1.006)
Percentage obese	0.973 (0.935 to 1.011)	0.974 (0.935 to 1.013)	0.972 (0.936 to 1.008)
Percentage female	1.087 (1.047 to 1.127)	..	..
Percentage of population aged 75 years or older <sup>§</sup>	1.096 (1.087 to 1.105)	1.097 (1.088 to 1.106)	1.095 (1.086 to 1.104)
Number of days below 0°C	1.011 (1.010 to 1.011)	1.011 (1.010 to 1.011)	1.011 (1.010 to 1.011)
Urban (vs rural) <sup>¶</sup>	0.998 (0.925 to 1.071)	0.998 (0.928 to 1.068)	0.998 (0.925 to 1.071)

\*Osteoporotic-related fractures include all hospital admissions with a primary diagnosis of hip, wrist, spine, and pelvis fractures only. †Estimated risk of hospital admissions of Medicare enrollees with a primary diagnosis of bone fracture associated with 1 IQR (4.18 µg/m<sup>3</sup>) increase in 1-year average concentrations of fine particulate matter less than 2.5 µm (PM<sub>2.5</sub>) across 3974 zip code areas in the northeast-mid-Atlantic area of the USA in the period 2003–10; adjusted estimates of each variable are presented. ‡Regression models also included indicator variables for year of hospital admission and state of residence, in addition to all the other independent variables listed. §In each zip code, age was reported in the Medicare data as the percentage of the population aged 65–74 years and the percentage aged 75 years or older. ¶Rural areas included large, small, and isolated rural categories.

**Table 1: Risk of hospital admissions by osteoporotic-related\* bone fractures associated with 1-year average concentrations of PM<sub>2.5</sub>†‡ in the Medicare analysis**

<100 cigarettes lifetime and not currently smoking), or former smokers (smoked >100 cigarettes lifetime and currently not smoking). In the case of former and current smokers, questions were administered to determine the usual number of cigarettes smoked per day and for how many years they had smoked; then, pack-years of smoking were calculated by multiplying the number of packs (20 cigarettes in one pack) smoked per day by the number of years smoked. Additional information about the BACH/Bone cohort has been published previously.<sup>22,25</sup>

We measured serum bio-intact parathyroid hormone, serum calcium at baseline, and serum 25(OH)D (ie, 25(OH)D<sub>2</sub>+25(OH)D<sub>3</sub>), as previously described.<sup>26</sup> Trained and certified technicians measured bone mineral density at both baseline and follow-up at five different locations (femoral neck, total hip, lumbar spine [L1–L4], distal radius, ultradistal radius) with dual-energy x-ray absorptiometry (DXA) using a Hologic/QDR4500W densitometer (Hologic Inc, Waltham, MA, USA). To facilitate study operations, and in consideration of the 6-year lag between the baseline and follow-up measure, we did not require the same technician to do the two bone mineral density scans on each participant. However, all technicians were specifically trained and certified to use standardised procedures to reduce between-operator variability. Unfortunately, no measures of operator variability were collected. However, the total variability was very small: indeed, to reduce technical variability in bone mineral density measurements, the DXA system was monitored weekly for drift and the coefficient of variations for bone mineral density were less than 1.5%. We calculated annualised changes in bone mineral density between baseline and follow-up scans, and we calculated annualised change in percentage from the difference between the first and last measurement.

Examinations, including in-person interviews, questionnaires, anthropometries, and blood draws were done at the BUSM-General Clinical Research Unit.

To estimate PM<sub>2.5</sub> concentrations, we used the same spatiotemporal hybrid modelling approach<sup>20</sup> described for the Medicare analysis, but using a 1×1 km model instead of zip code areas, which allowed more precise data about exposure.<sup>20</sup> Due to the unavailability of 1×1 km satellite data before 2003, PM<sub>2.5</sub> predictions could be obtained—as an annual average—only for participants with baseline visits in 2004–05 (ie, only 282 of the total 692 participants). We obtained finer-scale and more complete (n=692) estimates of particle concentrations by calculating concentrations of black carbon—a measure of particulate matter from vehicular traffic emissions and the dominant type of particulate matter in urban areas—using a validated spatiotemporal land-use regression model that provided daily estimates of black carbon concentrations throughout the greater Boston area since 1995, as previously reported.<sup>27</sup> To capture large local variability of vehicular traffic particles, the black carbon model generated estimates for each individual address rather than for grid cells. We calculated 1-year averages of PM<sub>2.5</sub> and black carbon at baseline using 365 daily estimates for each participant using their residential address before the date of their baseline bone mineral density assessment.

#### Statistical analysis

We used linear regression to estimate the association of long-term PM<sub>2.5</sub> and black carbon concentrations (1-year average PM<sub>2.5</sub> and black carbon concentrations before bone mineral density measurement) with baseline parathyroid hormone, calcium, and serum 25(OH)D

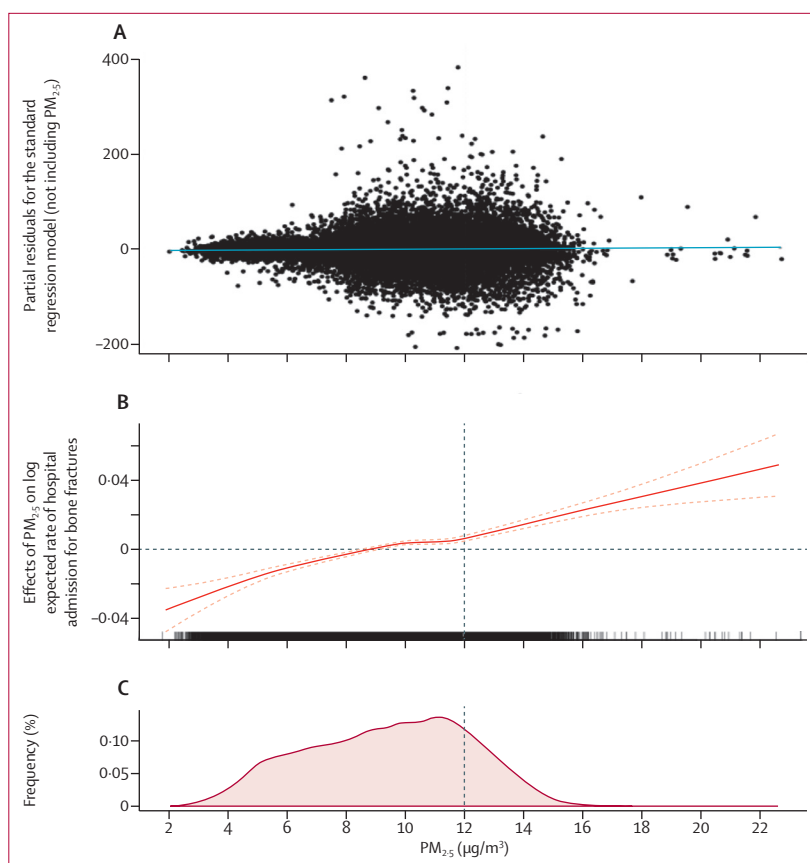
concentrations. We used three sets of models: unadjusted; adjusted for age, race, and height; and adjusted for age, race, height, smoking, per-capita household income, physical activity, caffeine consumption, and weight. We used similar sets of linear regression models to evaluate the association of baseline  $PM_{2.5}$  and black carbon concentrations (1-year average) with change in bone mineral density between baseline and approximately 8-year examinations.<sup>28</sup> We rescaled the effect estimate to percent change to facilitate comparison of results with previous studies.<sup>29,30</sup> SUDAAN software (RTI International, Research Triangle Park, NC, USA) was used for all analyses. Observations were weighted inversely to their probability of selection at baseline. Weights were also adjusted for non-response bias at the follow-up assessment and post-stratified to the Boston census population in 2000 (appendix p 8). The multivariate imputation by chained equations (MICE) algorithm in R was used to impute missing data,<sup>31</sup> taking into account the complex survey sampling design and maintaining the observed relationships in the data. MICE imputes missing values with estimated predictions from regression models and 15 datasets were multiply imputed and used for analysis.<sup>32,33</sup> Imputed missing data were less than 5% per variable.  $p < 0.05$  was considered significant.

### Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

In the Medicare analysis, the area included in the analysis had a total population of 62 million, of which about 9.2 million (about 15%) were Medicare beneficiaries. Characteristics of zip code areas are in the appendix (p 8). From 2003 to 2010, 763 630 Medicare beneficiaries were admitted with a primary diagnosis of osteoporosis-related bone fracture. Communities with higher annual  $PM_{2.5}$  concentrations had higher rates of bone fracture admissions in analyses controlling for relevant covariates. One IQR (4.18  $\mu\text{g}/\text{m}^3$ ) increase in  $PM_{2.5}$  was associated with a 4.1% (risk ratio [RR] 1.041, 95% CI 1.030 to 1.051;  $p=0.0001$ ) higher rate of hospital admission for bone fracture (table 1) in models adjusted for sociodemographic variables, geographical characteristics, obesity, number of days with freezing temperatures ( $<0^\circ\text{C}$ ), and calendar year. A plot of the corresponding partial residuals obtained from a model controlling for all covariates except  $PM_{2.5}$  demonstrated a subtle, near-linear covariate-adjusted association between  $PM_{2.5}$  and rates of bone fracture admissions (figure 2). The plot also showed that there remained substantial variability in bone fracture admission rates. Using a regression spline to fit  $PM_{2.5}$  concentration in the multivariable-adjusted regression model, we



**Figure 2: Long-term exposure to  $PM_{2.5}$  and risk of hospital admission for bone fractures**

(A) Scatter plot of the multivariable-adjusted residuals from the standard regression model (not including  $PM_{2.5}$ ) versus level of exposure to fine particulate matter less than  $2.5 \mu\text{m}$  ( $PM_{2.5}$ ). Blue line corresponds to zero partial residual value. (B) Spline for the multivariable-adjusted association between  $PM_{2.5}$  exposure and number of hospital admissions of Medicare enrollees per zip code, from 2003 to 2010. Horizontal dotted line represents zero effect. (C) Density plot of exposure to  $PM_{2.5}$  in the Medicare analysis. The vertical dotted line in B and C represents the primary annual  $PM_{2.5}$  standard of  $12 \mu\text{g}/\text{m}^3$  mandated by the US Environmental Protection Agency.

confirmed that the relationship between  $PM_{2.5}$  and rates of bone fractures was nearly linear across the entire range of  $PM_{2.5}$  concentrations (3–22  $\mu\text{g}/\text{m}^3$ ; figure 2). The associations of  $PM_{2.5}$  with bone fractures were robust and stable across six alternative regression models including different sets of covariates (appendix p 9). Risk ratios were similar between women (RR 1.046, 95% CI 1.036 to 1.056;  $p=0.0002$ ) and men (RR 1.037, 1.027 to 1.047;  $p=0.0008$ ; table 1). The association of  $PM_{2.5}$  with bone fracture admission rates was higher among those communities in the lowest obesity rate quartile (RR 1.105, 95% CI 1.080 to 1.129;  $p=0.0007$ ) compared with those with highest obesity rates (RR 1.038, 0.763 to 1.312;  $p=0.13$ ;  $p_{\text{interaction}}=0.011$ ). The effect modification by socioeconomic variables (percentage of population with high school level per zip code and median income per zip code), percentage of population white, non-Hispanic per zip code, and percentage of obesity per zip code, on the association between long-term  $PM_{2.5}$  and hospital admissions by bone fractures are shown in table 2.

	Risk ratio (95% CI)	P <sub>interaction</sub>
Percentage of population with high school level per zip code*	..	0.0008
1st quartile (7.31–25.52)	1.046 (1.023 to 1.070)	..
2nd quartile (25.53–32.21)	1.097 (1.075 to 1.118)	..
3rd quartile (32.22–38.32)	1.017 (0.988 to 1.046)	..
4th quartile (39.33–99.90)	1.067 (1.044 to 1.091)	..
Median income per zip code†	..	0.0003
1st quartile (19 230–37 280)	1.076 (1.052 to 1.100)	..
2nd quartile (37 290–48 650)	1.105 (1.084 to 1.126)	..
3rd quartile (48 660–61 830)	1.125 (1.102 to 1.149)	..
4th quartile (61 840–200 010)	0.937 (0.906 to 0.968)	..
Percentage of population white, non-Hispanic per zip code‡	..	0.0001
1st quartile (2.76–84.28)	1.099 (1.077 to 1.121)	..
2nd quartile (84.29–94.38)	0.944 (0.918 to 0.971)	..
3rd quartile (94.39–97.33)	1.102 (1.070 to 1.130)	..
4th quartile (97.34–100.00)	1.109 (1.089 to 1.130)	..
Percentage of obesity per zip code§	..	0.011
1st quartile (13.80–22.70)	1.105 (1.080 to 1.129)	..
2nd quartile (22.71–25.50)	1.118 (1.095 to 1.140)	..
3rd quartile (25.51–27.80)	0.968 (0.698 to 1.238)	..
4th quartile (27.81–35.60)	1.038 (0.763 to 1.312)	..

\* Adjusted by all variables included in table 1, except percentage of population with high school level per zip code.  
 † Adjusted by all variables included in table 1, except median income per zip code. ‡ Adjusted by all variables included in table 1, except percentage of population white, non-Hispanic per zip code. § Adjusted by all variables included in table 1, except percentage of obesity per zip code.

**Table 2: Risk of hospital admissions by osteoporosis-related bone fracture associated with PM<sub>2.5</sub> concentrations in each quartile of socioeconomic status, race, and obesity in the Medicare analysis**

Participants in the BACH/Bone study included men aged 30–79 years, including 523 (66.9%) participants with annual household income less than US\$30 000 and 274 (39.6%) who were white. We present additional characteristics of the participants at baseline, including bone mineral density, PM<sub>2.5</sub>, and black carbon concentrations in table 3. Participants living in locations with higher concentrations of black carbon had lower concentrations of serum parathyroid hormone ( $\beta=-1.16$ , 95% CI  $-1.93$  to  $-0.38$ ,  $p=0.004$  in the fully adjusted model for 1 IQR increase [ $0.106 \mu\text{g}/\text{m}^3$ ] in the 1-year average of black carbon concentrations). PM<sub>2.5</sub> also showed a negative association with serum parathyroid concentrations ( $\beta$  estimate= $-7.39$ , 95% CI  $-14.17$  to  $-0.61$ ,  $p=0.03$  in the fully adjusted model for 1 IQR [ $2.18 \mu\text{g}/\text{m}^3$ ] increase in the 1-year average of PM<sub>2.5</sub> concentrations). Black carbon and PM<sub>2.5</sub> concentrations were not associated with serum calcium or serum 25(OH) D concentrations and results were robust across alternative regression models (table 4).

At baseline, bone mineral density measures of the BACH/Bone study participants were not associated with PM<sub>2.5</sub> or black carbon concentrations at their residential address (table 5). During the 8-year follow-up, participants living at locations with higher concentrations of ambient particles, particularly black carbon concentrations, showed higher loss of bone mineral density at multiple anatomical

	n (%) or mean (SE)
Age (years)	
<40	139 (29.0%)
40–49	206 (31.7%)
50–59	183 (20.1%)
≥60	164 (19.2%)
Race	
Black	214 (30.9%)
Hispanic	204 (29.5%)
White	274 (39.6%)
Annual household income	
<US\$6000	146 (12.8%)
US\$6000–29 999	377 (54.1%)
≥US\$30 000	169 (33.1%)
Smoking	
Never	301 (47.3%)
Former	196 (28.3%)
Current	195 (24.4%)
Physical activity (PASE score)	
Low (0–99 units)	191 (24.9%)
Middle (100–249 units)	348 (51.2%)
High (>250 units)	153 (23.9%)
Dietary caffeine intake (mg/day)	
≤43.5	177 (24.7%)
43.5–164.5	169 (25.1%)
164.6–325.0	171 (25.1%)
>325.1	175 (25.0%)
Height (cm)	175.64 (0.35)
Weight (kg)	88.13 (0.82)
Serum 25(OH)D (ng/mL)	33.15 (0.80)
Parathyroid hormone (pg/mL)	28.91 (0.63)
Serum calcium (mg/dL)	9.42 (0.02)
PM <sub>2.5</sub> 1-year average ( $\mu\text{g}/\text{m}^3$ )*	11.65 (0.05)
Black carbon 1-year average ( $\mu\text{g}/\text{m}^3$ )†	0.77 (0.01)
Bone mineral density at baseline ( $\text{g}/\text{cm}^2$ )	
Femoral neck	0.88 (0.01)
Ultradistal radius	0.53 (0.004)
One-third distal radius	0.77 (0.004)
Total hip	1.03 (0.01)
L1–L4 lumbar vertebrae	1.05 (0.01)
Annualised change in bone mineral density, baseline to follow-up (%)	
Femoral neck	-1.14% (0.03)
Ultradistal radius	-0.56% (0.04)
One-third distal radius	0.26% (0.03)
Total hip	-0.29% (0.03)
L1–L4 lumbar vertebrae	0.10% (0.038)

25(OH)D=25-hydroxyvitamin D. PM<sub>2.5</sub>=fine particulate matter less than 2.5  $\mu\text{m}$ . PASE=Physical Activity Scale for the Elderly. \*Available only for 282 middle-aged, low-income men. †Available for 692 middle-aged, low-income men.

**Table 3: Demographic, physical, and clinical characteristics at baseline in the BACH/Bone study cohort**

sites (table 6). For each 1 IQR ( $0.106 \mu\text{g}/\text{m}^3$ ) increase in 1-year black carbon concentration at baseline, participants had a 0.08% per year (95% CI  $-0.14$  to  $-0.02$ ;  $p=0.009$ ) decrease in femoral neck bone mineral density and 0.06% per year ( $-0.12$  to  $-0.01$ ;  $p=0.04$ ) decrease in ultradistal radius bone mineral density in fully adjusted models, equivalent to 3914 cases per year attributable to  $\text{PM}_{2.5}$ . Bone mineral density showed non-significant negative associations at one-third distal radius, total hip, and L1–L4 vertebrae (table 6). Associations remained robust across alternative regression models (table 6) and relatively linear despite some non-influential outliers (appendix p 10). In the subset of participants with available  $\text{PM}_{2.5}$  data ( $n=282$ ), 1-year average  $\text{PM}_{2.5}$  concentrations at baseline were negatively, but non-significantly, associated with changes in bone mineral density for most anatomical sites evaluated (table 6).

## Discussion

In our analysis of approximately 9.2 million Medicare beneficiaries, we found evidence of an association between  $\text{PM}_{2.5}$  concentrations and rates of hospital admissions for bone fractures, independent of sex and community-level confounding factors.  $\text{PM}_{2.5}$  associations were stronger in communities with lower income, despite a protective influence of obesity rates. This result suggests that per each  $4.18 \mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$ , there is a 4.1% higher rate of hospital admission for bone fractures in older individuals. In the prospective BACH/Bone study of middle-aged, low-income men, we also found that participants living at addresses with higher concentrations of  $\text{PM}_{2.5}$  and black carbon exhibited lower serum parathyroid hormone concentrations. Black carbon was associated with decreases in bone mineral density over 8 years of follow-up. These findings indicate poor air quality as a possible risk factor for bone mineral density loss and fractures in older individuals, which might disproportionately affect low-income men. Reducing emissions as a result of innovation in technologies or policy changes in emission standards of this modifiable risk factor might reduce the impact of air pollution on bone fractures and osteoporosis.

Air particles might, directly or indirectly, impact bone biology and increase bone mineral loss. Air pollution particles have high potential to cause systemic oxidative damage<sup>34</sup> and inflammation,<sup>17</sup> both of which are established mechanisms for bone demineralisation and osteoporosis.<sup>35</sup> Tobacco smoke, which includes several chemo-physical components found in particulate matter, causes bone mineral loss in animal experiments<sup>36</sup> and has been associated with higher risk of bone fractures and increased bone mineral loss in studies of human beings.<sup>19</sup> Parathyroid hormone concentrations are also significantly lower in smokers<sup>37,38</sup> and return to non-smoking concentrations after smoking cessation.<sup>38</sup> Such parathyroid hormone alteration might represent an adaptive response to smoking-induced calcium mobilisation from bone.<sup>38</sup>

	Estimate unadjusted (95% CI)	Estimate adjusted for age, race, and height (95% CI)	Estimate fully adjusted† (95% CI)
<b><math>\text{PM}_{2.5}</math></b>			
Parathyroid hormone	-5.69 (-13.73 to 2.40)	-6.00 (-13.78 to 1.77)	-7.39 (-14.17 to -0.61)
Serum 25(OH)D	4.51 (-6.13 to 15.13)	1.16 (-7.76 to 10.05)	2.90 (-6.21 to 12.03)
Serum calcium	0.13 (-0.09 to 0.327)	0.13 (-0.07 to 0.33)	0.13 (-0.07 to 0.33)
<b>Black carbon</b>			
Parathyroid hormone	-1.29 (-2.05 to -0.53)	-1.32 (-2.23 to -0.42)	-1.16 (-1.93 to -0.38)
Serum 25(OH)D	0.63 (-0.31 to 1.58)	0.21 (-0.75 to 1.17)	0.27 (-0.69 to 1.22)
Serum calcium	0.01 (-0.01 to 0.04)	0.01 (-0.01 to 0.04)	0.01 (-0.01 to 0.04)

Estimates are coefficients.  $\text{PM}_{2.5}$ =fine particulate matter less than  $2.5 \mu\text{m}$ . 25(OH)D=25-hydroxyvitamin D. \*Regression coefficients for the association between 1 IQR increase in the baseline 1-year average of  $\text{PM}_{2.5}$  ( $2.18 \mu\text{g}/\text{m}^3$ ,  $n=282$ ) or black carbon ( $0.106 \mu\text{g}/\text{m}^3$ ,  $n=692$ ) concentrations and calcium homeostasis biomarkers (parathyroid hormone, serum vitamin D, and serum calcium). †Adjusted for age, race, height, weight, smoking, per-capita household income, physical activity, C-reactive protein, and caffeine consumption.

**Table 4: Association of long-term  $\text{PM}_{2.5}$  and black carbon with calcium homeostasis biomarkers in the BACH/Bone study\***

Our findings suggest that similar mechanisms might also be activated in response to particulate matter. Similarities between particulate matter and smoking might also suggest a potential role of renal calcium handling,<sup>39,40</sup> but unfortunately no data about renal calcium were available in the BACH/Bone cohort.

Very few studies have investigated the association of air pollution concentrations with bone health and bone fractures. A cross-sectional study of 5976 middle-aged and older individuals living in Norway (15.23% with forearm fractures, about 910 cases) described an association of long-term  $\text{PM}_{2.5}$  concentrations with the prevalence of self-reported forearm fractures after the age of 50 years, but the association was evident only among male smokers.<sup>41</sup> A previous study of 590 men aged 75–76 years showed a cross-sectional correlation of long-term  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$  concentrations with lower total body bone mineral density.<sup>42</sup> Previous studies have also reported higher rates of bone fractures and age-related osteoporosis in urban areas compared with rural regions.<sup>43,44</sup> For example, urban women have a 29% higher relative risk of forearm fracture and lower bone mineral density compared with women in rural areas.<sup>45</sup> Our Medicare analysis controlled for urban and rural locations. It is possible that our study is prone to residual confounding. However, considering the consistency between different models (appendix p 9), it is unlikely the observed association of particulate matter on hospital admissions by bone fractures reflects confounding due to lifestyle or other socioeconomic differences between urban and rural areas. We used yearly counts of admissions for each zip code area and specified a Poisson distribution. We applied generalised mixed models because we have counts for each zip code and then we included a random intercept for zip code to take into account the characteristics of each zip code. By using this Poisson regression, we accounted for temporal variation of counts by year and for the spatial variation with the zip code level. We did not evaluate daily time series because we were interested in

Estimates, fully adjusted† (95% CI)	
<b>PM<sub>2.5</sub></b>	
Femoral neck	0.262% (-0.044 to 0.094)
Ultradistal radius	0.017% (-0.050 to 0.085)
One-third distal radius	0.022% (-0.052 to 0.096)
Total hip	0.031% (-0.001 to 0.061)
L1-L4 lumbar vertebrae	0.011% (-0.020 to 0.039)
<b>Black carbon</b>	
Femoral neck	-0.001% (-0.007 to 0.009)
Ultradistal radius	-0.001% (-0.009 to 0.008)
One-third distal radius	-0.003% (-0.006 to 0.011)
Total hip	-0.001% (-0.003 to 0.004)
L1-L4 lumbar vertebrae	-0.001% (-0.004 to 0.004)

Estimates are coefficients. PM<sub>2.5</sub>=fine particulate matter less than 2.5 µm.  
 \*Regression coefficients for the association between a baseline 1 IQR increase in the 1-year average of PM<sub>2.5</sub> (2.18 µg/m<sup>3</sup>, n=282) and black carbon concentrations (0.106 µg/m<sup>3</sup>, n=692) and baseline bone mineral density in five anatomical sites in the BACH/Bone study cohort (n=692). †Adjusted for age, race, height, smoking, household income, physical activity, caffeine consumption, weight, and serum 25-hydroxyvitamin D concentration.

**Table 5: Estimated effects of PM<sub>2.5</sub> and black carbon concentrations on bone mineral density at baseline in the BACH/Bone study\***

	Percentage change unadjusted (95% CI)	Percentage change adjusted for age, race, and height (95% CI)	Percentage change fully adjusted† (95% CI)
<b>PM<sub>2.5</sub></b>			
Femoral neck	-0.09% (-0.44 to 0.26)	-0.13% (-0.50 to 0.22)	-0.13% (-0.52 to 0.26)
Ultradistal radius	0.22% (-0.20 to 0.63)	0.17% (-0.24 to 0.59)	0.22% (-0.20 to 0.63)
One-third distal radius	-0.07% (-0.37 to 0.22)	-0.09% (-0.37 to 0.22)	-0.04% (-0.35 to 0.24)
Total hip	-0.13% (-0.48 to 0.20)	-0.17% (-0.52 to 0.20)	-0.22% (-0.61 to 0.17)
L1-L4 lumbar vertebrae	-0.20% (-0.52 to 0.13)	-0.17% (-0.52 to 0.17)	-0.17% (-0.52 to 0.15)
<b>Black carbon</b>			
Femoral neck	-0.08% (-0.14 to -0.02)	-0.08% (-0.14 to -0.02)	-0.08% (-0.14 to -0.02)
Ultradistal radius	-0.06% (-0.11 to 0.01)	-0.06% (-0.11 to 0.01)	-0.06% (-0.12 to -0.01)
One-third distal radius	-0.03% (-0.07 to 0.01)	-0.03% (-0.07 to 0.01)	-0.03% (-0.07 to 0.01)
Total hip	-0.04% (-0.08 to 0.01)	-0.04% (-0.08 to 0.01)	-0.03% (-0.08 to 0.01)
L1-L4 lumbar vertebrae	-0.04% (-0.10 to 0.02)	-0.05% (-0.10 to 0.01)	-0.04% (-0.09 to 0.01)

PM<sub>2.5</sub>=fine particulate matter less than 2.5 µm. \*Annualised percentage change in bone mineral density at five anatomical sites, from 2002-05 to 2010-12, associated with 1 IQR increase in 1-year average exposure to PM<sub>2.5</sub> (2.18 µg/m<sup>3</sup>, n=282) and black carbon concentrations (0.106 µg/m<sup>3</sup>, n=692). †Adjusted for age, race, height, weight, smoking, per-capita household income, physical activity, caffeine consumption, C-reactive protein, and serum 25-hydroxyvitamin D.

**Table 6: Annualised percentage change in bone mineral density associated with PM<sub>2.5</sub> and black carbon exposure in the BACH/Bone study\***

the long-term effect of PM<sub>2.5</sub>. The magnitude of the relative risk we found in the Medicare analysis is similar to the very well established associations between air pollution and other health outcomes (eg, myocardial infarction, stroke, and total mortality).<sup>46</sup> Indeed, air pollution is considered a weak, but universal risk factor; therefore, it causes a proportionally higher number of attributable cases than other risk factors with higher relative risks but lower frequency.<sup>47</sup>

Several epidemiological studies have shown that socioeconomic factors, race,<sup>48,49</sup> and obesity<sup>50-52</sup> are related to bone mineral density. Low socioeconomic status has been associated with 25(OH)D insufficiency, higher concentrations of parathyroid hormone, lower values of bone mineral density, and a higher prevalence of fragility fractures.<sup>53</sup> Also, despite lower serum 25(OH)D concentrations and dietary calcium intake, African Americans have higher bone mineral density and develop osteoporosis less frequently than do European Americans.<sup>54</sup> Our Medicare analysis showed a significant interaction of socioeconomic variables (education and income), but also of race and obesity, confirming those previous factors. For example, we found that the association of PM<sub>2.5</sub> exposure with bone fracture admission rates was higher among those communities in the lowest obesity rate quartile compared with those with the highest obesity rates, suggesting a protective influence of obesity rates.

During the 8-year follow-up in the BACH/Bone study, middle-aged, low-income men living at locations with higher concentrations of black carbon had larger annualised decreases in bone mineral density. Black carbon, a major component of fine particles measured by PM<sub>2.5</sub>, is a tracer of particles from traffic and might share different toxicological properties compared with other components of particulate matter. Therefore, our results indicate that particles from traffic are crucial contributors to decreased bone health. PM<sub>2.5</sub> concentrations showed only weak and non-significant associations with both annualised changes in bone mineral density and serum parathyroid hormone concentrations. However, the PM<sub>2.5</sub> analysis included only about 40% of the BACH/Bone participants due to unavailability of PM<sub>2.5</sub> model predictions in the early years of the study. Lack of significance could be attributable to the lower number of middle-aged, low-income men—compared with the black carbon analysis—with long-term PM<sub>2.5</sub> data, but this result has the potential of selection bias for lack of data in the full BACH/Bone cohort. In the BACH/Bone study, we did not observe an association between long-term black carbon exposure and bone mineral density at baseline, but we found associations with yearly change between baseline and follow-up bone mineral density in the cross-sectional analysis. Lack of association in the cross-sectional analysis of 1-year average black carbon exposure and bone mineral density at baseline might indicate that individuals are less susceptible to black carbon at a younger age and, consequently, effects were observed only as participants aged during the follow-up analysis.<sup>55</sup>

We observed a negative association between long-term black carbon exposure and reduction in femoral neck and ultradistal radius bone mineral density. Although non-significant, negative associations between black carbon and one-third distal radius, total hip, and lumbar vertebral bone mineral density were also observed. Our study is consistent with the finding that air pollution



contributes to bone health impairment reported by different groups.<sup>42,56–58</sup> Chen and colleagues<sup>58</sup> showed that traffic-related exposure was associated with lower body bone mineral density. Also, Chang and colleagues<sup>57</sup> found an association between air pollution (carbon monoxide and nitrogen dioxide) and increased risk of osteoporosis. The difference in observed associations across multiple anatomical sites might be explained by differential anatomical susceptibility to the effects of particulate matter on bones.<sup>59</sup> Alvaer and colleagues<sup>42</sup> reported sex differences in the association between air pollution and bone mineral density, with an association observed only for men. However, our finding from the Medicare analysis suggested that the impacts of ambient particulate air pollution on bone health might not be different between men and women. The difference in conclusion and findings between our study and the Oslo Health Study might be explained by age differences of the participants. This finding suggests that the potential adverse consequences of ambient particulate air pollution on bone health might be similar in men and women.

The two studies reported in this paper have notable limitations. The Medicare analysis used an ecological design and has limited capability of establishing causality. The analysis was done at zip code level and does not allow for evaluating the association of long-term PM<sub>2.5</sub> exposure with hospital admissions at the individual level. To avoid the potential ecological fallacy,<sup>60</sup> we complemented the Medicare analysis with the BACH/Bone study to investigate the impact of individual-level environmental risk factors on bone health. However, the Medicare analysis included a large number of hospital admissions for osteoporotic-related bone fractures in older individuals, over a large and heterogeneous geographical region in the USA. The Medicare analysis might also be subject to selection bias, which is always a concern in observational studies. However, all individuals aged 65 years or older are encouraged to enrol in the free Medicare programme. Based on the enrolment criteria of Medicare beneficiaries, we assume that the Medicare enrollees are representative of the ageing population in the northeast-mid-Atlantic USA. We acknowledge a major limitation in that the hospital admission data were not validated, therefore we cannot exclude coding errors. However, based on study operations, misclassification is unlikely to be differential in areas with low and high particulate matter concentrations. Therefore, coding errors are likely to result by non-differential measurement error, and are expected to bias the association towards the null rather than producing the observed associations. Furthermore, although our Medicare analysis was adjusted for risk factors of fractures at the zip code level, there are other known risk factors for falls and bone fractures that were not available from Medicare data. However, most factors were accounted for at the individual level in the BACH/Bone study. Therefore, combining the two studies

limits concerns about population-level analysis and bias from known confounders.

We acknowledge that the analysis done in the BACH/Bone study has several limitations due to moderate sample size and lack of generalisability, given that the cohort included 692 men only. However, to the best of our knowledge, only one study has reported the association between particulate matter exposure and bone fractures.<sup>41</sup> Nonetheless, the BACH/Bone study is distinctly unique because of the prospective bone mineral density assessment at two timepoints. Furthermore, in the Medicare analysis, we found similar associations of PM<sub>2.5</sub> with bone fracture rates in both men and women, which strengthened and complemented the findings from the BACH/Bone study. However, we assigned the closest particulate matter exposure available both in the Medicare study as in the BACH/Bone study but long-term particulate matter exposure was not directly measured and no personal data were available. Also, our results could be influenced by other unmeasured individual factors, such as ultraviolet exposure or calcium intake, among others, that can modify bone health and that were not evaluated here. Likewise, although our models used specifically concentrations of PM<sub>2.5</sub> (for the Medicare study and for a subset of participants in the BACH/Bone study) and black carbon (for the BACH/Bone study), we cannot exclude that the effect we observed might be mediated by other air pollutants or by the combination of them. Additionally, the DXA-based bone mineral density measures used might not detect microstructural alterations that are not readily apparent. Therefore, bone mineral density might fail to fully capture alterations related to bone health.<sup>61</sup> We also acknowledge potential misclassification, especially in the BACH/Bone study, but this is likely to be non-differential (ie, the measurement error of exposure in the BACH/Bone study is unlikely to be dependent on bone mineral density status), therefore it is expected to bias our results towards the null. Other air pollutants such as carbon monoxide and nitrogen dioxide have been previously associated with bone loss and osteoporosis.<sup>42,57</sup> Unfortunately, we did not have access to carbon monoxide and nitrogen dioxide exposure data for the Medicare study nor for the BACH/Bone study, limiting our capability to explore these associations. Further analyses to evaluate the role of PM<sub>2.5</sub> and black carbon, as well as of carbon monoxide and nitrogen dioxide on bone health are warranted. Finally, although we have adjusted for multiple potential confounders (smoking, race, physical activity, and income) in the BACH/Bone study, our results might not be sufficient to rule out selection bias, especially in the PM<sub>2.5</sub> model in which the number of participants was low.

We found evidence of an association between air particle concentrations and increased rates of hospital admissions for bone fractures in older Medicare

beneficiaries, particularly in low-income communities. In the BACH/Bone study follow-up of middle-aged low-income men, participants living in areas with higher air particle concentrations had lower serum parathyroid hormone concentrations and reductions in bone mineral density. All associations were linear and observed—at least for part of the PM<sub>2.5</sub> distribution—at PM<sub>2.5</sub> concentrations below the annual average limits set by the US Environmental Protection Agency (12 µg/m<sup>3</sup>) and the European Union (25 µg/m<sup>3</sup>),<sup>62</sup> as well by other countries, such as China (40 µg/m<sup>3</sup>)<sup>63</sup> and Japan (15 µg/m<sup>3</sup>).<sup>64</sup> Our findings support an association between long-term exposure to particulate air pollution and reduced bone health, particularly among low-income older individuals. Improvements in particulate air pollution concentrations could contribute to substantial better bone health, prevent bone fractures, and reduce the health costs associated with fractures, particularly in elderly and low-income populations.

#### Contributors

DP, JZ, BB, and AAB contributed to the design of the Medicare study and the BACH/Bone study analysis. DP, EC, AZ, and JS contributed to the statistical modelling for the Medicare study, as well as obtaining Medicare data. ND, SCF, and BB contributed to the statistical modelling for the BACH/Bone study. IK, AZ, and JS contributed to the modelling of particulate matter and black carbon exposures for the Medicare and the BACH/Bone study. DP ran the statistical models for the Medicare study. ND ran the statistical models for the BACH/Bone study. DP, JMZ, MH, LAH, LH, FD, and AAB contributed to the design of the integration of both cohorts and contributed actively to the discussion of results and its interpretation. DP, AZ, BB, JZ, EC, FD, and AAB also contributed to the discussion of results. BB was the principal investigator for the BACH/Bone cohort and AAB was the principal investigator for the Medicare study. DP and JZ wrote the manuscript and the revisions.

#### Declaration of interests

We declare no competing interests.

#### Acknowledgments

This work was supported by the National Institutes of Health, Institute on Aging (R01AG020727), National Institute of Environmental Health Sciences (R01ES02173 and R01ES00002 to AAB, R01ES05172 to JS), and the US Environmental Protection Agency (RD-83479801 to JS). DP was financially supported by Consejo Nacional de Ciencia y Tecnología (CONACYT) and the Fundación México en Harvard. The authors are thankful to Douglas Dockery for helpful discussions of the study findings and insightful advice and to Cheng Peng for assistance with figure preparation.

#### References

- Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res* 2007; **22**: 465–75.
- Leibson CL, Tosteson ANA, Gabriel SE, Ransom JE, Melton LJ. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. *J Am Geriatr Soc* 2002; **50**: 1644–50.
- Li Y, Zhang Z, Liu X, et al. miR-124 functions as a tumor suppressor in the endometrial carcinoma cell line HEC-1B partly by suppressing STAT3. *Mol Cell Biochem* 2014; **388**: 219–31.
- Iacono MV. Osteoporosis: a national public health priority. *J Perianesth Nurs* 2007; **22**: 175–80.
- Wilkins CH, Birge SJ. Prevention of osteoporotic fractures in the elderly. *Am J Med* 2005; **118**: 1190–95.
- Peng RD, Chang HH, Bell ML, et al. Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among Medicare patients. *JAMA* 2008; **299**: 2172–79.
- Ye X, Peng L, Kan H, et al. Acute effects of particulate air pollution on the incidence of coronary heart disease in Shanghai, China. *PLoS One* 2016; **11**: e0151119.
- Du Y, Xu X, Chu M, Guo Y, Wang J. Air particulate matter and cardiovascular disease: the epidemiological, biomedical and clinical evidence. *J Thorac Dis* 2016; **8**: E8–19.
- Xing Y-F, Xu Y-H, Shi M-H, Lian Y-X. The impact of PM<sub>2.5</sub> on the human respiratory system. *J Thorac Dis* 2016; **8**: E69–74.
- Franchini M, Mengoli C, Cruciani M, Bonfanti C, Mannucci PM. Association between particulate air pollution and venous thromboembolism: a systematic literature review. *Eur J Intern Med* 2016; **27**: 10–13.
- Di Lorenzo G, Federico P, De Placido S, Buonerba C. Increased risk of bladder cancer in critical areas at high pressure of pollution of the Campania region in Italy: a systematic review. *Crit Rev Oncol Hematol* 2015; **96**: 534–41.
- Li J, Li WX, Bai C, Song Y. Particulate matter-induced epigenetic changes and lung cancer. *Clin Respir J* 2015; published online Sept 25. DOI:10.1111/crj.12389.
- Clifford A, Lang L, Chen R, Anstey KJ, Seaton A. Exposure to air pollution and cognitive functioning across the life course—a systematic literature review. *Environ Res* 2016; **147**: 383–98.
- Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. *Environ Health Perspect* 2010; **119**: 682–87.
- Schikowski T, Vossoughi M, Vierkotter A, et al. Association of air pollution with cognitive functions and its modification by APOE gene variants in elderly women. *Environ Res* 2015; **142**: 10–16.
- Møller P, Loft S. Oxidative damage to DNA and lipids as biomarkers of exposure to air pollution. *Environ Health Perspect* 2010; **118**: 1126–36.
- Bind M-A, Baccarelli A, Zanobetti A, et al. Air pollution and markers of coagulation, inflammation, and endothelial function: associations and epigenome–environment interactions in an elderly cohort. *Epidemiology* 2012; **23**: 332–40.
- Krall EA, Dawson-Hughes B. Smoking and bone loss among postmenopausal women. *J Bone Miner Res* 1991; **6**: 331–38.
- Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. *BMJ* 1997; **315**: 841–46.
- Kloog I, Koutrakis P, Coull BA, Lee HJ, Schwartz J. Assessing temporally and spatially resolved PM<sub>2.5</sub> exposures for epidemiological studies using satellite aerosol optical depth measurements. *Atmos Environ* 2011; **45**: 6267–75.
- Kloog I, Nordio F, Zanobetti A, Coull BA, Koutrakis P, Schwartz JD. Short term effects of particle exposure on hospital admissions in the Mid-Atlantic states: a population estimate. *PLoS One* 2014; **9**: e88578.
- Piccolo RS, Araujo AB, Pearce N, McKinlay JB. Cohort profile: the Boston Area Community Health (BACH) survey. *Int J Epidemiol* 2012; **43**: 42–51.
- Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol* 1993; **46**: 153–62.
- Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol* 1986; **124**: 453–69.
- McKinlay JB, Link CL. Measuring the urologic iceberg: design and implementation of the Boston Area Community Health (BACH) Survey. *Eur Urol* 2007; **52**: 389–96.
- Chen TC, Turner AK, Holick MF. Methods for the determination of the circulating concentration of 25-hydroxyvitamin D. *J Nutr Biochem* 1990; **1**: 315–19.
- Gryparis A, Coull BA, Schwartz J, Suh HH. Semiparametric latent variable regression models for spatiotemporal modelling of mobile source particles in the greater Boston area. *J Royal Stat Soc C* 2007; **56**: 183–209.
- Hannan MT, Litman HJ, Araujo AB, et al. Serum 25-hydroxyvitamin D and bone mineral density in a racially and ethnically diverse group of men. *J Clin Endocrinol Metab* 2008; **93**: 40–46.
- Austin M, Yang Y-C, Vittinghoff E, et al. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Miner Res* 2012; **27**: 687–93.

- 30 Wei RL, Jung BC, Manzano W, et al. Bone mineral density loss in thoracic and lumbar vertebrae following radiation for abdominal cancers. *Radiother Oncol* 2016; **118**: 430–36.
- 31 Bates D, Chambers J, Dalgaard P, et al. R: a language and environment for statistical computing, 2011. [www.r-project.org](http://www.r-project.org). (accessed Jan 1, 2015).
- 32 Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. *J Stat Software* 2011; **45**: 1–67.
- 33 US Census Bureau. Census 2000 summary file 3 (SF 3) 2002. [www.census.gov/prod/www/decennial.html](http://www.census.gov/prod/www/decennial.html) (accessed March 1, 2015).
- 34 Knaapen AM, Borm PJA, Albrecht C, Schins RPF. Inhaled particles and lung cancer. Part A: mechanisms. *Int J Cancer* 2004; **109**: 799–809.
- 35 Smith BJ, Lerner MR, Bu SY, et al. Systemic bone loss and induction of coronary vessel disease in a rat model of chronic inflammation. *Bone* 2006; **38**: 378–86.
- 36 Ajiro Y, Tokuhashi Y, Matsuzaki H, Nakajima S, Ogawa T. Impact of passive smoking on the bones of rats. *Orthopedics* 2010; **33**: 90–95.
- 37 Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Factors associated with elevated or blunted PTH response in vitamin D insufficient adults. *J Intern Med* 2009; **265**: 488–95.
- 38 Jorde R, Saleh F, Figenschau Y, Kamycheva E, Haug E, Sundsfjord J. Serum parathyroid hormone (PTH) levels in smokers and non-smokers. The Fifth Tromsø Study. *Eur J Endocrinol* 2005; **152**: 39–45.
- 39 Tamadon MR, Nassaji M, Ghorbani R. Cigarette smoking and nephrolithiasis in adult individuals. *Nephrourol Mon* 2013; **5**: 702–05.
- 40 Liu C-C, Huang S-P, Wu W-J, et al. The impact of cigarette smoking, alcohol drinking and betel quid chewing on the risk of calcium urolithiasis. *Ann Epidemiol* 2009; **19**: 539–45.
- 41 Alver K, Meyer HE, Falch JA, Sogaard AJ. Outdoor air pollution, bone density and self-reported forearm fracture: the Oslo Health Study. *Osteoporos Int* 2010; **21**: 1751–60.
- 42 Alvaer K, Meyer HE, Falch JA, Nafstad P, Sogaard AJ. Outdoor air pollution and bone mineral density in elderly men—the Oslo Health Study. *Osteoporos Int* 2007; **18**: 1669–74.
- 43 Bjørgul K, Reikerås O. Incidence of hip fracture in southeastern Norway: a study of 1,730 cervical and trochanteric fractures. *Int Orthop* 2007; **31**: 665–69.
- 44 Cooley HM, Jones G. Symptomatic fracture incidence in southern Tasmania: does living in the country reduce your fracture risk? *Osteoporos Int* 2002; **13**: 317–22.
- 45 Omsland TK, Ahmed LA, Grønskog A, et al. More forearm fractures among urban than rural women: the NOREPOS study based on the Tromsø study and the HUNT study. *J Bone Miner Res* 2011; **26**: 850–56.
- 46 Nawrot TS, Perez L, Künzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet* 2011; **377**: 732–40.
- 47 Baccarelli A, Benjamin EJ. Triggers of MI for the individual and in the community. *Lancet* 2011; **377**: 694–96.
- 48 Nam H-S, Kweon S-S, Choi J-S, et al. Racial/ethnic differences in bone mineral density among older women. *J Bone Miner Metab* 2013; **31**: 190–98.
- 49 Nam H-S, Shin M-H, Zmuda JM, et al. Race/ethnic differences in bone mineral densities in older men. *Osteoporos Int* 2010; **21**: 2115–23.
- 50 Douchi T, Yamamoto S, Oki T, et al. Difference in the effect of adiposity on bone density between pre- and postmenopausal women. *Maturitas* 2000; **34**: 261–66.
- 51 Guney E, Kisakol G, Ozgen G, Yilmaz C, Yilmaz R, Kabalak T. Effect of weight loss on bone metabolism: comparison of vertical banded gastroplasty and medical intervention. *Obes Surg* 2003; **13**: 383–88.
- 52 Radak TL. Caloric restriction and calcium's effect on bone metabolism and body composition in overweight and obese premenopausal women. *Nutr Rev* 2004; **62**: 468–81.
- 53 Navarro MDC, Saavedra P, Jódar E, Gómez de Tejada MJ, Mirallave A, Sosa M. Osteoporosis and metabolic syndrome according to socio-economic status, contribution of PTH, vitamin D and body weight: the Canarian Osteoporosis Poverty Study (COPS). *Clin Endocrinol (Oxf)* 2013; **78**: 681–86.
- 54 Freedman BI, Register TC. Effect of race and genetics on vitamin D metabolism, bone and vascular health. *Nat Rev Nephrol* 2012; **8**: 459–66.
- 55 Cashman KD. Diet, nutrition, and bone health. *J Nutr* 2007; **137**: 2507S–512S.
- 56 Meyer HE, Berntsen GKR, Sogaard AJ, et al. Higher bone mineral density in rural compared with urban dwellers: the NOREPOS study. *Am J Epidemiol* 2004; **160**: 1039–46.
- 57 Chang K-H, Chang M-Y, Muo C-H, et al. Exposure to air pollution increases the risk of osteoporosis: a nationwide longitudinal study. *Medicine (Baltimore)* 2015; **94**: e733.
- 58 Chen Z, Salam MT, Karim R, et al. Living near a freeway is associated with lower bone mineral density among Mexican Americans. *Osteoporos Int* 2015; published online Feb 13. DOI:10.1007/s00198-015-3051-z.
- 59 Kanis JA, Odén A, Johnell O, Jónsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. *Osteoporos Int* 2001; **12**: 417–27.
- 60 Piantadosi S, Byar DP, Green SB. The ecological fallacy. *Am J Epidemiol* 1988; **127**: 893–904.
- 61 Fonseca H, Moreira-Gonçalves D, Coriolano H-JA, Duarte JA. Bone quality: the determinants of bone strength and fragility. *Sports Med* 2014; **44**: 37–53.
- 62 Jacquemin B, Siroux V, Sanchez M, et al. Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). *Environ Health Perspect* 2015; **123**: 613–21.
- 63 Department of Environmental Science. Air quality standards, DCE, National Center for Miljo of Energy. June, 2016. [http://www2.dmu.dk/AtmosphericEnvironment/Expost/database/docs/AQ\\_limit\\_values.pdf](http://www2.dmu.dk/AtmosphericEnvironment/Expost/database/docs/AQ_limit_values.pdf) (accessed Aug 7, 2016).
- 64 Miller J. Japan: air quality standards. TransportPolicy.net. February 26, 2016. [http://transportpolicy.net/index.php?title=Japan:\\_Air\\_Quality\\_Standards](http://transportpolicy.net/index.php?title=Japan:_Air_Quality_Standards) (accessed Aug 7, 2016).