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

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CONTRIBUTIONS
DP, JZ, BB, and AB contributed in the designing of the Medicare Study and the BACH/Bone Analysis. DP, EC, AZ, and JS contributed in the statistical modeling for the Medicare Study, as well as obtaining Medicare data. ND, SF, and BB contributed in the statistical modelling for the BACH/Bone Study. IK, AZ, and JS contributed in the modeling of PM and Black Carbon exposures for the Medicare and the BACH/Bone Study. DP run the statistical models for the Medicare Study. ND run the statistical models for the BACH/Bone Study. DP run the statistical models for the Medicare Study, ND run the statistical models for the BACH/Bone Study. DP, JMZ, MH, LAH, LH, FD, and AB contributed in the designing of the integration of both cohorts and contributed actively in the discussion of results and its interpretation. DP, AZ, BB, JZ, EC, FD, and AB also contributed in the discussion of results. BB was the PI for the BACH/Bone cohort and AB was the PI for the Medicare Study. DP and JZ wrote the manuscript and the revisions.

DECLARATION OF INTEREST
We declare that we have no conflicts of interest.
Abstract

Background—Air particulate matter (PM) is a ubiquitous environmental exposure associated with oxidation, inflammation, and age-related chronic disease. Whether PM is associated with loss of bone mineral density (BMD) and risk of bone fractures is undetermined.

Methods—We conducted two complementary studies of: (i) long-term PM <2.5 μm (PM$_{2.5}$) levels and osteoporosis-related fracture hospital admissions among 9.2 million Medicare enrollees of the Northeast/Mid-Atlantic United States between 2003–2010; (ii) long-term black carbon [BC] and PM$_{2.5}$ levels, serum calcium homeostasis biomarkers (parathyroid hormone, calcium, and 25-hydroxyvitamin D), and annualized BMD reduction over a 8-year follow-up of 692 middle-aged (46.7±12.3 yrs), low-income BACH/Bone cohort participants.

Findings—In the Medicare analysis, risk of bone fracture admissions at osteoporosis-related sites was greater in areas with higher PM$_{2.5}$ levels (Risk ratio [RR] 1.041, 95% Confidence Interval [CI], 1.030, 1.051). This risk was particularly high among low-income communities (RR 1.076; 95% CI, 1.052, 1.100). In the longitudinal BACH/Bone study, baseline BC and PM$_{2.5}$ levels were associated with lower serum PTH (Estimate for baseline one interquartile increase in 1-year average BC= −1.16, 95% CI −1.93, −0.38; Estimate for baseline one interquartile increase in 1-year average PM$_{2.5}$= −7.39; 95%CI −14.17, −0.61). BC level was associated with higher BMD loss over time at multiple anatomical sites, including femoral neck (−0.08%/year per one interquartile increase; 95% CI −0.14, −0.02%/year) and ultradistal radius (−0.06%/year per one interquartile increase; 95% CI −0.12, −0.01%/year).

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

INTRODUCTION

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

Ambient levels of particulate matter (PM) air pollution have been associated with increased morbidity, hospitalization, and mortality from cardiovascular6–8 and respiratory diseases,9,10 as well as with cancer11,12 and impaired cognition.13–15 PM causes systemic oxidative damage16 and inflammation,17 which may result in accelerated bone loss and increased risk of bone fractures in older individuals. Tobacco smoke, which contains several toxic components also found in PM, has been repeatedly associated with decreased bone mineral density (BMD)18 and increased risk of bone fractures.19 However, evidence on whether individuals living in areas with higher PM levels have higher risk of bone fractures is
inconclusive. To date, no longitudinal study has investigated ambient PM in relation to bone mineral loss over time, and there is no available data on PM and calcium homeostasis in adults.

To determine the relationship between ambient PM levels and bone health, we conducted two independent studies with complementary designs, objectives, and measures: (i) using data on 763,630 hospital admissions from 9.2 million Medicare enrollees in the Northeast/Mid-Atlantic U.S. from 2003 to 2010, we determined whether communities with higher levels of PM <2.5 μm in aerodynamic diameter (PM$_{2.5}$) had higher rates of hospital admissions for osteoporosis-related bone fractures among older persons (>65 yrs old); (ii) in a longitudinal study of 692 middle-aged (mean age=47.5 years), low-income men from the Boston Area Community Health/Bone Survey cohort (BACH/Bone Study), we determined whether PM$_{2.5}$ levels and traffic-derived ambient PM—as traced through ambient levels of black carbon (BC)—were associated with altered markers of calcium homeostasis, including serum parathyroid hormone (PTH), 25-hydroxyvitamin D, and calcium, as well as changes in BMD over an ~8-year follow-up.

METHODS

Medicare analysis: PM and hospital admissions for fractures

Medicare data—We obtained 2003–2010 hospital admission data for osteoporosis-related bone fractures from ~9.2 million beneficiaries of Medicare, ≥65 years old, who lived in 3,974 zip codes of 13 Northeast/Mid-Atlantic U.S. states located east of the 81° W meridian, for which we recently developed a high-resolution hybrid model for estimating PM$_{2.5}$ levels (Figure 1).20 We identified primary hospital admissions for osteoporotic-related fractures using the International Classification of Diseases, 9th revision (ICD-9) (see Supplementary Table 1) and compiled data on number of admissions per year per zip code. Covariate data at the zip code levels were collected from various sources and were presented in its original unit to ensure accuracy. Medicare data are previously collected administrative data and, therefore, did not require individual patient consent.

Particulate matter data—Annual PM$_{2.5}$ levels between 2003–2010 were estimated using a recently developed and validated (mean out-of-sample $R^2$=0.88) spatio-temporal prediction model that incorporates satellite Aerosol Optical Depth data, spatial smoothing and local predictors.21 We generated daily PM$_{2.5}$ predictions at 1×1 km spatial resolution, as previously described20 and calculated 1-year averages of PM$_{2.5}$ levels specific to each zip code for each calendar year. The exposure dataset with yearly averages of PM$_{2.5}$ concentrations at a 1×1 km spatial resolution was matched to zipcodes using ArcGIS 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 methods—We estimated the association of 1-year PM$_{2.5}$ average with annual rates of bone fracture hospital admissions using generalized linear mixed models (PROC GLIMMIX, SAS Institute, Cary, NC) with Poisson distribution and random intercepts for zip code. We considered the Akaike information criterion (AIC) and residuals’ plots to evaluate goodness-of-fit. We adjusted the final model for the multiple zip code-level
confounders described in Supplementary Table 2. We used Medicare data on age that provides per each zip code the percent of the population between 65 to 74 years old and the percent >75 years. We also adjusted for number of days below 0°C to minimize 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 U.S. Department of Agriculture, which classify U.S. census tracts using measures of population density, urbanization and daily commuting. In separate models, we tested interaction terms between zip-code characteristics and PM<sub>2.5</sub> levels. Findings at p<0.05 were considered significant.

**BACH/Bone Study: Air pollution, BMD, and calcium homeostasis**

**Study participants, sociodemographic, physical and diet information**—The BACH/Bone Study is a population-based longitudinal study of musculoskeletal health, including 1,219 low-income black, Hispanic, and white male residents of Greater Boston, MA, aged 30–79 years. 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 followup assessments. Physical activity level was measured using the Physical Activity for the Elderly (PASE) scale. Frequency and duration of leisure activities, work (hours/week), and housework and similar duties (yes/no) over the previous week were recorded for each subject. The PASE score was computed by multiplying the amount of time spent in each activity (hours/week) in each activity by empirical item weights and summing over all activities. PASE measurements were categorized as Low (0–99), Middle (100–249), and High (250+). Measurements of subjects’ height and weight were obtained using a stadiometer (Seca Corp., Hanover, MD) and digital scale (Tanita, Arlington Heights, IL), respectively. Body mass index (BMI) was calculated from by dividing measured weight (kg) by the square of measured height (m<sup>2</sup>). Information about dietary habits was obtained by survey in participants’ homes using the diet with Block food frequency questionnaire. 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 < 100 cigarettes lifetime and not currently smoking), or former smokers (smoked > 100 cigarettes lifetime and currently not smoking). In 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. The Institutional Review Boards at the New England Research Institute and Boston University School of Medicine (BUSM) approved protocols. Each participant provided written informed consent.

**Air particle data**—To estimate PM<sub>2.5</sub> levels, we used the same spatiotemporal hybrid modeling approach described above for the Medicare analysis, but using a 1×1 km model instead of zip code areas, which allowed us more precise data about exposure. Due to the unavailability 1×1 km of satellite data before 2003, PM<sub>2.5</sub> predictions could be obtained—as annual average—only for participants with baseline visits in 2004–2005 (i.e., only 282 of the total 692 participants). We obtained finer-scale and more complete (n=692) estimates of
particle levels by calculating levels of BC—a measure of PM from vehicular traffic emissions and the dominant type of PM in urban areas—using a validated spatiotemporal land-use regression model that provided daily estimates of BC concentrations throughout the greater Boston area since 1995, as previously reported. To capture large local variability of vehicular traffic particles, the BC model generated estimates for each individual address rather than for grid cells. We calculated 1-year averages of PM$_{2.5}$ and BC at baseline using 365 daily estimates for each participant using their residential address before the date of their baseline BMD assessment.

**Phenotype measures**—Examinations, including in-person interviews, questionnaires, anthropometries, and blood draws were conducted at the BUSM-General Clinical Research Unit. We measured serum bio-intact parathyroid hormone (PTH), serum calcium at baseline, and serum 25-hydroxyvitamin D [25(OH)D, i.e., 25(OH)D$_2$ + 25(OH)D$_3$], as previously described. Trained and certified technicians measured BMD at both baseline and follow-up at five different locations (femoral neck, total hip, lumbar spine [L1–L4], distal radius, ulnadistal radius) with dual-energy X-ray absorptiometry (DXA) using a Hologic/QDR4500W densitometer (Hologic Inc., Waltham, MA). 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 perform the two BMD scans on each subject. However, all technicians were specifically trained and certified to use standardized 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 BMD measurements, the DXA system was monitored weekly for drift and the coefficient of variation (CV) for BMD were less than 1.5%. We calculated annualized changes in BMD between baseline and follow-up scans, and we calculated annualized change in percentage from the difference between the first and last BMD measurement.

**Statistical analysis**—We used linear regression to estimate the association of long-term PM$_{2.5}$ and BC levels (1-year average PM$_{2.5}$ and BC levels before BMD measurement) with baseline PTH, calcium levels, and serum 25(OH)D. 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 BC levels (1-year average) with change in BMD between baseline and ~8-year examinations. We rescaled the effect estimate to percent change to facilitate result comparison with previous studies. SUDAAN software (RTI International, Research Triangle Park, NC) 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 (see Supplementary Table 3). The Multivariate Imputation by Chained Equations (MICE) algorithm in R was used to impute missing data, 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 fifteen datasets were multiply imputed and used for analysis. Imputed missing data was less than 5% per variable. Findings at p<0.05 were 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

Medicare analysis

PM$_{2.5}$ levels and rates of hospital admissions for bone fractures—The area included in the analysis had a total population of 62 million, of which ~9.2 million (~15%) were Medicare beneficiaries. Characteristics of zip code areas are shown in Supplementary Table 4. From 2003–2010, 763,630 Medicare beneficiaries were admitted with a primary diagnosis of osteoporosis-related bone fracture. Communities with higher annual PM$_{2.5}$ levels had higher rates of bone fracture admissions in analyses controlling for relevant covariates. An interquartile-range (4.18 μg/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<0.001) higher rate of hospital admission for bone fracture (Table 1) in models adjusted for socio-demographic variables, geographic characteristics, obesity, number of days with freezing temperatures (<0 °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 illustrated that there remained substantial variability in bone fracture admission rates. Using a regression spline to fit PM$_{2.5}$ level in the multivariable-adjusted regression model, we confirmed that the relationship between PM$_{2.5}$ and rates of bone fractures was nearly linear across the entire range of PM$_{2.5}$ levels (3–22 μg/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 (Supplementary Table 5). Relative risks were similar between females (RR=1.046; 95% CI, 1.036 to 1.056; p<0.001) and males (RR=1.037; 95% CI, 1.027 to 1.047; p<0.001) (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< 0.001) compared to those with highest obesity rates (RR=1.038; 95% CI, 0.763 to 1.312; p= 0.13; p-for-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.

BACH/Bone Study

Association of PM$_{2.5}$ and BC levels with markers of calcium homeostasis—Participants in the BACH/Bone Study included 30–79-year-old males, including 66.9% participants with annual household income <$30,000 and 58.9% Caucasians. We present additional characteristics of the participants at baseline, including BMD, PM$_{2.5}$, and BC levels, in Table 3. Participants living in locations with higher BC levels had lower levels of serum PTH ($\beta =-1.16;$ 95% CI, −1.93 to −0.38, p=0.004 in the fully adjusted model for an interquartile increase [0.106 μg/m$^3$] in 1-year average in BC levels). PM$_{2.5}$ showed also a
negative association serum PTH levels ($\beta=-7.39$; 95%CI, $-14.17$ to $-0.61$, $p=0.03$ in the fully adjusted model for an interquartile increase [2.18 $\mu g/m^3$] in 1-year average in PM$_{2.5}$ levels). BC and PM$_{2.5}$ were not associated with serum calcium, or serum 25(OH)D levels and results were robust across alternative regression models (Table 4).

**Estimated Effects of Particulate Matter <2.5 μm and Black Carbon levels on Bone Mineral Density**—At baseline, BMD measures of the study participants were not associated with PM$_{2.5}$ or BC levels at their residential address (Table 5). During the 8-year follow-up, participants living at locations with higher levels of ambient particles, particularly BC levels, showed higher loss of BMD at multiple anatomical sites (Table 6). For each one interquartile (0.106 $\mu g/m^2$) increase in 1-year BC level at baseline, participants had 0.08% per year (95% CI, $-0.14$ to $-0.02$%; $p=0.009$) more decrease in femoral neck BMD and 0.06% per year (95% CI, $-0.12$ to $-0.01$%; $p=0.04$) in ultra-distal radius BMD in fully-adjusted models, equivalent to 3,914 cases/year attributable to PM$_{2.5}$. BMD also showed non-significant negative associations at one-third distal radius, total hip, and L1–L4 (Table 6). Associations remained robust across alternative regression models (Table 6) and relatively linear despite some non-influential outliers (Figure S1). In the subset of participants with available PM$_{2.5}$ data (n=282), one-year average PM$_{2.5}$ levels at baseline were negatively, but non-significantly, associated with changes in BMD for most anatomical sites evaluated (Table 6).

**DISCUSSION**

In our analysis of ~9.2 million Medicare beneficiaries, we found evidence of an association between PM$_{2.5}$ levels and rates of hospital admissions for bone fractures, independent of gender and community-level confounding factors. 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 $\mu g/m^3$ increase in PM$_{2.5}$, there is an increase in 4.1% higher rate of hospital admission for bone fractures in older individuals. In the prospective BACH/Bone Study of middle-aged, low-income males, we also found that participants living at addresses with higher levels of PM$_{2.5}$ and BC exhibited lower serum PTH levels. BC was associated with decreases in BMD over an 8-year follow-up. These findings indicate poor air quality as a possible risk factor for BMD loss and fractures in older individuals, which may disproportionately affect low-income males. Reducing emissions as a result of innovation in technologies or policy changes in emission standards of this modifiable risk factor may reduce the impact of air pollution on bone fractures and osteoporosis.

Air particles may, directly or indirectly, impact bone biology and increase bone mineral loss. Air pollution particles have high potential to cause systemic oxidative damage and inflammation, both of which are established mechanisms for bone demineralization and osteoporosis.

Tobacco smoke, which includes several chemo-physical components found in PM, causes bone mineral loss in animal experiments and has been associated with higher risk of bone fractures and increased bone mineral loss in human studies. PTH levels are also significantly lower in smokers and return to non-smoking levels after smoking.
cessation. Such PTH alteration may represent an adaptive response to smoking-induced calcium mobilization from bone. Our findings suggest that similar mechanisms may also be activated in response to PM. Similarities between PM and smoking may also suggest a potential role of renal calcium handling, but unfortunately, no data about renal calcium was available in the BACH/Bone cohort.

To date, very few studies have investigated the association of air pollution levels with bone health and bone fractures. A cross-sectional study of 5,976 middle-aged and older individuals living in Norway (15.23% with forearm fractures, ~910 cases) described an association of long-term PM\textsubscript{2.5} levels with the prevalence of self-reported forearm fractures after the age of 50 years, but the association was evident only among male smokers. A previous study of 590 men aged 75–76 years showed a cross-sectional correlation of long-term PM\textsubscript{2.5} and PM\textsubscript{10} levels with lower total body BMD. Previous studies have also reported higher rates of bone fractures and age-related osteoporosis in urban areas compared to rural regions. For example, urban women have a 29% higher relative risk of forearm fracture and lower BMD compared to women in rural areas. 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 (Supplementary Table 5), it is unlikely the observed association of PM on hospital admissions by bone fractures reflect confounding due to lifestyle or other socioeconomically differences between urban and rural areas. We used yearly counts of admissions for each zip code area and specified a Poisson distribution. We applied generalized mixed models because we have counts for each zip code and then, we included a random intercept for zip code to take in account of 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 the long-term effect of PM\textsubscript{2.5}. The magnitude of the relative risk we found in Medicare analysis is similar to the very well established associations between air pollution and other health outcomes (e.g. myocardial infarction, stroke, total mortality). 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.

Several epidemiological studies have shown that socioeconomic factors, race, and obesity are related to a bone mineral density. Low socio-economic status has been associated with 25-OHD insufficiency, higher values of PTH, lower values of BMD and a higher prevalence of fragility fractures. Also, despite lower serum 25-hydroxyvitamin D concentrations and dietary calcium intake and, African Americans have higher BMD and develop osteoporosis less frequently than do European Americans. 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\textsubscript{2.5} exposure with bone fracture admission rates was higher among those communities in the lowest obesity rate quartile compared to those with highest obesity rates, suggesting a protective influence of obesity rates.

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During the 8-year follow-up, middle-aged, low-income males living at locations with higher BC levels had larger annualized decreases in BMD. BC, a major component of fine particles measured by PM$_{2.5}$, is a tracer of particles from traffic and might share different toxicological properties compared to other PM components. Therefore, our results indicate that particles from traffic are critical contributors to decreased bone health. PM$_{2.5}$ levels showed only weak and non-significant associations with both BMD annualized changes and serum PTH levels. However, the PM$_{2.5}$ analysis included only ~40% of the BACH/Bone participants due to unavailability of PM$_{2.5}$ model predictions in the early years of the study. Lack of significance could be attributable to the lower number of middle-aged, low-income males —compared to the BC analysis—with long-term PM$_{2.5}$ 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 association between long-term BC exposure and BMD at baseline, but we found associations with yearly change between baseline and follow up BMD in the longitudinal analysis. Lack of association in the cross-sectional analysis of 1-year average BC exposure and BMD at baseline might indicate that individuals are less susceptible to BC at a younger age and, consequently, effects were observed only as participants aged during the follow-up analysis.$^{55}$

We observed a negative association between long-term BC exposure and reduction in femoral neck and ultradistal radius BMD. Although non-significant, negative associations between BC and ultradistal radius, total hip, and lumbar vertebral BMD were also observed. Our study is consistent with the finding that air pollution contributes to bone health impairment reported by different groups.$^{42,56–58}$ Chen et al. showed that traffic-related exposure was associated with lower body BMD.$^{58}$ Also, Chang et al. found an association between air pollution (carbon monoxide and nitrogen dioxide) and increased risk of osteoporosis.$^{57}$ The difference in observed associations across multiple anatomical sites might be explained by differential anatomical susceptibility to the effects of PM on bones.$^{59}$ Alvaer et al. reported gender differences in the association between air pollution and BMD, with association observed only for men.$^{42}$ However, our finding from the Medicare analysis suggested that the impacts of ambient particulate air pollution on bone health may 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 may 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 conducted at zip code level and does not allow for evaluating the association of long-term PM$_{2.5}$ exposure with hospital admissions at the individual level. To avoid the potential ecological fallacy,$^{60}$ 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 U.S. The Medicare analysis may also be subject to selection bias, which is always a concern in observational studies. However, all individuals ≥65 years old are encouraged to enroll in the free Medicare program. Based on the enrollment criteria of
Medicare beneficiaries, we assume that the Medicare enrollees are representative of the aging population in the Northeast/Mid-Atlantic U.S. 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 PM levels. 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 limit concerns about population-level analysis and bias from known confounders.

We acknowledge that the analysis conducted in the BACH/Bone study has several limitations due to moderate sample size and lack of generalizability, given that the cohort included 692 males only. However, to the best of our knowledge, only one study has reported the association between PM exposure and bone fractures. Nonetheless, the BACH/Bone study is distinctively unique because of the prospective BMD assessment at two time points. Further, in the Medicare analysis, we found similar associations of PM$_{2.5}$ 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 PM exposure available both in the Medicare study as in the BACH/Bone study but long-term PM exposure was not directly measured and no personal data was available. Also, our results may be influenced by other unmeasured individual factors, such as UV exposure or calcium intake, among others, that can modify bone health and that were not evaluated here. Likewise, although our models used specifically levels of PM$_{2.5}$ (for Medicare study and for a subset of participants in the BACH/Bone study) and black carbon (for BACH/Bone Study), we cannot exclude that the effect we observed might be mediated by other air pollutants or by the combination of them. In addition, the DXA-based BMD measures used may not detect microstructural alterations that are not readily apparent. Therefore, BMD may fail to fully capture alterations related to bone health. We also acknowledge potential misclassification, especially in the BACH/Bone study, but this is likely to be non-differential (i.e. the measurement error of exposure in the BACH/Bone study is unlikely to be dependent on BMD status), therefore it is expected to bias our results towards the null. On the other hand, other air pollutants such as carbon monoxide (CO) and nitrogen dioxide (NO$_2$) have been previously associated with bone loss and osteoporosis. Unfortunately, we did not have access to CO and NO$_2$ exposure data in for the Medicare study nor for BACH/Bone, limiting our capability to explore these associations. Further analyses to evaluate the role PM$_{2.5}$ and BC, as well as of CO and NO$_2$ on bone health are warranted. Finally, although we have adjusted for multiple potential confounders (smoking, race, physical activity, income, etc.) in the BACH/Bone study, our results might not be sufficient to rule out selection bias, especially in the PM$_{2.5}$ model where the number of participants was low.
CONCLUSIONS

We found evidence of an association between air particle levels 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 with higher air particle levels had lower serum PTH levels and reductions in BMD. All associations were linear and observed—at least for part of the PM$_{2.5}$ distribution—at PM$_{2.5}$ concentrations below the annual average limits set by the U.S. Environmental Protection Agency (12 μg/m$^3$) and the European Union (25 μg/m$^3$), as well by other countries, such as for instance China (40 μg/m$^3$) and Japan (15 μg/m$^3$). 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 levels 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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RESEARCH IN CONTEXT

Evidence before this study
Exposure to particulate Matter (PM) induces oxidative damage and inflammation, which may affect bone health, particularly of older populations. Smoking, which contains several PM components, has been consistently associated with bone damage. However, whether ambient PM levels 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 PM$_{2.5}$ levels. Participants living at addresses with higher levels of traffic-derived PM particles exhibit lower serum parathyroid hormone (PTH) levels and higher decreases in bone mineral density (BMD) over an 8-year follow-up.

Implications of all the available evidence
This study provides evidence that long-term PM exposure—a persistent environmental issue in Europe and globally—is an independent risk factor for bone fractures, possibly involving changes in PTH. These associations may disproportionately impact least-favored communities. We found PM association well below the annual average limits set by the U.S. Environmental Protection Agency and the European Union. Improvements in particulate air pollution levels may ameliorate bone health, prevent bone fractures, and reduce the health cost burden associated with fractures in older individuals.
Figure 1. Population and levels of fine air particulate pollution in the Northeast/Mid-Atlantic United States
Panel A: Medicare population by zip code.
Panel B: Average PM$_{2.5}$ levels per zip code between 2003–2010.
Figure 2. Long-term exposure to PM$_{2.5}$ and risk of hospital admission for bone fractures
Panel 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 <2.5 μm (PM$_{2.5}$).
Panel B: Spline for the multivariable-adjusted association between PM$_{2.5}$ exposure and number of hospital admissions of Medicare enrollees per zip code, from 2003–2010.
Panel C: Density plot of exposure to PM$_{2.5}$ in the Medicare analysis.
Dotted line represents the primary annual PM$_{2.5}$ standard of 12 μg/m$^3$ mandated by the U.S. Environmental Protection Agency.
Table 1

Risk of hospital admissions by osteoporotic-related bone fractures associated with 1-year average levels of PM$_{2.5}$ in the Medicare analysis

|                          | Females          | Males          |
|--------------------------|------------------|----------------|
| Number of Medicare beneficiaries | 9,271,035        | 5,192,340      | 4,079,695 |
| Number of hospital admissions, 2003–2010 | 763,630$^*$       | 449,105        | 314,525  |

|                          | RR (95% CI) Females | RR (95% CI) Males |
|--------------------------|---------------------|-------------------|
| PM$_{2.5}$               | 1.041 (1.030, 1.051)| 1.046 (1.036, 1.056)| 1.037 (1.027, 1.047)|
| % white, non-Hispanic    | 1.045 (1.038, 1.052)| 1.044 (1.037, 1.051)| 1.045 (1.036, 1.054)|
| % high school graduate   | 1.035 (0.998, 1.072)| 1.037 (0.998, 1.076)| 1.033 (0.996, 1.070)|
| Median income            | 0.998 (0.992, 1.004)| 0.997 (0.995, 0.999)| 0.996 (0.991, 1.006)|
| % obese                  | 0.973 (0.935, 1.011)| 0.974 (0.935, 1.013)| 0.972 (0.936, 1.008)|
| % female                 | 1.087 (1.047, 1.127)| –                 | –                  |
| % of population that are 75 yrs or older$^c$ | 1.096 (1.087, 1.105) | 1.097 (1.088, 1.106) | 1.095 (1.086, 1.104) |
| Number of days below 0°C | 1.011 (1.010, 1.011)| 1.011 (1.010, 1.011)| 1.011 (1.010, 1.011)|
| Urban (vs. rural)$^d$    | 0.998 (0.925, 1.071)| 0.998 (0.928, 1.068)| 0.998 (0.925, 1.071)|

$^a$ Estimated risk of hospital admissions of Medicare enrollees with a primary diagnosis of bone fracture associated with an interquartile range (4.18 μg/m$^3$) increase in 1-year average in the levels of fine particulate matter <2.5μm (PM$_{2.5}$) across 3,974 zip code areas in the U.S. North/Mid-Atlantic area in the period from 2003–2010. The adjusted estimates of each variable were presented in the table.

$^b$ The 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 the table.

$^c$ In each zipcode, age was reported in the Medicare data as the percent of the population 65 to 74 years old and the percent 75 years or older.

$^d$ Rural areas included large, small, and isolated rural categories.

RR=Risk ratio; 95% CI= Confidence Interval.

$^*$ Osteoporotic related fractures include all hospital admissions with a primary diagnosis of hip, wrist, spine and pelvis fractures only.
Table 2
Risk of hospital admissions by osteoporosis-related bone fracture associated with PM$_{2.5}$ levels in each quartile of socioeconomic status, race, and obesity.

| % of population with high school level per zip code$^{d}$ | RR   | 95% CI      | $p$ value for interaction |
|----------------------------------------------------------|------|-------------|---------------------------|
| 1st quartile (7.31 – 25.52)                              | 1.046| (1.023, 1.070)|                          |
| 2nd quartile (25.53 – 32.21)                             | 1.097| (1.075, 1.118)| <0.001                    |
| 3rd quartile (32.22 – 38.32)                             | 1.017| (0.988, 1.046)|                          |
| 4th quartile (39.33 – 99.90)                             | 1.067| (1.044, 1.091)|                          |
| Median income per zip code$^{b}$                         |      |             |                           |
| 1st quartile (19.23 – 37.28k)                            | 1.076| (1.052, 1.100)| <0.001                    |
| 2nd quartile (37.29 – 48.65k)                            | 1.105| (1.084, 1.126)| <0.001                    |
| 3rd quartile (48.66 – 61.83k)                            | 1.125| (1.102, 1.149)| <0.001                    |
| 4th quartile (61.84 – 200.01k)                           | 0.937| (0.906, 0.968)|                          |
| % of population white non-Hispanic per zip code$^{c}$    |      |             |                           |
| 1st quartile (2.76 – 84.28)                              | 1.099| (1.077, 1.121)| <0.001                    |
| 2nd quartile (84.29 – 94.38)                             | 0.944| (0.918, 0.971)| <0.001                    |
| 3rd quartile (94.39 – 97.33)                             | 1.102| (1.070, 1.130)| <0.001                    |
| 4th quartile (97.34 – 100.00)                            | 1.109| (1.089, 1.130)| <0.001                    |
| % of obesity per zip code$^{d}$                          |      |             |                           |
| 1st quartile (13.80 – 22.70)                             | 1.105| (1.080, 1.129)| 0.011                     |
| 2nd quartile (22.71 – 25.50)                             | 1.118| (1.095, 1.140)|                          |
| 3rd quartile (25.51 – 27.80)                             | 0.968| (0.698, 1.238)|                          |
| 4th quartile (27.81 – 35.60)                             | 1.038| (0.763, 1.312)|                          |

RR=Risk ratio; 95% CI=95% Confidence interval.

$^{a}$Adjusted by all variables included in Table 1, except % of population with high school level per zip code.

$^{b}$Adjusted by all variables included in Table 1, except Median income per zip code.

$^{c}$Adjusted by all variables included in Table 1, except % of population white non-Hispanic per zip code.

$^{d}$Adjusted by all variables included in Table 1, except % of obesity per zip code.
| Characteristic                          | N (%) or mean (SE) |
|----------------------------------------|--------------------|
| **Age**                                |                    |
| <40 years                              | 139 (29.0%)        |
| 40–49 years                            | 206 (31.7%)        |
| 50–59 years                            | 183 (20.1%)        |
| >60 years                              | 164 (19.2%)        |
| **Race**                               |                    |
| Black                                  | 214 (28.0%)        |
| Hispanic                               | 204 (13.2%)        |
| White                                  | 274 (58.9%)        |
| **Household income**                   |                    |
| <$6k                                   | 146 (12.8%)        |
| $6k–$29.9k                             | 377 (54.1%)        |
| ≥$30k                                  | 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**                   |                    |
| ≤43.5 mg                               | 177 (24.7%)        |
| 43.5 – 164.5 mg                        | 169 (25.1%)        |
| 164.6 – 325.0 mg                       | 171 (25.1%)        |
| >325.1 mg                              | 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)        |
| **PM2.5 1-year average (μg/m3)**       | 11.65 (0.05)       |
| **BC 1-year average (μg/m3)**          | 0.77 (0.01)        |
| **BMD at baseline (g/cm²)**            |                    |
| Femoral neck                           | 0.88 (0.01)        |
| Ultradistal radius                     | 0.53 (0.004)       |
| 1/3 distal radius                      | 0.77 (0.004)       |
| Total hip                              | 1.03 (0.01)        |
| L1–L4                                  | 1.05 (0.01)        |
| Characteristic          | N (%) or mean (SE) |
|------------------------|--------------------|
| Annualized change in BMD, baseline to follow-up (%) |                   |
| Femoral neck           | −1.14 (0.03)       |
| Ultradistal radius     | −0.56 (0.04)       |
| 1/3 distal radius      | 0.26 (0.03)        |
| Total hip              | −0.29 (0.03)       |
| L1–L4                  | 0.10 (0.038)       |

PM$_{2.5}$ = fine particulate matter <2.5 μm; PASE = physical activity scale for the elderly; BC = black carbon; BMD = bone mineral density; L1–L4 = lumbar vertebrae.

* Available only for 282 middle-aged, low-income males.
** Available for 692 middle-aged, low-income males. ‘k’ in Median income= thousands.
Table 4
Association of long-term PM$_{2.5}$ and black carbon with calcium homeostasis biomarkers in the BACH/Bone Study$^a$

|                   | Unadjusted Estimate (95% CI) | Adjusted for age, race and height Estimate (95% CI) | Fully adjusted$^b$ Estimate (95% CI) |
|-------------------|------------------------------|-----------------------------------------------------|-------------------------------------|
| **PM$_{2.5}$**    |                              |                                                     |                                     |
| Parathyroid hormone | $-5.69 (-13.73, 2.40)$       | $-6.00 (-13.78, 1.77)$                               | $-7.39 (-14.17, -0.61)$             |
| Serum 25(OH)D     | $4.51 (-6.13, 15.13)$        | $1.16 (-7.76, 10.05)$                               | $2.90 (-6.21, 12.03)$               |
| Serum calcium     | $0.13 (-0.09, 0.327)$        | $0.13 (-0.07, 0.33)$                                | $0.13 (-0.07, 0.33)$               |
| **BC**            |                              |                                                     |                                     |
| Parathyroid hormone | $-1.29 (-2.05, -0.53)$       | $-1.32 (-2.23, -0.42)$                               | $-1.16 (-1.93, -0.38)$             |
| Serum 25(OH)D     | $0.63 (-0.31, 1.58)$         | $0.21 (-0.75, 1.17)$                                | $0.27 (-0.69, 1.22)$               |
| Serum calcium     | $0.01 (-0.01, 0.04)$         | $0.01 (-0.01, 0.04)$                                | $0.01 (-0.01, 0.04)$               |

$^a$ Regression coefficients for the association between one interquartile range increase in baseline PM$_{2.5}$ (2.18 μg/m$^3$, N=282) or black carbon (0.106 μg/m$^3$, N=692, BC) 1-year average and calcium homeostasis biomarkers (parathyroid hormone, serum vitamin D, and serum calcium) in the BACH/Bone Study cohort.

$^b$ Adjusted for age, race, height, weight, smoking, per-capita household income, physical activity, C-reactive protein and caffeine consumption.

PM$_{2.5}$ = fine particulate matter <2.5μm. BC = black carbon. 95% CI=95% confidence interval.
Table 5

Estimated effects of PM$_{2.5}$ and black carbon levels on bone mineral density at baseline in the BACH/Bone Study$^a$

| Anatomical site       | Percent change (95% CI) |
|-----------------------|-------------------------|
| **PM$_{2.5}$**        |                         |
| Femoral neck          | 0.262 (−0.044, 0.094)   |
| Ultradistal radius    | 0.017 (−0.050, 0.085)   |
| One-third distal radius | 0.022 (−0.052, 0.096)   |
| Total hip             | 0.031 (−0.001, 0.061)   |
| L1–L4                 | 0.011 (−0.020, 0.039)   |
| **BC**                |                         |
| Femoral neck          | −0.001 (−0.007, 0.009)  |
| Ultradistal radius    | −0.001 (−0.009, 0.008)  |
| One-third distal radius | −0.003 (−0.006, 0.011)  |
| Total hip             | −0.001 (−0.003, 0.004)  |
| L1–L4                 | −0.001 (−0.004, 0.004)  |

$^a$Regression coefficients for the association between baseline one interquartile range increase in PM$_{2.5}$ (2.18 μg/m$^3$, N=282) and black carbon levels (0.106 μg/m$^3$, N=692) 1-year average and baseline bone mineral density in five anatomical sites in the BACH/Bone Study cohort (N=692).

$^b$Adjusted for age, race, height, smoking, household income, physical activity, caffeine consumption, weight, and serum 25(OH)D level.

PM$_{2.5}$ = fine particulate matter <2.5 μm; BC = black carbon; 95% CI = 95% confidence interval; L1–L4 = lumbar vertebrae.
Table 6
Annualized percent change in BMD associated with PM$_{2.5}$ and black carbon exposure in the BACH/Bone Study$^a$

|          | Unadjusted | Adjusted for age, race, and height | Fully adjusted$^b$ |
|----------|------------|-----------------------------------|-------------------|
|          | Percent change (95% CI) | Percent change (95% CI) | Percent change (95% CI) |
| PM$_{2.5}$ |             |                                   |                   |
| Femoral neck | $-0.09 (-0.44, 0.26)$ | $-0.13 (-0.50, 0.22)$ | $-0.13 (-0.52, 0.26)$ |
| Ultradistal radius | $0.22 (-0.20, 0.63)$ | $0.17 (-0.24, 0.59)$ | $0.22 (-0.20, 0.63)$ |
| One-third distal radius | $-0.07 (-0.37, 0.22)$ | $-0.09 (-0.37, 0.22)$ | $-0.04 (-0.35, 0.24)$ |
| Total hip | $-0.13 (-0.48, 0.20)$ | $-0.17 (-0.52, 0.20)$ | $-0.22 (-0.61, 0.17)$ |
| L1–L4 | $-0.20 (-0.52, 0.13)$ | $-0.17 (-0.52, 0.17)$ | $-0.17 (-0.52, 0.15)$ |
| BC |             |                                   |                   |
| Femoral neck | $-0.08 (-0.14, -0.02)$ | $-0.08 (-0.14, -0.02)$ | $-0.08 (-0.14, -0.02)$ |
| Ultradistal radius | $-0.06 (-0.11, 0.01)$ | $-0.06 (-0.11, 0.01)$ | $-0.06 (-0.12, -0.01)$ |
| One-third distal radius | $-0.03 (-0.07, 0.01)$ | $-0.03 (-0.07, 0.01)$ | $-0.03 (-0.07, 0.01)$ |
| Total hip | $-0.04 (-0.08, 0.01)$ | $-0.04 (-0.08, 0.01)$ | $-0.03 (-0.08, 0.01)$ |
| L1–L4 | $-0.04 (-0.10, 0.02)$ | $-0.05 (-0.10, 0.01)$ | $-0.04 (-0.09, 0.01)$ |

$^a$Annualized percent change in bone mineral density (BMD) at five anatomical sites, from 2002–2005 to 2010–2012, associated with one interquartile range increase in PM$_{2.5}$ (2.18 μg/m$^3$, N=282) and black carbon levels (0.106 μg/m$^3$, N=692) 1-year average exposure in the BACH/Bone Study.

$^b$Adjusted for age, race, height, weight, smoking, per-capita household income, physical activity, caffeine consumption, C-reactive protein, and serum 25(OH)D.

PM$_{2.5}$ = fine particulate matter <2.5μm. BMD= Bone Mineral Density. BC= black carbon. 95% CI=95% confidence interval; L1–L4= lumbar vertebral mineral density.