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Clinical Research Article

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The Association Between Long-term Exposure to Ambient Air Pollution and Bone Strength in China

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Abbreviations: BMD, bone mineral density; BMI, body mass index; BUA, broadband ultrasound attenuation; CMEC, China Multi-Ethnic Cohort; NO_2, nitrogen dioxide; PM_1, particulate matter ≤ 1 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter ≤ 2.5μm in aerodynamic diameter; PM_{10}, particulate matter ≤ 10 μm in aerodynamic diameter; QUI, quantitative ultrasound index; QUS, quantitative ultrasound; SOS, speed of sound.

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Abstract

Context: Evidence regarding the association of long-term exposure to air pollution on bone strength or osteoporosis is rare, especially in highly polluted low- and middle-income countries. Little is known about whether the association between air pollution and bone strength changes at different bone strength distributions.

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Objective: Using the baseline data from the China Multi-Ethnic Cohort, we investigated the association between long-term air pollution exposure and bone strength.
Methods: We used multiple linear models to estimate the association between air pollution and bone strength, and we conducted quantile regression models to investigate the variation of this association in the distribution of bone strength. The 3-year concentrations of PM_1, $PM_{2.5}$, PM_{10}, and NO_2 for each participant were assessed using spatial statistical models. Bone strength was expressed by the calcaneus quantitative ultrasound index (QUI) measured by quantitative ultrasound, with higher QUI values indicating greater bone strength.
Results: A total of 66 598 participants were included. Our analysis shows that every 10 $\mu g/m^3$ increase in 3-year average PM_1, $PM_{2.5}$, PM_{10}, and NO_2 was associated with –5.38 units (95% CI: –6.17, –4.60), –1.89 units (95% CI: –2.33, –1.44), –0.77 units (95% CI: –1.08, –0.47), and –2.02 units (95% CI: –2.32, –1.71) changes in the QUI, respectively. In addition, populations with higher bone strength may be more susceptible to air pollution.
Conclusion: Long-term exposure to PM_1, $PM_{2.5}$, PM_{10}, and NO_2 was significantly associated with decreased bone strength in southwestern China adults. Air pollution exposure has a more substantial adverse effect on bones among populations with higher bone strength.

Key Words: ambient air pollution, particulate matter, nitrogen dioxide, osteoporosis, bone strength

Bones bear the critical responsibility of mechanically supporting the whole body. Bone homeostasis is characterized by constant bone resorption and deposition processes (1). Disturbance of bone homeostasis leads to reduced bone mineral density (BMD) and bone architecture deterioration and thus a decrease in bone strength (1). A continued reduction in bone strength and consequent osteoporosis substantially increases the incidence of fractures (2) and results in a large burden of disabilities and premature deaths (3-5). More than 200 million people suffer from osteoporosis worldwide (6). In 2010, for people over 50 years of age, the prevalence of osteoporosis was about 10.3% in the USA (7); the prevalence in the European Union was 6.6% and 22.1% for men and women, respectively. (8). It has been reported that the burden of osteoporosis is reaching a plateau in many developed economies (9), while in developing areas, the burden of osteoporosis is still rising (3, 9). In China, it is predicted that the annual number of osteoporosis-related fractures will increase from 2.3 million in 2010 to 5.99 million in 2050 (10). Given inadequate medical resources, low awareness, and low treatment rates in low- and middle-income countries, osteoporosis will cause more health losses in these regions (11-13). Therefore, attention should be paid to preventing bone strength reduction.

Long-term exposure to air pollution has been reported to be associated with osteoporosis. Air pollution exposure results in systemic inflammation (14) and increased oxidative stress (15), which may lead to bone metabolic disorders (16, 17). Several studies have investigated the effect of long-term exposure to air pollution on osteoporosis or bone strength indicators such as BMD and bone mineral content. However, findings from these studies were still controversial. For instance, a study in Southern California among Mexican Americans reported that ambient air pollutants (NO_2, O_3, $PM_{2.5}$) were not associated with BMD (18). No association was found between lower BMD and $PM_{2.5}$ exposure among women in Oslo, Norway (19). In contrast, one cross-sectional study of 3717 participants from the peri-urban area of South India showed that a lower bone mineral content was associated with higher $PM_{2.5}$ exposure (20). A prospective study based on the Taiwan Longitudinal Health Insurance database reported that individuals living in areas with high CO and NO2 concentrations were associated with an increased risk of osteoporosis (21). The relatively small sample size in some analyses might restrict their statistical power (18, 19). In addition, most studies have been conducted in developed economies (18, 19, 21-23) where the air pollution is at a low level, while few studies were carried out in low- and middle-income countries where air pollution concentrations are much higher than those of their counterparts (20, 24). Furthermore, existing studies typically focused on a specific population, such as the elderly (19, 22, 23) or children (25). Evidence from the general population with a large sample size is lacking.

Given that bone strength reduction is an ongoing process, identifying whether specific individuals with different bone strength levels are more vulnerable to ambient air pollution is of important public health relevance. None of these studies explored associations between air pollution and bone strength at specific percentiles of bone strength distribution. We used quantile regression to provide more comprehensive information about the relationship between bone strength and air pollution at specific quantiles of bone strength. The quantile regression exploited the entire

range of bone strength to detect potential heterogeneity in exposure-outcome associations according to individual bone strength levels.

This cross-sectional study from a population-based cohort of nearly 100 000 adults aged 30 to 79 years in Southwest China (26) was aimed to explore the hypothesis that long-term exposure to air pollution (particulate matter ≤ 1 μm in aerodynamic diameter [PM_1], $PM_{2.5}$, PM_{10}, and nitrogen dioxide [NO_2]) is related to decreased bone strength. We also considered the populations that were potentially susceptible to ambient air pollution by quantile regression and strata analysis.

Methods

Population and Study Design

We analyzed data from the baseline of the China Multi-Ethnic Cohort (CMEC) study, a population-based cohort involving 5 provinces (Sichuan, Chongqing, Guizhou, Tibet, and Yunnan) in Southwest China. The study design and method of the CMEC have been reported previously (26). In brief, a total of 99 556 participants aged 30 to 79 were recruited using a multistage stratified cluster sampling method. The baseline survey was conducted between May 2018 and September 2019. The estimated population response rate was 60% (60%-90% in rural areas and 40%-60% in urban areas). The CMEC study elicited information on demographic characteristics, socioeconomic status, lifestyle (eg, diet, physical activity, smoking status, and alcohol consumption), and other health-related factors from face-to-face interviews. Interviews were conducted by trained investigators via a tablet computer with a self-developed application. Moreover, a range of medical examinations, including blood pressure, chest radiography, and calcaneal quantitative ultrasound (QUS) measurements, were performed for each participant. Furthermore, the CMEC also collected the current residential address and length of residence for each participant, allowing us to obtain environmental exposure characteristics.

We excluded participants who were Tibetan living in high plateau areas. Tibetans in Lhasa were recruited from adjacent townships or streets with few air pollution variations. In addition, both living at high altitudes and under hypoxic conditions are correlated with bone metabolism (27, 28). The combination of these 2 factors severely decreases population comparability and could cause unadjustable confounders. In addition, Tibetans in Aba were herdsmen without a fixed residence. We also excluded participants with an incomplete residential address or with less than 3 years of residency at the present address. Participants with self-reported osteoporosis were excluded to avoid causal reversal. Participants who lacked information on air pollution exposure, health outcomes, or other covariates were also excluded. Ultimately, a total of 66 598 participants were considered in the present study (Supplement Fig. A1 (29)). Each participant provided written informed consent. Ethical approval was received from the Sichuan University Medical Ethical Review Board (K2016038).

Outcome

We chose the quantitative ultrasound index (QUI), an indicator of bone strength as assessed by QUS, as the outcome in this study. QUS measurements were performed using an OSTEOKJ3000 ultrasonic bone densitometer (KeJin, Inc, Nanjing, China). The calcaneus is the most common QUS measurement site because it possesses 2 lateral surfaces, and the soft tissue covering the bone is relatively thin, which facilitates ultrasound conduction (30). Compared with dual-energy x-ray absorptiometry (DXA), considered the gold standard of osteoporosis studies, QUS devices are free of harmful radiation, quick, cost-effective, and more suitable for large-scale epidemiological studies (31). The same method has been applied in several previous large cohort studies (24, 32, 33).

Through the QUS measurement, we obtained 2 parameters, the quantitative ultrasound speed of sound (SOS, m/s) and broadband ultrasound attenuation (BUA, dB/MHz). By combining the BUA and SOS (ie, QUI = 0.41 × (BUA + SOS) – 571), the QUI was acquired (34). High QUI values indicate better bone strength (35).

Exposure Assessment

The daily concentrations of PM_{10}, $PM_{2.5}$, and PM_1, with a 1-km spatial resolution, were estimated using the space-time extremely randomized trees (STET) model (36). This model incorporated information on the aerosol optical depth (AOD), meteorological properties, topographical properties, land use, and pollution emissions with excellent predictive performance. The cross-validation coefficient of determination and root-mean-square error (CV-R2 [RMSE]) for the daily PM_1, $PM_{2.5}$, and PM_{10} concentrations were 0.77 (14.6), 0.90 (10.09), and 0.86 (24.28), respectively (37-39). In addition, the NO_2 was estimated by a random forest model with a 10-km spatial resolution (40).

We assigned daily PM_1, $PM_{2.5}$, PM_{10}, and NO_2 concentrations to the participants based on their current geocoded residential addresses. We calculated the previous 3-year average exposures to PM_1, $PM_{2.5}$, PM_{10}, and NO_2 before the baseline survey as a proxy for long-term air pollution exposure.

Covariates

Covariates were the possible confounders of the association of long-term exposure to air pollution and osteoporosis, as previous studies have reported (20, 23, 24). The covariates included demographic characteristics (age, sex, ethnicity, region, and rural/urban areas), socioeconomic variables (annual family income and educational level), health behavior variables (smoking status, alcohol drinking status, physical activity level, sedentary time, passive smoking, and indoor pollution), supplement intake (calcium and vitamin D), diet (milk, red meat, poultry meat, vegetable, and fresh fruit), health status variable (body mass index [BMI]), and environmental variable (ultraviolet radiation at the surface).

The detailed definitions and categories of the covariates are shown in Supplement Table A1 (29).

Statistical Analysis

The baseline characteristics were summarized using the mean (standard deviation [SD]) for continuous variables and the number (%) for categorical variables. We performed separate multiple linear regression analyses to examine the relationship between single air pollution (PM_1, $PM_{2.5}$, PM_{10}, or NO_2) and bone strength. Adjustments for covariates were conducted sequentially using 4 models (5-22 covariates). Model 1 was adjusted for participant age, sex, ethnicity, region, and rural/urban residency. Model 2 was further adjusted for smoking status, alcohol consumption status, physical activity level, BMI, and sedentary time. Model 3 additionally accounted for the educational level, annual family income, calcium intake status, and vitamin D intake status. Lastly, model 4 was also adjusted for dietary variables (including consumption of milk, red meat, poultry meat, vegetables, and fresh fruits) and ultraviolet radiation at the surface. Model 4 was the main model because it accounted for the most comprehensive covariates.

Quantile regression was conducted at percentiles of the outcome distribution in the 10% increments from 10% to 90% using the same covariates in the main model reported above.

To explore the population sensitivity to long-term air pollution exposure, we conducted stratified analyses according to participant sex (male, female), age (≤45 years, 45-65 years, ≥65 years), rural/urban residency, smoking status (never smoker, ever smoker), and alcohol drinking status (never drinker, ever drinker). The stratified analyses were explored through interaction terms, and the likelihood ratio test was used to examine the significance. The concentration-response relationship between the 3-year average of air pollution (PM_1, $PM_{2.5}$, PM_{10}, and NO_2) and QUI was estimated using a penalty spline based on model 4 with the package "mgcv" in R software version 4.0.3.

The robustness of the association between air pollution and bone health status was assessed with a range of sensitivity analyses: (1) a pair pollution models were implemented to explore the potential influence between different pollutants; (2) the 2-year and 4-year average concentrations of air pollutants were employed to evaluate the possible impact of cumulative exposure time; (3) we used the main model with sequential exclusion criteria, gradually excluding participants with diseases (rheumatoid arthritis, rheumatic arthritis, diabetes, and chronic hepatitis/cirrhosis) that could potentially the association between air pollution and bone health; (4) the dose of smoking and alcohol drinking were included in model 4 as continuous covariates; and (5) we also tested the influence of not-excluded participants who had lived in their present address for less than 3 years.

All the analyses were performed using R software version 4.0.3. A 2-sided P value of less than 0.05 was considered statistically significant.

Results

Descriptive Statistics

A total of 66 598 participants with complete information were included in this study. The mean (SD) age was 52.46 (11.38) years, and 40 621 (61%) participants were female. A total of 62.2% of the participants were of Han ethnicity, and 48.1% lived in rural areas. The detailed characteristics of the study sample are presented in Table 1.

The median (range) 3-year average exposure concentrations were 27.45 μg/m^3 (13.45-53.57 μg/m^3), 37.29 μg/m^3 (18.24-105.29 μg/m^3), 63.65 μg/m^3 (33.26-165.19 μg/m^3), and 24.01 μg/m^3 (9.99 μg/m^3-63.03 μg/m^3) for PM_1, $PM_{2.5}$, PM_{10}, and NO_2, respectively. Details about daily averages and ranges are shown in Table A2 (29). The 3-year average PM_1, $PM_{2.5}$, PM_{10}, and NO_2 exposure for each participant are displayed in Fig. 1.

Association Between Air Pollution and Bone Strength

Significantly negative associations between the 3-year average of air pollution (PM_1, $PM_{2.5}$, PM_{10}, and NO_2) and the QUI were found (Table 2). In the main model (model 4), after adjustment for the covariates (eg, demographic characteristics, socioeconomic variables, health behavior, diet), every 10 μg/m^3 increase in the 3-year average PM_1, $PM_{2.5}$, PM_{10}, and NO_2 were associated with −5.38 units (95% CI: −6.17, −4.60), −1.89 units (95% CI: −2.33, −1.44), −0.77 units (95% CI: −1.08, −0.47), and −2.02 units (95% CI: −2.32, −1.71) of change in the QUI, respectively (Table 2). The concentration-response relationships between outdoor air pollutions and bone strength were approximately linear (Fig. 2).

Table 1. Characteristics of the study participants

Characteristics	Participants (N = 66 598)
Age (mean ± SD), years	52.46 ± 11.38
Female (%)	40 621 (61.0)
Region (%)	
Sichuan	17 612 (26.4)
Chongqing	14 299 (21.5)
Yunnan	19 475 (29.2)
Guizhou	15 212 (22.8)
Ethnicity (%)	
Han	41 442 (62.2)
Dong	5932 (8.9)
Bouyi	4818 (7.2)
Yi	4356 (6.5)
Miao	4462 (6.7)
Bai	5588 (8.4)
Living in rural areas (%)	32 005 (48.1)
Education level (%)	
Illiteracy	16 108 (24.2)
Primary school	17 302 (26.0)
Junior high school	18 138 (27.2)
High school	7863 (11.8)
Junior college or higher	7187 (10.8)
Occupation (%)	
Agriculture and related	24 664 (37.0)
Factory worker	4840 (7.3)
Clerk	10 115 (15.2)
Self-employed	4220 (6.3)
Unemployed	19 202 (28.8)
Other	3557 (5.3)
Annual family income (%)	
<12 000	11 806 (17.7)
12 000-20 000	11 504 (17.3)
20 000-60 000	24 422 (36.7)
60 000-100 000	9985 (15.0)
>=100 000	8881 (13.3)
Smoking status (%)	
Never	49 173 (73.8)
Quit	3412 (5.1)
Current	14 013 (21.0)
Dose of smoking (mean ± SD), cigarettes/week	24.28 ± 55.41
Alcohol drinking status (%)	
Never	37 435 (56.2)
Occasionally	19 861 (29.8)
Often	9302 (14.0)
Dose of alcohol intake (mean ± SD), grams/week	25.61 ± 81.8
Physical activity (mean ± SD), METs/day	26.83 ± 18.40
Sedentary time (%), hours/week	
Quartile 1 [0, 9]	14 939 (22.4)
Quartile 2 (9, 14)	19 234 (28.9)
Quartile 3 (14, 21)	15 804 (23.7)
Quartile 4 (21, 120)	16 621 (25.0)
Passive smoking	34 640 (52.0)
Indoor pollution (%)	
Light	10 339 (15.5)
Medium	52 797 (79.3)
Heavy	3462 (5.2)
Use indoor heating	42 072 (63.2)
Intake calcium supplement (%)	9140 (13.7)
Intake vitamin D supplement (%)	1374 (2.1)
Drink milk (%)	23 138 (34.7)
Eat poultry meat (%)	19 037 (28.6)
Eat red meat (%)	60 676 (91.1)
Eat fruit (%)	54 657 (82.1)
Eat vegetables (%)	66 236 (99.5)
BMI (mean ± SD), kg/m^2	24.00 ± 3.43
Ultraviolet radiation (mean ± SD), kJ/m^2	162.86 ± 24.89
QUS parameters	
QUI (mean ± SD)	70.21 ± 26.77
SOS (mean ± SD), m/s	1531.51 ± 50.52
BUA (mean ± SD), dB/MHz	32.42 ± 40.93

Abbreviations: BMI, body mass index; BUA, broadband ultrasound attenuation; MET, metabolic equivalent task; QUI, quantitative ultrasound index; QUS, quantitative ultrasound; SOS, speed of sound.

The quantile regression results showed that the associations between long-term exposure to PM_1, $PM_{2.5}$, PM_{10}, and NO_2 and bone strength gradually increased with the increasing quantiles of bone strength (Fig. 3). For instance, among participants with a QUI > 88.36 units (ie, 90th percentile), a 10-μg/m^3 increase in 3-year PM_1 exposure was significantly associated with a decrease of 5.21 units (95% CI: −5.90, −4.29) in the QUI, whereas among individuals with a QUI < 53.71 units (ie, 10th percentile), a 10μg/m^3 increase in 3-year PM_1 exposure was significantly associated with a decrease of 0.92 units (95% CI: −1.31, −0.52) in the QUI.

Stratified Analysis

Evidence of effect modification by several factors was generally consistent among the 4 air pollution types. The results suggested that the adverse impact of these pollutants might be more significant in people younger than 65 years, never smokers, urban residents, and females (Fig. 4).

Sensitivity Analysis

The results of the 2 pollution models are shown in Table 3. The effects of PM_1, $PM_{2.5}$, and NO_2 on bone strength

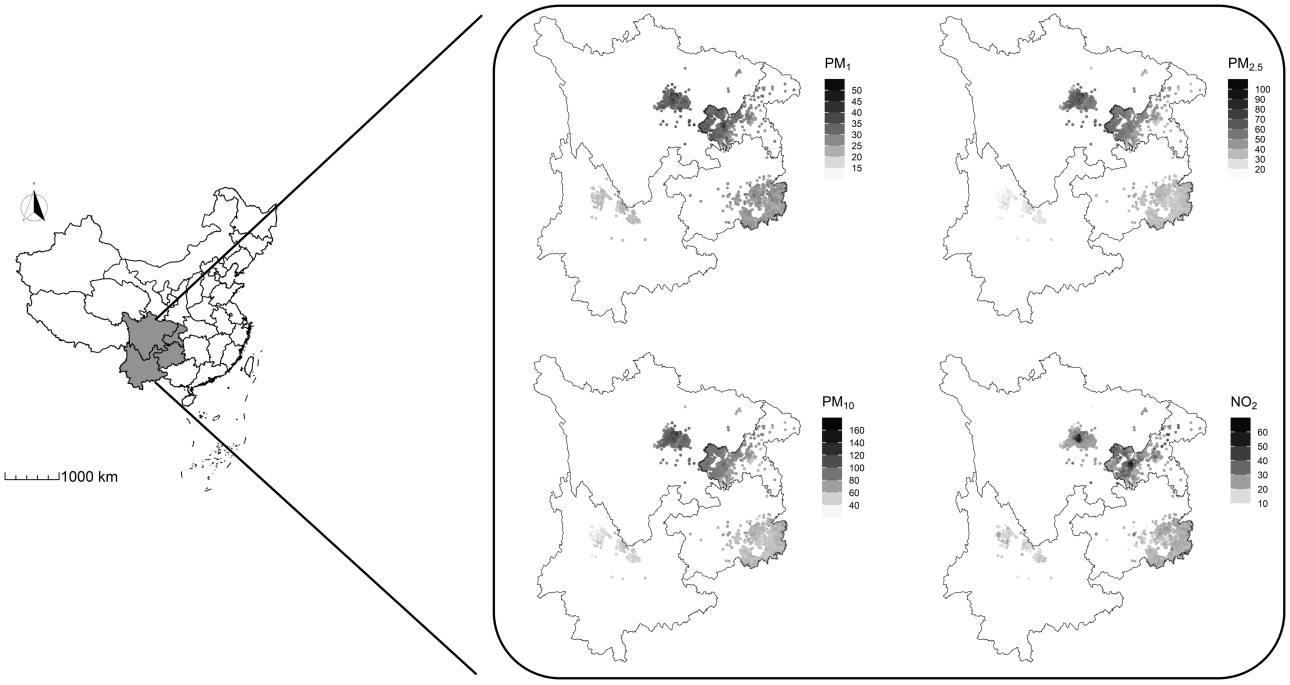

Figure 1. The 3-year average PM_1, $PM_{2.5}$, PM_{10}, and NO_2 exposures for the study participants (66 598) in the 4 provinces (Sichuan, Chongqing, Guizhou, and Yunnan) of Southwest China.

Table 2. The mean difference in the QUI associated with each 10-μg/m^3 increase in the 3-year average PM_1, $PM_{2.5}$, PM_{10}, and NO_2 concentrations

Pollutant	Mean difference(*95%CI*)			
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
PM_1	-6.05 (-6.83, -5.28)	-5.44 (-6.22, -4.66)	-5.44 (-6.23, -4.66)	-5.38 (-6.17, -4.6)
$PM_{2.5}$	-2.06 (-2.49, -1.63)	-1.81 (-2.24, -1.37)	-1.81 (-2.25, -1.37)	-1.89 (-2.33, -1.44)
PM_{10}	-0.86 (-1.16, -0.57)	-0.72 (-1.02, -0.42)	-0.72 (-1.02, -0.43)	-0.77 (-1.08, -0.47)
NO_2	-2.33 (-2.62, -2.03)	-2.03 (-2.33, -1.73)	-2.03 (-2.33, -1.73)	-2.02 (-2.32, -1.71)

Abbreviations: NO_2, nitrogen dioxide; PM_1, particulate matter ≤1μm in aerodynamic diameter; $PM_{2.5}$, particulate matter ≤2.5μm in aerodynamic diameter; PM_{10}, particulate matter ≤10μm in aerodynamic diameter.

[a] Model 1 was adjusted for age, sex, ethnicity, region, rural/urban.

[b] Model 2 was further adjusted for smoking status, alcohol consumption status, physical activity level, BMI, and sedentary time.

[c] Model 3 was additionally accounted for educational level, annual family income, calcium intake status, and vitamin D intake status.

[d] Model 4 was also adjusted for diet variables (including milk, red meat, poultry meat, vegetables, and fresh fruits), ultraviolet radiation, occupation, and indoor heating use.

were generally consistent after the inclusion of another pollutant, but the effect of PM_{10} lost statistical significance after further adjusting the NO_2 in the main model (Table 3). Furthermore, 2-year and 4-year average concentrations of air pollutants were used as the exposure variables, and the results were consistent (Table 4). In addition, we sequentially excluded participants with rheumatoid arthritis, rheumatic arthritis, diabetes, and chronic hepatitis/cirrhosis, and no substantial change was observed (Table 5). After including the participants that had lived in their current residences less than 3 years, the conclusion was also consistent (Supplemental Table A3 (29)). Lastly, after using the dose of smoking and alcohol drinking as continuous covariates, the mean differences for a 10-μg/m^3 increase in the 3-year average PM_1, $PM_{2.5}$, PM_{10}, and NO_2 were −5.41 units (95% CI: −6.20, −4.63), −1.89 units (95% CI: −2.34, −1.45), −0.78 units (95% CI: −1.1, −0.48), and −2.02 units (95% CI: −2.33, −1.72), respectively.

Discussion

We investigated the associations between long-term exposure to air pollution (PM_1, $PM_{2.5}$, PM_{10}, and NO_2) and bone strength. To the best of our knowledge, this is the

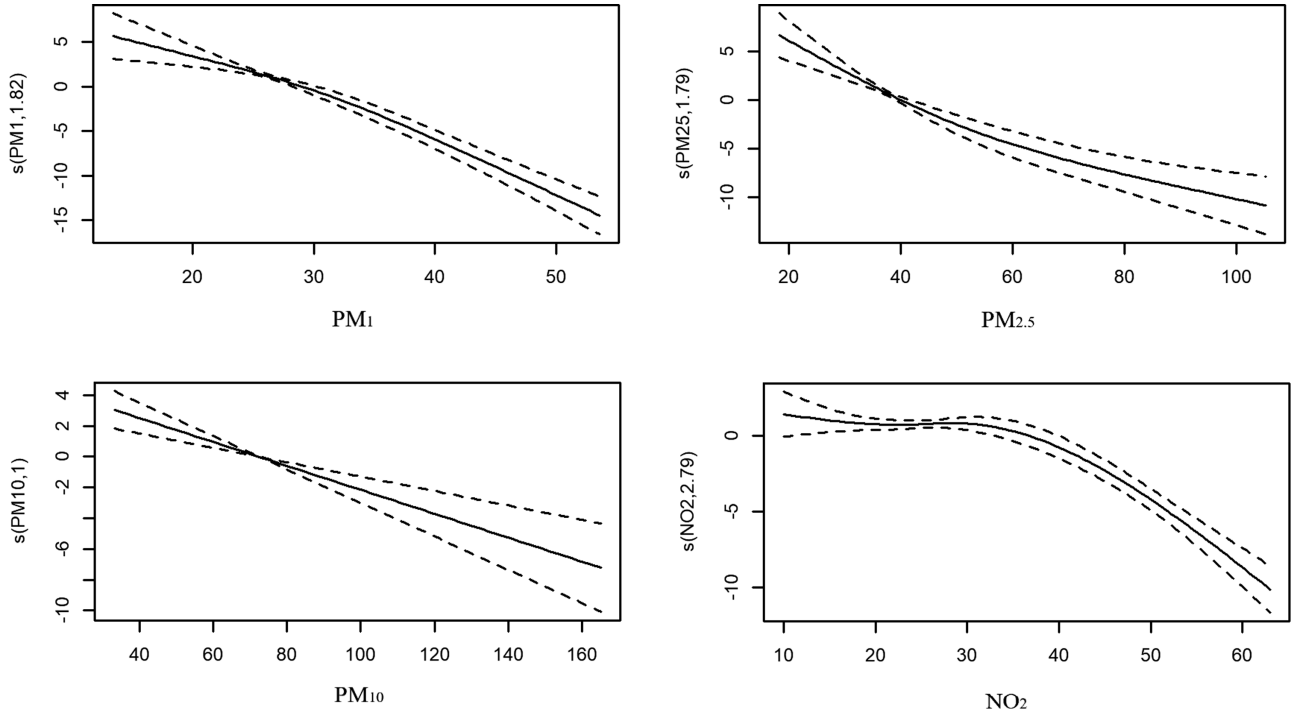

Figure 2. Concentration-response curves for the association between long-term exposure to air pollution (PM_1, $PM_{2.5}$, PM_{10}, and NO_2) and the QUI. The x-axis is 3-year average concentration of air pollution. The y-axis indicates the contribution of the smoother to the fitted values after adjusting for the covariates.

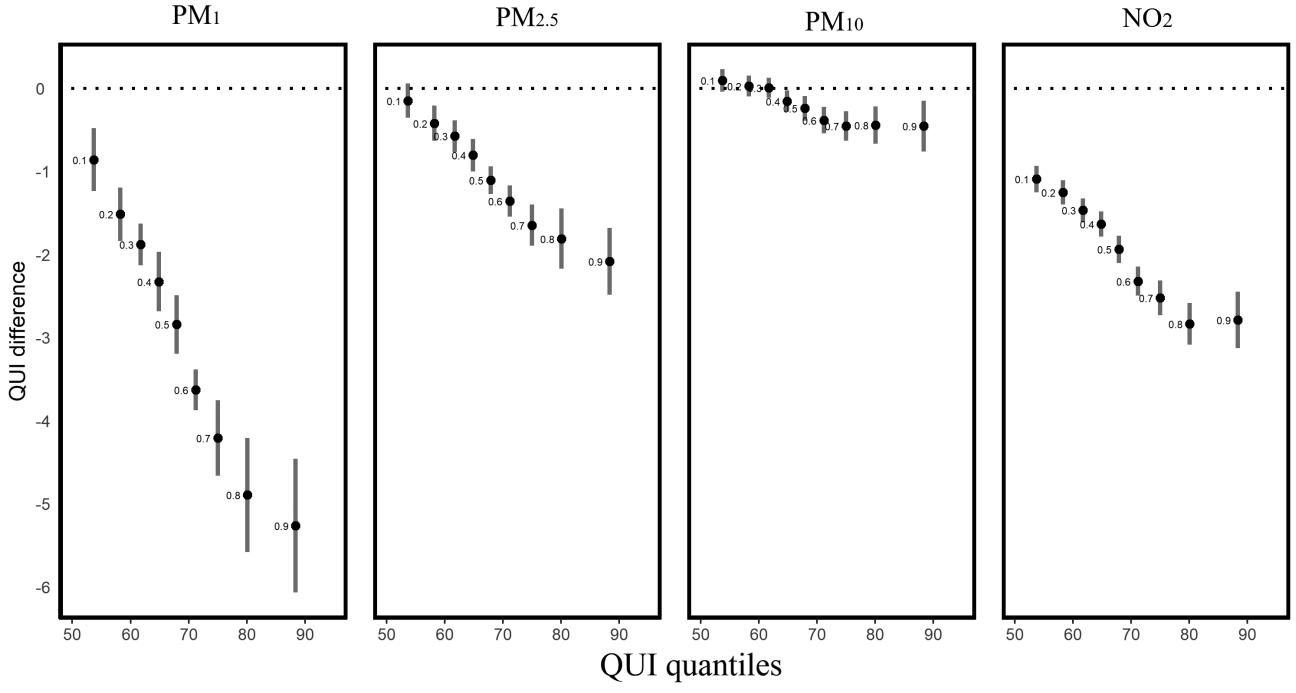

Figure 3. Associations between 10-μg/m^3 increases in long-term air pollution exposure and quantiles of QUI. The x-axis represents the location at the distribution (ie, quantile) of the QUI; the y-axes represent the QUI difference for a 10-μg/m^3 increase in exposure. The error bars represent a 95% bootstrap CI. The numbers next to each point estimate indicate the deciles. Adjustments were made for participant age, sex, ethnicity, region, rural/urban, smoking status, alcohol drinking status, physical activity level, BMI, sedentary time, educational level, annual family income, calcium intake status, vitamin D intake status, diet variables (including milk, red meat, poultry meat, vegetable, and fresh fruits), ultraviolet radiation, occupation, and indoor heating use.

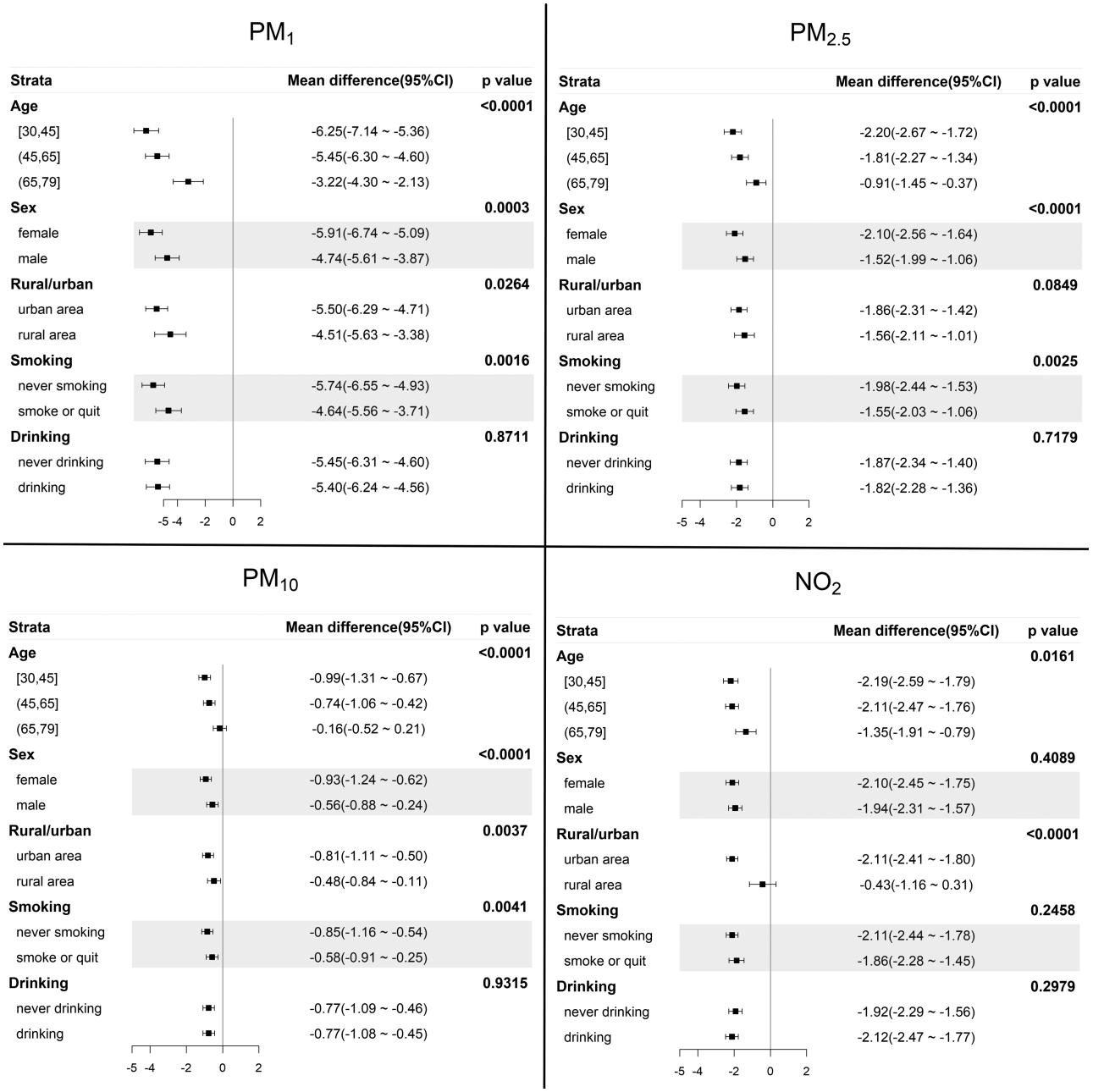

Figure 4. Mean difference with 95% CIs in QUI per 10-μg/m^3 increase in air pollutants, as stratified by age, sex, rural/urban status, smoking status, and alcohol drinking status. Statistically significant modifier effects were tested using a likelihood ratio test. Adjustments were made for participant age, sex, ethnicity, region, rural/urban status, smoking status, alcohol drinking status, physical activity level, BMI, sedentary time, educational level, annual family income, calcium intake status, vitamin D intake status, diet variables (including milk, red meat, poultry meat, vegetable, and fresh fruits), ultraviolet radiation, occupation, and indoor heating use.

first large-scale epidemiological study using high-resolution model-based exposure estimation. In this study, we found that long-term exposure to ambient air pollution (PM_1, $PM_{2.5}$, PM_{10}, and NO_2) was significantly associated with decreased bone strength as measured by QUS, independent of a series of confounders. Moreover, the quantile regression analyses revealed that the negative correlations between exposure to air pollution and bone strength are stronger among individuals with higher bone strength.

The mechanism is still understudied, but there are 4 potential pathways (41). First, ambient air pollutants induce systemic inflammation (14), which may affect the differentiation and function of osteoblasts and osteoclasts and then disturb bone homeostasis (16, 17). Second, gases and metal compounds in air pollution, such as NO_2, O_3, and heavy metals, can lead to free radical formation and then cause inflammatory responses (15, 42), or even directly induce bone aging due to their capacity to cross cell membranes

(43). Third, some endocrine-disrupting chemicals have been shown to disturb bone homeostasis (41). These substances are widely present in air pollution (44). Fourth, air pollution can cause vitamin D deficiency directly and indirectly (45). Atmospheric pollution in the troposphere can absorb ultraviolet radiation and reduce the ultraviolet radiation reaching the surface (45). In addition, serious air pollution may be associated with decreased outdoor activities, resulting in less vitamin D production.

Our conclusions regarding the association between long-term air pollution exposure and bone health are generally consistent with some previous studies. A cross-sectional study conducted in Oslo found that bone health was negatively associated with long-term exposure to air pollution in men aged 75 to 76 years (22). Consistent with our results, evidence from India showed that a lower BMD was associated with a higher annual mean of $PM_{2.5}$ exposure (20). A prospective study of the Taiwan Longitudinal Health Insurance database showed that individual exposure to a high quartile of CO and NO_2 concentrations was associated with an increased risk of osteoporosis (21).

Stratified analyses showed that urban residents, females, never smokers, and those below 65 years old were more sensitive to the effects of long-term air pollution exposure on bone health. There is some biological rationality in the results of the stratified analyses. The difference between urban and rural areas might have occurred because of the different sources and composition of air pollution in urban and rural areas (46-48). Studies have indicated that there is a toxicity difference in different air pollution sources (49, 50). Besides, these pollutions we studied were associated with some other traffic or industrial pollutants, resulting in the urban-rural differences in the effect. A more negative association was found among female subjects in our study. Women are more susceptible to osteoporosis (51). The decline of estrogen during the perimenopausal period will decrease the inhibitory effect on osteoclasts (52); therefore, bone metabolism might be more easily disturbed by air pollution. The same result was also found in never smokers. This result might occur because the majority of never smokers were female.

In contrast to previous studies suggesting that elderly individuals are more susceptible (20, 24), our study showed that the impact of air pollution on bone strength was significantly higher among participants aged ≤65 years. The results of the quantile regression may explain this age-related difference. In the quantile regression, people with lower bone strength are less sensitive to air pollution, and the elderly usually have weaker bones (11, 13). In addition, the decline in bone strength in elderly patients is primarily due to the aging of bone tissue, so the effect of air pollution may be correspondingly weakened.

The quantile regressions showed that the more substantial effects of air pollution exposure were found at higher quantiles of bone strength. The same trends were found among all 4 air pollutants. Given the observed association

Table 3. Results of 2-pollutant models for the association between long-term air pollution and QUI

Pollutant	Mean difference (95% CI)
PM_1 + NO_2 [a]	
PM_1 [b]	-4.17 (-4.99, -3.34)
NO_2 [c]	-1.50 (-1.82, -1.18)
$PM_{2.5}$ + NO_2	
$PM_{2.5}$	-1.17 (-1.63, -0.71)
NO_2	-1.79 (-2.11, -1.47)
PM_{10} + NO_2	
PM_{10}	-0.22 (-0.54, 0.10)
NO_2	-1.95 (-2.26, -1.63)

Adjustments were made for participant age, sex, ethnicity, region, rural/urban status, smoking status, alcohol drinking status, physical activity level, BMI, sedentary time, educational level, annual family income, calcium intake status, vitamin D intake status, diet variables (including milk, red meat, poultry meat, vegetable, and fresh fruits), ultraviolet radiation, occupation, and indoor heating use.

Abbreviations: NO_2, nitrogen dioxide; PM_1, particulate matter ≤1 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤10 μm in aerodynamic diameter.

[a] Pollutants included in the model.

[b] result for PM_1 in two-pollutant model.

[c] result for NO_2 in two-pollutant model.

Table 4. Association of bone strength with each 10-μg/m^3 increase in the PM_1, $PM_{2.5}$, PM_{10}, and NO_2 concentrations with different cumulative exposure times

	Mean difference (95% CI)			
	PM_1	$PM_{2.5}$	PM_{10}	NO_2
2-year average	-4.83 (-5.63, -4.04)	-1.93 (-2.36, -1.51)	-0.87 (-1.18, -0.55)	-2.11 (-2.42, -1.80)
3-year average	-5.38 (-6.17, -4.60)	-1.89 (-2.33, -1.44)	-0.77 (-1.08, -0.47)	-2.02 (-2.32, -1.71)
4-year average	-5.98 (-6.78, -5.24)	-2.15 (-2.61, -1.69)	-0.91 (-1.22, -0.60)	-2.05 (-2.36, -1.74)

Abbreviations: NO_2, nitrogen dioxide; PM_1, particulate matter ≤1 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤10 μm in aerodynamic diameter.

Table 5. The association of QUI with each 10-μg/m3 increase over the 3-year average PM_1, $PM_{2.5}$, PM_{10}, and NO_2 concentrations after sequentially excluding participants

	Mean difference (95%CI)			
	PM_1	$PM_{2.5}$	PM_{10}	NO_2
Rheumatic arthritis[a]	-5.29 (-6.07, -4.5)	-1.90 (-2.35, -1.45)	-0.77 (-1.08, -0.46)	-1.98 (-2.29, -1.68)
Rheumatoid arthritis[b]	-5.32 (-6.12, -4.52)	-1.92 (-2.37, -1.46)	-0.78 (-1.09, -0.47)	-2.00 (-2.31, -1.69)
Diabetes[c]	-5.20 (-6.01, -4.39)	-1.86 (-2.32, -1.39)	-0.74 (-1.06, -0.43)	-2.03 (-2.34, -1.71)
Chronic hepatitis/cirrhosis[d]	-5.21 (-6.02, -4.39)	-1.88 (-2.35, -1.41)	-0.73 (-1.05, -0.41)	-2.08 (-2.4, -1.76)

Adjusted for age, sex, ethnicity, region, rural/urban status, smoking status, alcohol drinking status, physical activity level, BMI, sedentary time, educational level, annual family income, calcium intake status, vitamin D intake status, diet variables (including consumption of milk, red meat, poultry meat, vegetable, and fresh fruits), ultraviolet radiation, occupation, and indoor heating use.

Abbreviations: NO_2, nitrogen dioxide; PM_1, particulate matter ≤1 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter; PM_{10}, particulate matter ≤10 μm in aerodynamic diameter.

[a] Excluded 4480 participants with rheumatoid arthritis.

[b] Excluded 1276 participants with rheumatic arthritis.

[c] Excluded 6945 participants with diabetes.

[d] Excluded 1237 participants with chronic hepatitis or cirrhosis.

between long-term exposure to air pollution and decreased bone strength, air pollution may lead to severe bone loss in many developing countries, which have severe air pollution and younger populations. Therefore, air pollutions may lead to a higher prevalence of osteoporosis in developing countries in the future.

There are several strengths in this study. First, this is the first study to explore the relationship between long-term exposure to air pollution and bone strength on the whole distribution of bone strength. Second, our study was based on an established cohort, allowing us access to a rich set of detailed covariates. Third, in this study, the range of pollution concentrations was broad, which led to a better representation of the whole pattern in the negative effect of air pollution on bones. Fourth, this is the first study to take ultraviolet radiation into account, thereby excluding the effect of insufficient ambient ultraviolet light.

Several limitations were associated with this work. First, only the baseline survey data of the cohort were used in this study. The cross-sectional design restricted us to a noncausal relationship between air pollution exposure and bone strength. Second, we did not adjust the covariates of air conditioning use, hormone use, and diseases (eg, chronic kidney disease and chronic gastroenteritis). Third, we used the QUI as measured by calcaneus QUS as the indicator of bone strength because it is difficult to apply measurements such as the dual-energy x-ray absorptiometry to a large-size population study. However, epidemiological studies have shown that QUS measurements are independent risk factors for osteoporotic fracture (53, 54). The ability of the QUS parameters to predict osteoporotic fractures is at least the same as the BMD (55, 56). Fourth, we used residential ambient air pollution concentration with 1-km^2 resolution as the proxy of individual air pollution exposure. Individual air pollution exposure is related to the locations that the person moves through as well as the time spent in each location. This time-activity pattern of individuals was not considered in this study, resulting in exposure estimation bias. Future studies considering time-activity patterns of individuals are needed to estimate the association between long-term exposure to air pollution and bone strength.

Conclusion

Our findings demonstrated that long-term ambient air pollution exposure was significantly associated with decreased bone strength in Chinese adults. Long-term air pollution exposure has a more substantial adverse effect on bone health among populations with higher bone strength. In addition, those aged ≤65 years, females, never smokers, and those living in urban areas might be more susceptible than others to the negative effect of long-term exposure to air pollution. Our study can serve as a reference on pollution control in highly polluted low- and middle-income countries.

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