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Living near greenness is associated with higher bone strength: A large cross-sectional epidemiological study in China

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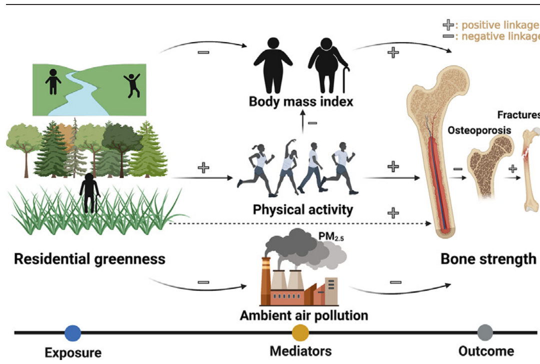
HIGHLIGHTS

- New evidence from the general population on residential greenness and bone health.
- Residential greenness was positively associated with bone strength.
- Stronger linkages were found in males, city dwellers, richer, smokers, and drinkers.
- Ambient air pollution, physical activity, and BMI partially mediated those associations.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Living near green spaces may benefit various health outcomes. However, no studies have investigated the greenness-bone linkage in the general population. Moreover, to which extent ambient air pollution (AAP), physical activity (PA), and body mass index (BMI) mediate this relationship remains unclear. We aimed to explore the association between greenness and bone strength and the potential mediating roles of AAP, PA, and BMI in Chinese adults.
Methods: This cross-sectional analysis enrolled 66,053 adults from the China Multi-Ethnic Cohort in 2018–2019. The normalized difference vegetation index (NDVI) and enhanced vegetation index (EVI) were employed to define

Abbreviations: AAP, Ambient air pollution; BMD, Bone mineral density; BMI, Body mass index; BUA, Broadband ultrasound attenuation; CMEC, China Multi-Ethnic Cohort; EVI, Enhanced vegetation index; MET, Metabolic equivalent; NDVI, Normalized difference vegetation index; PA, Physical activity; PM, Particulate matter; QUI, Quantitative ultrasound index; QUS, Quantitative ultrasound; SOS, Speed of sound; SEM, Structural equation modeling.

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residential greenness. The calcaneus quantitative ultrasound index (QUI) was used to indicate bone strength. Multiple linear regression models and mediation analyses were used to estimate the residential greenness-bone strength association and potential pathways operating through AAP (represented by $PM_{2.5}$ [particulate matter <2.5 μm in diameter]), PA, and BMI. Stratification analyses were performed to identify susceptible populations.
Results: Higher residential exposure to greenness was significantly associated with an increase in QUI, with changes (95% confidence interval) of 3.28 (3.05, 3.50), 3.57 (3.34, 3.80), 2.68 (2.46, 2.90), and 2.93 (2.71, 3.15) for every interquartile range increase in $NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m}, respectively. Sex, urbanicity, annual family income, smoking, and drinking significantly modified the association of greenness-bone strength, with more remarkable associations in males, urban residents, subjects from wealthier families, smokers, and drinkers. For the $NDVI_{500m}$/EVI_{500m}-QUI relationship, the positive mediating roles of $PM_{2.5}$ and PA were 6.70%/8.50 and 2.43%/2.69%, respectively, whereas those negative for BMI and PA-BMI were 0.88%/1.06% and 0.05%/0.05%, respectively.
Conclusion: Living in a greener area may predict higher bone strength, particularly among males, urban residents, wealthier people, smokers, and drinkers. AAP, PA, BMI, and other factors may partially mediate the positive association. Our findings underscore the importance of optimizing greenness planning and management policies.

1. Introduction

Osteoporosis, a degenerative skeletal disorder (Compston et al., 2019), and related fractures threaten public health globally. Worldwide, more than 200 million people are affected by osteoporosis (Pisani et al., 2016), with over 8.9 million osteoporosis-related fracture cases reported annually (Pouresmaeili et al., 2018). A distinctive characteristic of osteoporosis is compromised bone strength (Compston et al., 2019). Persistent loss of bone strength and ensuing osteoporosis can increase the susceptibility to fractures, which may substantially restrict human activities for daily living and contribute to premature mortality (Fischer et al., 2017). Therefore, improving bone strength can decrease osteoporosis, the related fracture risk, and the accompanying personal and societal burdens.

Identifying and understanding the risk and protective factors of osteoporosis are essential for improving bone strength. Recently, residential greenness has attracted interest as a modifiable environmental factor with a wide range of benefits for human health (Fong et al., 2018; Twohig-Bennett and Jones, 2018), such as positive effects on metabolism-related diseases (Dong et al., 2021a; Dong et al., 2021b; Yang et al., 2020; Zhang et al., 2021), mental health (Ihlebaek et al., 2018; Liu et al., 2019a; Liu et al., 2019b), and mortality (Barboza et al., 2021; Bauwelinck et al., 2021; Crouse et al., 2017; Ji et al., 2019).

Previous studies provide some biological rationale for the mechanisms of greenness's protective effects. It is generally considered that residential greenness improves health by mitigating harmful environmental exposure (e.g., ambient air pollution [AAP], sound, and heat waves), boosting physical activity (PA), alleviating physical and mental stress, and promoting social connections (Markevych et al., 2017). In addition, higher greenery for a living may reduce the risk of adiposity (Fan et al., 2022; Huang et al., 2020a; Huang et al., 2020b). Greenness and body mass index (BMI) exhibit a negative relationship, possibly because living in green environments leads to increased PA levels (Markevych et al., 2017; Villeneuve et al., 2018).

Some beneficial reactions to residential exposure to greenness influence human bone strength (Compston et al., 2019; Pouresmaeili et al., 2018). Long-term exposure to AAP has been associated with lower bone mineral density (BMD) (Alvaer et al., 2007; Chen et al., 2015), lower bone mineral content (Ranzani et al., 2020), and higher osteoporosis (Chang et al., 2015) and fracture risks (Prada et al., 2017). Additionally, extensive studies have revealed the benefits of enhanced PA in improving bone strength and decreasing the risk of osteoporosis and related fractures (Cauley and Giangregorio, 2020) (Compston et al., 2017). Furthermore, BMI is positively associated with BMD, and a low BMI is a vitally important predictor of bone loss and hip fracture risk (De Laet et al., 2005; Felson et al., 1993; Reid, 2002).

Therefore, we hypothesized that residential exposure to greenness is a potentially protective factor against decreased bone strength. To date, only one study has focused on the possible links between residential greenness and bone and suggested the adverse effects of residential greenness exposure on bone among the elderly in Hongkong (Lin et al., 2021). Epidemiological evidence on the relationship between greenness and bone health in the general population is lacking, particularly in large samples. Furthermore, although epidemiological evidence implies a latent role of alleviated AAP exposure, increased PA levels, and decreased BMI in the relationship between residential greenness-related bone status, the degree to which these factors mediate the relationship is unknown.

Accordingly, we examined the associations between residential exposure to greenness and bone strength among approximately 70,000 adults aged 30–79 years in southwest China. The extent to which the residential greenness-bone strength association was mediated through alleviated AAP (represented by $PM_{2.5}$ [particulate matter <2.5 μm in diameter]), promotion of PA, reduced BMI, and one intertwined path (i.e., ↑residential greenness→ ↑PA→ ↓BMI→ ↓bone strength) was also assessed.

2. Material and methods

2.1. Study design and population

We employed a cross-sectional, observational design. Baseline data from the China Multi-Ethnic Cohort (CMEC) study, a large community-based longitudinal study in Southwest China, were utilized. The CMEC was assessed for the prevalence and risk factors affecting non-communicable diseases in undeveloped regions of China. Detailed information on the sampling and survey methods used in the CMEC study has been described in the profile (Zhao et al., 2021). Briefly, a multistage stratified cluster sampling method was used in the CMEC study. A total of 99,556 participants aged 30–79 years were recruited from five provinces (Sichuan, Chongqing, Guizhou, Tibet, and Yunnan) between May 2018 and September 2019. Specific baseline data were collected through computerized questionnaires and physical and biochemical examinations. The CMEC study was approved by the ethics committee of Sichuan University (Approval number: K2016038, K2020022), and written informed consent was obtained from all participants.

The exclusion criteria for subjects were as follows: (i) Lhasa and Aba Tibetans who were nomads without a fixed abode and lived at high altitudes in a hypoxic environment, the latter of which may alter autonomic nervous system and endocrine functions (Facco et al., 2005); (ii) lack of residential address and residing at the current address for fewer than three years; (iii) pregnancy; (iv) baseline self-reported osteoporosis; and (v) missing information on variables (greenness, mediators, indicators for bone strength, and critical covariates) required for the analyses. After exclusion, 66,053 participants remained for further analysis (Fig. S1). The baseline characteristics of the included and excluded populations with missing variable information are presented in Table S1.

2.2. Outcome measurement

As a critical measure of bone health, bone strength is determined by integrating bone quality and quantity (Schnitzler et al., 1993). We used the quantitative ultrasound index (QUI) as an indicator of bone strength. The QUI, which indicates risks related to BMD, osteoporosis, and fractures

(Olszynski et al., 2013), was determined using a linear combination of calcaneal broadband ultrasound attenuation (BUA) and speed of sound (SOS): QUI = 0.41 × (BUA + SOS) − 571 (Magkos et al., 2005). BUA and SOS were measured using quantitative ultrasound (QUS) with an OSTEOKJ3000 ultrasonic bone densitometer (KeJin, Inc., Nanjing, China) operated by both standardized, locally-trained doctors and nurses at local medical centers at each baseline survey site from May 2018 to September to 2019. QUS is a noninvasive method commonly adopted to evaluate bone strength without causing radiation damage (Baroncelli, 2008; Correa-Rodriguez et al., 2017; Qiao et al., 2020). QUS parameters are independent risk factors for osteoporotic fractures (Schalamon et al., 2004) with at least the same predictive power as BMD (Moayyeri et al., 2012) obtained from dual-energy X-ray absorptiometry. A lower QUI value indicates lower bone strength. Detailed information regarding the measurement of bone strength has been described previously (Wu et al., 2021).

2.3. Exposure measurement

The normalized difference vegetation index (NDVI) and enhanced vegetation index (EVI) were calculated to measure individual residential exposure to greenness for each participant as previously described (James et al., 2016; Pereira et al., 2012; Wu et al., 2014). The NDVI and EVI values range between −1 and 1. A value closer to 1 indicates higher vegetation density (James et al., 2016; Wu et al., 2014). Negative values for NDVI/EVI were not removed and were treated as zero in all modeling processes (Markevych et al., 2017).

Briefly, 92 images of 16-day Moderate Resolution Imaging Spectroradiometer/ Terra sensor satellite images (https://modis.gsfc.nasa.gov/data/dataprod/mod13.php) for the period 2015–2018 acquired in April 2020 were utilized to obtain both NDVI and EVI measurements for 250-m pixels and to derive the mean yearly NDVI/EVI values (Dong et al., 2021b; McMorris et al., 2015; Thiering et al., 2016). The mean yearly values of NDVI/EVI were allocated to participants according to their baseline geocoded dwellings, and the three-year average NDVI/EVI prior to baseline was calculated for 500 and 1000 m buffers as a surrogate for residential exposure to greenness.

2.4. Covariates and potential mediators

2.4.1. Covariates

During the study period, a standardized and validated questionnaire was administered to the participants by well-trained investigators to collect demographic information, socioeconomic status, health-related behaviors, physician-diagnosed diseases, medication history, family history, reproductive history, PA, dietary habits, and psychological status. This information was used to adjust for an extensive set of covariates.

Referring to previous studies of residential greenness or bone health (Lin et al., 2021; Markevych et al., 2017; Pisani et al., 2016; Pouresmaeili et al., 2018; Wu et al., 2020; Wu et al., 2021), covariates were identified, including demographic information (age, sex, ethnicity, region, and urbanicity), socioeconomic status (annual family income, education level, occupation), health-related behavior (smoking status, drinking status, passive smoking, and indoor air pollution), dietary intake and supplement (milk, red meat, poultry meat, vegetables, fresh fruit, calcium supplement, and vitamin D supplement), and an environmental factor (ultraviolet radiation). The exhaustive definitions and classifications of these variables are presented in Table S2.

2.4.2. Mediators

Three potential mediators, the AAP ($PM_{2.5}$), level of PA, and BMI, were examined. First, the $PM_{2.5}$ daily concentration over 1 km^2 was estimated using by space-time extremely randomized trees (STET) model, integrating data from multiple sources (aerosol optical depth, land-use status, ground-monitored AAP emission, meteorology, etc.) (Wei et al., 2019; Wei et al., 2020; Wei et al., 2021). The model performance was assessed through ten-fold cross-validation and showed an R^2 of 0.86–0.90 and root mean square error of 10.0–18.4 μg m^{-3} on a daily basis. After mapping the daily concentrations of $PM_{2.5}$ to each participant based on the geocoded residence location of the participant, a three-year mean $PM_{2.5}$ exposure concentration before the survey was calculated as a mediator. Second, the level of PA was measured using a subjective PA domain-specific questionnaire, which contained questions on PA frequency, intensity, and duration of daily housework, leisure time, commuting, and work during the year preceding the baseline survey (Du et al., 2013; Matthews et al., 2003; Wareham et al., 2002). Metabolic equivalent (MET) values were used to measure PA intensity and were allocated to diverse physical activities. The daily MET (MET/day) scores of different domains, determined to continuously express PA levels, were calculated from the product of MET and duration (h/day) and summed for each domain to represent the total amount of PA for each participant (Ainsworth et al., 2011; Whitman et al., 2001). Third, BMI (kg/m^2) was computed as the ratio of weight (kg) to height (m^2) according to the baseline anthropometric measurements to characterize the adiposity status of the subjects.

2.5. Statistical analyses

The distributions of all variables are summarized. Continuous variables are presented as the mean ± standard deviation (SD) or median ± interquartile range (IQR), whereas categorical variables are presented as numbers (%). Three multivariate linear regression models with different covariates were constructed to adjust for potential confounders between single residential greenness indicators ($NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m}) and bone strength. Model 1 was adjusted for age, sex, ethnicity, region, rural and urban areas, educational level, and annual family income. Model 2 included occupation, smoking status, drinking status, secondary smoking, and indoor air pollution. Model 3 adjusted Model 2 plus additional dietary and supplemental variables (calcium supplement, vitamin D supplement, milk, red meat, poultry meat, vegetables, and fresh fruits) and three-year average ultraviolet radiation. In addition to the mediation analyses, Model l, defensively adjusted for confounding factors, was used as the primary model. The mediation models were adjusted in accordance with Model 3.

The modification effects were measured after the study subjects were stratified by age (30–45, 45–65, 65–79 years), sex (male, female), rural/urban areas, annual family income (<20,000, ≥20,000 yuan), smoking (never smoke, ever smoke or quit), and drinking (never drink, ever drink). A heterogeneity test was performed to assess the significance of differences among the strata. Serial two-mediator and parallel one-mediator mediation models (Dzhambov et al., 2020) were used to calculate the mediating effects of $PM_{2.5}$, PA, and BMI in association with residential greenness in the 500 buffer ($NDVI_{500m}$ and EVI_{500m}) exposure on bone strength based on structural equation modeling (SEM) using the 'lavaan' R package (Rosseel, 2012). Sensitivity analyses to evaluate the robustness of the results were conducted as follows: (i) greenness indicators were converted into categorical variables depending on their quartiles to estimate the non-linear average change in bone strength across Q2–Q4 of greenness compared with that of Q1; (ii) quantile regression was used to examine the population-level exposure-outcome links across the distribution of bone strength with a range of quantiles (0.10–0.90 at intervals of 0.1, total of ten quartiles) (Koenker and Bassett, 1978); (iii) participants with certain diseases were progressively excluded, such as those with rheumatoid/rheumatic arthritis, diabetes, chronic kidney disease, and chronic hepatitis/cirrhosis, which may distort the effect of greenness on bone health; (iv) multiple imputation combined inverse probability weighting (Seaman et al., 2012) was used to account for the effects of the missing information on covariates and outcome variable due to participant attrition; (v) $NDVI_{1000m}$ and EVI_{1000m} were used to reproduce the mediation analysis; and (vi) $PM_{2.5}$, PA, and BMI were not assumed to be on the causal pathway from residential greenness to bone strength and were regarded as effect modifiers.

All analyses were performed using *R* software version 4.1.0 (www.r-project.org; The R Project for Statistical Computing, Vienna, Austria). The results were considered statistically significant at a two-tailed *P*-value <0.05.

3. Results

3.1. Descriptive statistics

The mean ± SD or median ± IQR, or numbers (%) of each index for the covariates, mediators, and QUS parameters are shown in Table 1. The 66,053 participants had a mean age of 52.45 years, and more than half were female (61%). Most participants were of Han ethnicity (62.2%), with a family income of ≥12,000 Yuan per year (82.3%). The basic descriptive statistics (e.g., mean ± SD) of $NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m} for the three-year average are presented in Table S3. The spatial variations in the greenness values ($NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m}) among the survey points are presented in Fig. S2. For instance, $NDVI_{500m}$ ranged from −0.09 to 0.71, and EVI_{500m} ranged from −0.03 to 0.46. The correlation matrix of the exposure, mediator, and outcome variables is presented in Table S4.

Table 1
Baseline characteristics of participants according to quartiles (Q) of NDVI (500 m buffer).

Characteristics	Overall	Q1	Q2	Q3	Q4
		[−0.09,0.29][a]	(0.29,0.43][a]	(0.43,0.50][a]	(0.50,0.71][a]
Number of people	66,053	16,513	16,512	16,464	16,564
Age***[b] (mean ± SD), years	52.45 ± 11.35	51.17 ± 11.72	52.37 ± 11.42	53.12 ± 10.94	53.16 ± 11.18
Male***[b] (%)	25,789 (39.0)	6804 (41.2)	6255 (37.9)	6240 (37.9)	6490 (39.2)
Region***[b] (%)					
Chongqing	14,148 (21.4)	5415 (32.8)	4123 (25.0)	2624 (15.9)	1986 (12.0)
Sichuan	17,448 (26.4)	7477 (45.3)	4597 (27.8)	2784 (16.9)	2590 (15.6)
Yunnan	19,396 (29.4)	1803 (10.9)	4541 (27.5)	7655 (46.5)	5397 (32.6)
Guizhou	15,061 (22.8)	1818 (11.0)	3251 (19.7)	3401 (20.6)	6591 (39.8)
Minority***[b] (%)	24,968 (37.8)	1860 (11.3)	6463 (39.1)	7369 (44.8)	9276 (56.0)
Living in rural areas***[b] (%)	42,922 (65.0)	4648 (28.1)	9936 (60.2)	13,842 (84.1)	14,496 (87.5)
Education level***[b] (%)					
Illiteracy	16,018 (24.3)	1502 (9.1)	3383 (20.5)	4939 (30.0)	6194 (37.4)
Primary school	17,216 (26.1)	2803 (17.0)	4267 (25.8)	5420 (32.9)	4726 (28.5)
Junior high school	18,001 (27.3)	5022 (30.4)	4833 (29.3)	4289 (26.1)	3857 (23.3)
High school	7778 (11.8)	3445 (20.9)	2067 (12.5)	1157 (7.0)	1109 (6.7)
Junior college or higher	7040 (10.7)	3741 (22.7)	1962 (11.9)	659 (4.0)	678 (4.1)
Annual family income***[b] (%), yuan					
<12,000	11,723 (17.7)	1388 (8.4)	2388 (14.5)	3491 (21.2)	4456 (26.9)
12,000–19,999	11,428 (17.3)	1809 (11.0)	2611 (15.8)	3449 (20.9)	3559 (21.5)
20,000–59,999	24,235 (36.7)	5569 (33.7)	6048 (36.6)	6619 (40.2)	5999 (36.2)
60,000–99,999	9892 (15.0)	3754 (22.7)	2815 (17.0)	1722 (10.5)	1601 (9.7)
≥100,000	8775 (13.3)	3993 (24.2)	2650 (16.0)	1183 (7.2)	949 (5.7)
Occupation***[b] (%)					
Agriculture and related	24,555 (37.2)	1518 (9.2)	4784 (29.0)	8940 (54.3)	9313 (56.2)
Worker	4799 (7.3)	1322 (8.0)	1323 (8.0)	1072 (6.5)	1082 (6.5)
Clerk	9974 (15.1)	4395 (26.6)	2828 (17.1)	1374 (8.3)	1377 (8.3)
Self-employed	4192 (6.3)	1307 (7.9)	1227 (7.4)	927 (5.6)	731 (4.4)
Unemployed	19,048 (28.8)	6714 (40.7)	5316 (32.2)	3528 (21.4)	3490 (21.1)
Other	3485 (5.3)	1257 (7.6)	1034 (6.3)	623 (3.8)	571 (3.4)
Smoking status***[b] (%)					
Never smoke	48,763 (73.8)	11,992 (72.6)	12,222 (74.0)	12,263 (74.5)	12,286 (74.2)
Quit smoking	3391 (5.1)	1037 (6.3)	879 (5.3)	738 (4.5)	737 (4.4)
Smoke	13,899 (21.0)	3484 (21.1)	3411 (20.7)	3463 (21.0)	3541 (21.4)
Drinking status***[b] (%)					
Never drinking	37,158 (56.3)	7864 (47.6)	9160 (55.5)	10,384 (63.1)	9750 (58.9)
Occasionally drinking	19,662 (29.8)	6265 (37.9)	5115 (31.0)	3883 (23.6)	4399 (26.6)
Regularly drinking	9233 (14.0)	2384 (14.4)	2237 (13.5)	2197 (13.3)	2415 (14.6)
Secondary smoking (%)	34,341 (52.0)	8664 (52.5)	8678 (52.6)	8457 (51.4)	8542 (51.6)
Indoor air pollution***[b] (%)					
Light	10,238 (15.5)	2705 (16.4)	2516 (15.2)	2482 (15.1)	2535 (15.3)
Medium	52,374 (79.3)	13,571 (82.2)	13,291 (80.5)	12,897 (78.3)	12,615 (76.2)
Heavy	3441 (5.2)	237 (1.4)	705 (4.3)	1085 (6.6)	1414 (8.5)
Calcium supplement***[b] (%)	9052 (13.7)	2730 (16.5)	2400 (14.5)	2049 (12.4)	1873 (11.3)
Vitamin D supplement***[b] (%)	1358 (2.1)	606 (3.7)	339 (2.1)	227 (1.4)	186 (1.1)
Milk intake***[b] (median ± IQR), g/week	14.38 ± 500	250 ± 1050	35 ± 500	0 ± 250	0 ± 163.33
Poultry meat intake***[b] (median ± IQR), g/week	46.67 ± 82.74	70.00 ± 126.67	46.67 ± 81.33	37.33 ± 88.33	30.68 ± 58.33
Red meat intake***[b] (median ± IQR), g/week	450 ± 490	525 ± 400	420 ± 490	375 ± 500	525 ± 640
Fruit intake***[b] (median ± IQR), g/week	700 ± 1200	750 ± 1050	700 ± 1150	700 ± 1200	500 ± 910
Vegetable intake***[b] (median ± IQR), g/week	2100 ± 1400	2100 ± 2100	2100 ± 1750	2100 ± 1400	2100 ± 1400
Ultraviolet radiation***[b] (mean ± SD), kJ/m^2	162.93 ± 24.92	153.09 ± 16.34	162.07 ± 24.98	172.39 ± 27.32	164.21 ± 25.64
$PM_{2.5}$***[b], μg/m^3	41.99 ± 16.25	53.31 ± 15.07	43.53 ± 15.74	35.93 ± 14.70	35.17 ± 12.29
Physical activity***[b] (mean ± SD), METs/day	25.29 ± 17.04	20.66 ± 14.30	23.76 ± 16.47	28.32 ± 18.11	28.39 ± 17.75
BMI***[b] (mean ± SD), kg/m^2	23.98 ± 3.39	24.23 ± 3.22	24.24 ± 3.38	23.69 ± 3.45	23.78 ± 3.45
QUS parameters					
QUI***[b] (mean ± SD)	69.83 ± 14.73	68.28 ± 13.21	70.00 ± 15.13	69.90 ± 15.25	71.13 ± 15.08
SOS***[b] (mean ± SD), m/s	1531.63 ± 34.12	1527.58 ± 29.84	1532.15 ± 35.36	1531.88 ± 35.58	1534.91 ± 34.96
BUA***[b] (mean ± SD), dB/MHz	31.37 ± 8.84	31.63 ± 8.92	31.27 ± 8.99	31.30 ± 8.63	31.27 ± 8.82

Abbreviations: SD, standard error; MET, metabolic equivalent task; BMI, body mass index; $PM_{2.5}$, particle with aerodynamic diameter ≤ 2.5 μm; IQR, interquartile range; BUA, broadband ultrasound attenuation; QUI, quantitative ultrasound index; QUS, quantitative ultrasound; SOS, speed of sound.

[a] $NDVI_{500m}$ was turned into four groups according to its quartiles.

[b] Significance level: *P < 0.05, **P < 0.01, ***P < 0.001.

Table 2

The estimated mean difference and 95% CI in the QUI associated with one IQR[a] increment in the three-year average residential greenness ($NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m}) exposure.

Greenness indicators	Mean difference (95%CI)		
	Model1[b]	Model2[c]	Model3[d]
$NDVI_{500m}$	3.28 (3.05, 3.50)	3.07 (2.84, 3.29)	3.05 (2.82, 3.27)
$NDVI_{1000m}$	3.57 (3.34, 3.80)	3.37 (3.14, 3.60)	3.36 (3.12, 3.59)
EVI_{500m}	2.68 (2.46, 2.90)	2.47 (2.25, 2.68)	2.45 (2.23, 2.67)
EVI_{1000m}	2.93 (2.71, 3.15)	2.73 (2.51, 2.95)	2.72 (2.50, 2.94)

Abbreviations: CI, confidence interval; IQR, interquartile range; NDVI, normalized difference vegetation index; EVI, enhanced vegetation index.

[a] IQR was 0.22 for $NDVI_{500m}$ and 0.21 for $NDVI_{1000m}$; 0.13 for EVI_{500m}, EVI_{1000m}.

[b] Model 1: adjusted for age, sex, ethnicity, region, urban/rural areas, educational levels, and annual family income.

[c] Model 2: further included smoking status, drinking status, indoor air pollution, and occupation.

[d] Model 3: Model 2 plus additional dietary variables (calcium supplement, vitamin D supplement, milk, red meat, poultry meat, vegetables, and fresh fruits) and three-year average ultraviolet radiation.

3.2. Association between residential exposure to greenness and bone strength

As shown in Table 2, different residential greenness indicators ($NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, or EVI_{1000m}) were significantly positively associated with the bone strength metric (QUI) in Models 1, 2, and 3. In terms of Model 1, per IQR (0.22 unit for $NDVI_{500m}$ and 0.21 unit for $NDVI_{1000m}$; 0.13 unit for EVI_{500m}, EVI_{1000m}) increases in the three-year averages of $NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m} were associated with increases of 3.28 units [95% confidence interval (CI): 3.05, 3.50], 3.57 units (95% CI: 3.34, 3.80), 2.68 units (95% CI: 2.46, 2.90), and 2.93 units (95% CI: 2.71, 3.15) in QUI, respectively (Table 2). According to stratified analyses by multiple covariates, the beneficial effect of greenness on bone strength did not significantly differ according to age at $NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m} (Table 3). In addition, the benefits of greenness related to bone strength may be positively associated with male participants, living in urban areas, with an annual family income ≥20,000 yuan, smokers (current or ever), and drinkers (current or ever). For example, the mean difference in QUI for each IQR increase in $NDVI_{500m}$ was 4.23 (95% Cl: 3.83, 4.62) for males, 3.91 (95% CI: 3.65, 4.18) for urban residents, 3.80 (95% Cl: 3.52, 4.08) for people with an annual family income of more than 20,000 yuan, 3.99 (95% Cl: 3.52, 4.45) for smokers, and 4.30 (95% Cl: 3.93, 4.66) for drinkers. Similar results were obtained for $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m} (Table 3).

3.3. Mediation analyses

Serial two-mediator mediation analyses were performed to test the greenness-QUI association via the previously specified path of ↑residential greenness→ ↑PA→ ↓BMI→ ↓bone strength. Simultaneously, the mediating role of $PM_{2.5}$ in linking residential greenness to bone strength was examined through a parallel one-mediator analysis. A summary of the fit measures for the structural equation model (Table S5) showed that the mediation models were acceptable. The $NDVI_{500m}$/EVI_{500m} was indirectly and positively associated with QUI through all four pathways (Path 1, higher residential greenness exposure was associated with a higher level of PA, lower BMI, and lower bone strength [↑residential greenness→ ↑PA→ ↓BMI→ ↓bone strength]; Path 2, higher residential greenness exposure was associated with a higher level of PA and higher bone strength [↑residential greenness→ ↑PA→ ↑bone strength]; Path 3, higher residential greenness exposure was associated with lower BMI and lower bone strength [↑residential greenness→ ↓BMI→ ↓bone strength]; Path 4, higher residential greenness exposure was associated with a lower $PM_{2.5}$ concentration and higher bone strength [↑residential greenness→ ↓$PM_{2.5}$→ ↑bone strength]); these results were found to be significant (see Fig. 1 and Table 4). Collectively, the four indirect paths accounted for 8.19%/10.08% of the $NDVI_{500m}$/EVI_{500m}-QUI association. In detail, the relationship between residential greenness and bone strength was partially

Table 3

The estimated mean difference and 95% CI in QUI per IQR[a] increase in three-year average residential greenness, as above stratified by age, sex, annually family income, urban/rural areas, smoking and drinking. Statistical significance of the modifiers was performed by a heterogeneity test.

Effect modifiers	$NDVI_{500m}$		$NDVI_{1000m}$		EVI_{500m}		EVI_{1000m}	
	Difference (95% CI)[b]	I^2 and P value	Difference (95% CI)[b]	I^2 and P value	Difference (95% CI)[b]	I^2 and P value	Difference (95% CI)[b]	I^2 and P value
Age, years								
[30,45]	3.11 (2.68, 3.54)	I^2 = 1.4%; P = 0.36	3.41 (2.96, 3.87)	I^2 = 48.1%; P = 0.16	2.48 (2.06, 2.90)	I^2 = 25.1%; P = 0.36	2.78 (2.34, 3.22)	I^2 = 60.5%; P = 0.08
(45,65]	3.11 (2.83, 3.39)		3.32 (3.04, 3.60)		2.63 (2.36, 2.91)		2.97 (2.69, 3.25)	
(65,79]	3.13 (2.61, 3.66)		3.25 (2.72, 3.77)		2.63 (2.10, 3.15)		2.71 (2.18, 3.24)	
Sex								
Male	4.23 (3.83, 4.62)	I^2 = 97.6%; P < 0.001	4.68 (4.27, 5.10)	I^2 = 97.8%; P < 0.001	3.43 (3.05, 3.82)	I^2 = 96.2%; P < 0.001	3.83 (3.43, 4.23)	I^2 = 96.5%; P < 0.001
Female	2.46 (2.21, 2.71)		2.65 (2.39, 2.91)		2.10 (1.84, 2.35)		2.22 (1.97, 2.46)	
Annual family income, yuan								
<20,000	1.58 (1.32, 1.84)	I^2 = 96.9%; P < 0.001	1.84 (1.56, 2.11)	I^2 = 96.1%; P < 0.001	1.21 (0.95, 1.47)	I^2 = 96.6%; P < 0.001	1.38 (1.11, 1.64)	I^2 = 96.0%; P < 0.001
≥20,000	3.80 (3.52, 4.08)		4.21 (3.92, 4.50)		3.18 (2.91, 3.44)		3.65 (3.36, 3.95)	
Urban/rural areas								
Urban area	3.91 (3.65, 4.18)	I^2 = 99.6%; P < 0.001	4.52 (4.20, 4.83)	I^2 = 99.3%; P < 0.001	3.57 (3.29, 3.84)	I^2 = 99.5%; P < 0.001	3.85 (3.54, 4.16)	I^2 = 99.1%; P < 0.001
Rural area	1.21 (1.04, 1.37)		1.49 (1.31, 1.66)		0.95 (0.78, −1.13)		1.20 (1.02, 1.37)	
Smoking								
Never smoking	2.88 (2.63, 3.12)	I^2 = 91.8%; P < 0.001	3.16 (2.91, 3.41)	I^2 = 87.0%; P < 0.001	2.40 (2.16, 2.65)	I^2 = 88.6%; P < 0.001	2.65 (2.40, 2.89)	I^2 = 80.8%; P < 0.001
Smoking or quit	3.99 (3.52, 4.45)		4.19 (3.71, 4.68)		3.30 (2.84, 3.75)		3.51 (3.03, 3.98)	
Drinking								
Never drinking	2.23 (1.98, 2.48)	I^2 = 97.6%; P < 0.001	2.41 (2.17, 2.66)	I^2 = 96.5%; P < 0.001	1.87 (1.62, 2.12)	I^2 = 99.8%; P < 0.001	2.02 (1.78, 2.25)	I^2 = 94.7%; P < 0.001
Drinking	4.30 (3.93, 4.66)		4.61 (4.23, 4.99)		3.54 (3.19, 3.90)		3.90 (3.52, 4.27)	

Abbreviations: CI, confidence interval; QUI, quantitative ultrasound index; IQR, interquartile range; NDVI, normalized difference vegetation index; EVI, enhanced vegetation index.

[a] IQR = 0.13 for EVI_{500m}, EVI_{1000m}; IQR = 0.22 for $NDVI_{500m}$ and 0.21 for $NDVI_{1000m}$.

[b] Adjusted for age, sex, ethnicity, region, urban/rural areas, educational levels, and annual family income.

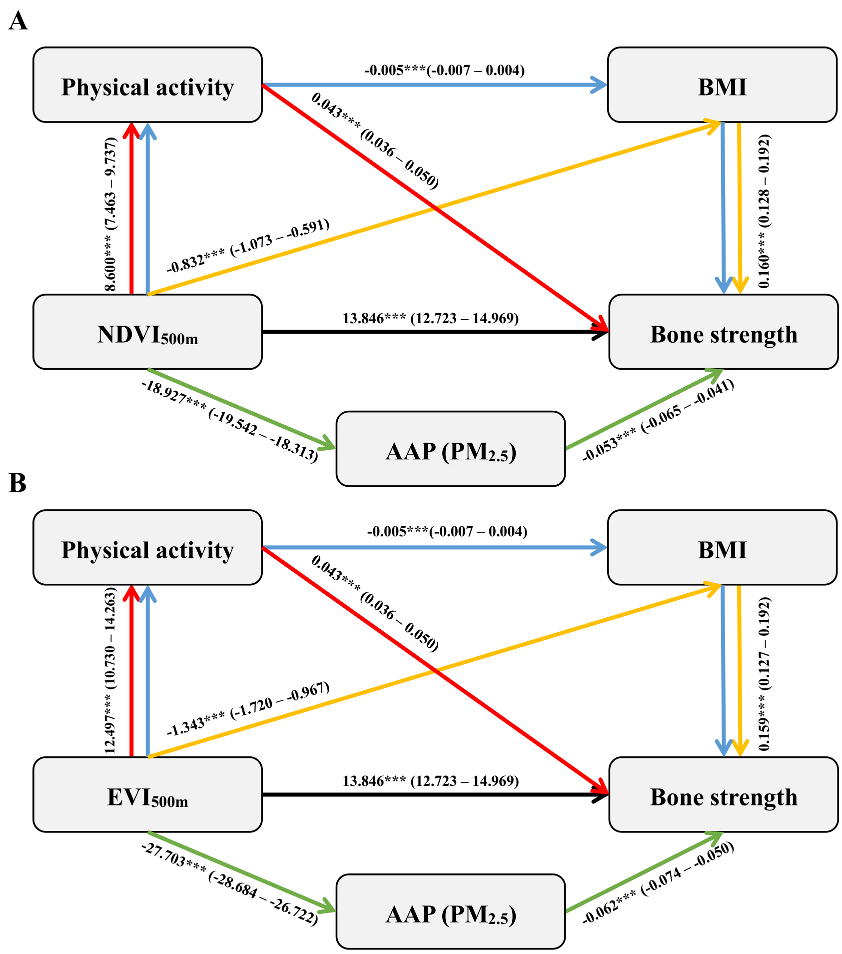

Fig. 1. Mediation analyses of residential greenness and bone strength. Serial two-mediator and parallel one-mediator analyses of the assumed indirect pathways (green, red, blue, and orange arrows), and direct effect (black arrow) of $NDVI_{500m}$/EVI_{500m} on bone strength. Coefficients (Beta) with 95% CI based on structural equation modeling are reported. A: $NDVI_{500m}$; B: EVI_{500m}. Significance level: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Abbreviations: NDVI, normalized difference vegetation index; EVI, enhanced vegetation index; AAP, ambient air pollution; $PM_{2.5}$, particle with aerodynamic diameter ≤ 2.5 μm; BMI, body mass index.

positively mediated by $PM_{2.5}$ (6.70% and 8.50% for $NDVI_{500m}$ and EVI_{500m}, respectively) and PA (2.43% and 2.69% for $NDVI_{500m}$ and EVI_{500m}, respectively) levels, but weakly back-mediated by BMI (0.88% and 1.06% for $NDVI_{500m}$ and EVI_{500m}, respectively) and PA-BMI path (0.05% and 0.05% for $NDVI_{500m}$ and EVI_{500m}, respectively).

3.4. Sensitivity analyses

The results of non-linear analysis are presented in Supplementary Material Table S6. Using Q1 as the reference group, the beneficial effects of $NDVI_{1000m}$ and EVI_{500m} on QUI peaked in Q3, and those of EVI_{1000m} peaked

Table 4
Total, indirect and direct effects linking residential greenness with 500 m buffer to bone strength in this study ($n = 66{,}053$).

Pathways	$NDVI_{500m}$			EVI_{500m}		
	Direct effect	Indirect effect	Total effect	Direct effect	Indirect effect	Total effect
	Beta (95% CI) [a]	Beta (95% CI)[a]	Beta (95% CI)[a]	Beta (95% CI)[a]	Beta (95% CI)[a]	Beta (95% CI)[a]
Greenness → $PM_{2.5}$ → Bone strength		1.009***[b] (0.780, 1.237)			1.710***[b] (1.375, 2.045)	
Greenness → PA → Bone strength		0.367***[b] (0.291, 0.443)			0.542***[b] (0.429, 0.656)	
Greenness → BMI → Bone strength		−0.133***[b] (−0.181 −0.085)			−0.214***[b] (−0.289, −0.140)	
Greenness → PA → BMI → Bone strength		−0.007***[b] (−0.010, −0.004)			−0.010***[b] (−0.015, −0.006)	
Greenness → Bone strength	13.846***[b] (12.723, 14.969)	1.235***[b] (0.996, 1.474)	15.081***[b] (13.971. 16.192)	18.085***[b] (16.326, 19.843)	2.028***[b] (1.674, 2.382)	20.113***[b] (18.383, 21.842)

Abbreviations: CI, confidence interval; NDVI, normalized difference vegetation index; EVI, enhanced vegetation index; $PM_{2.5}$, the particle with aerodynamic diameter ≤ 2.5 μm; PA, physical activity; BMI, body mass index. Coefficients (Beta) with 95% CI based on structural equation models were reported.

[a] Adjusted for age, sex, ethnicity, region, urban/rural areas, smoking status, drinking status, educational level, occupation, annual family income, indoor air pollution, dietary variables (calcium and vitamin D supplements, milk, red and poultry meat, vegetables, and fresh fruits) and three-year average ultraviolet radiation.

[b] Significance level: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

in Q2. Additionally, the results of the quantile regression model (Fig. S3) indicated that the effects of one IQR increase in the three-year average greenness ($NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m}) on QUI successively increased and reached a peak at the 90% percentile of QUI (88.20 units). Moreover, there were no significant changes in the relationship between exposure and outcomes after excluding individuals reported to have rheumatoid arthritis/rheumatoid arthritis, diabetes, chronic kidney disease, or chronic hepatitis/cirrhosis at baseline (Table S7). The association between residential greenness and bone strength did not significantly change in multiple imputation combined inverse probability weighting (Table S8). Similar results were observed in mediation analyses (see Fig. S4 and Table S9) using $NDVI_{1000m}$ and EVI_{1000m} as substitutes for greenness indicators. Analysis of $PM_{2.5}$, PA, and BMI as effect modifiers (Table S10) indicated that $PM_{2.5}$ significantly modified the positive linkage between greenness and bone strength, revealing a higher association in participants living in highly polluted states. A modifying effect of PA was also observed, except for with $NDVI_{500m}$. Additionally, the strength of the $NDVI_{500m}$/EVI_{500m}-QUI association varied across BMI strata (under, normal, overweight, and obese).

4. Discussion

To our knowledge, this is the first and largest epidemiological study to assess the association between residential exposure to greenness ($NDVI_{500m}$, $NDVI_{1000m}$, EVI_{500m}, and EVI_{1000m}) and bone strength (QUI), and estimated the magnitude of the mediating effects of AAP ($PM_{2.5}$), PA, and BMI in the general population. We observed that higher residential exposure to greenness, defined as EVI/NDVI in 500 m/1000 m radii, was independently associated with higher bone strength in a representative cohort of nearly 70,000 adults aged 30–79 years recruited from southwest China. Concurrently, the protective effects of residential exposure to greenness on bone strength were more substantial in men, participants from urban areas, the wealthy, smokers, and drinkers. Moreover, the linkage between residential greenness and bone strength was mediated in part by the AAP ($PM_{2.5}$), PA, BMI, and PA-BMI serial pathways.

4.1. Comparisons with other studies

The relationship between residential greenness and bone health has not been widely examined. Only one study reported a longitudinal association between greenness, BMD, and event fracture in 3944 elderly Hong Kong adults aged 65 years and above (Lin et al., 2021). The study showed that higher greenness ($NDVI_{300m}$ and $NDVI_{500m}$) levels were non-linearly associated with a slower increase in the BMD of the lumbar spine and a higher risk of fracture. However, there were no convincing associations in BMD change in the total hip, femoral neck, and whole-body. Alternatively, Lin et al. (Lin et al., 2021) did not find that greenness is a protective factor for bone health. This negative association between residential exposure to greenness and bone status may be attributable to the specific study population (the elderly) and a smaller sample size. In contrast, our results may suggest that residential exposure to greenness may positively influence bone health.

4.2. Underlying mechanisms

The current study provides important new insight into the biological mechanisms underlying the effects of residential greenness exposure on bone health. The data pointed to several mechanisms connecting residential greenness exposure with bone strength via the ↓AAP, ↑PA, ↓BMI, and sequential ↑PA-↓BMI routes.

Specifically, lower concentrations of $PM_{2.5}$ and higher-level PA partly mediate the observed positive relationship between residential exposure to greenness and bone strength. This agrees with previous evidence suggesting that vegetation-related mitigation of airborne particulate matter concentrations and a greater opportunity to participate in PA occur in areas with higher residential exposure to greenness (Diener and Mudu, 2021; Garrett et al., 2020). In addition, multiple studies showed that long-term exposure to AAP can disturb bone homeostasis through systematic inflammation (Liang et al., 2018), oxidative stress (Yang and Omaye, 2009), aging of bone by crossing the cell membrane directly (Almeida and OBrien, 2013), endocrine disruption (Prada et al., 2020), and vitamin D deficiency (Manicourt and Devogelaer, 2008), subsequently increasing the risk of bone strength loss (Compston et al., 2019). An increased PA level is associated with a higher BMD and 1–40% decrease in fracture risk (Cauley and Giangregorio, 2020). Moreover, significant but small inversely mediating pathways through BMI and intertwined PA-BMI were detected, which indicated that BMI and PA-BMI weakly attenuated the linkage between residential greenness and bone strength. Several studies reported that residents of greener areas have a lower BMI (Fan et al., 2022; Huang et al., 2020a; Huang et al., 2020b). The association between a higher BMI and increased BMD is widely accepted (De Laet et al., 2005; Felson et al., 1993; Reid, 2002). Engagement in PA increases energy expenditure (Rising et al., 1994), and elevated adiposity events can be attributed to decreased levels of PA to some degree (Stubbs and Lee, 2004). However, evidence of the mediating role of PA in the correlation between residential greenness exposure and adiposity is inconsistent. A study performed in the United States showed that PA weakened the beneficial association of greenness with adiposity by 32% among 50,884 women (Villeneuve et al., 2018). Nevertheless, quite a few greenness-BMI studies which conducted the mediation analysis of PA claimed that no significant mediation effect was observed for PA (Bao et al., 2021; Fan et al., 2022; Huang et al., 2020a; Huang et al., 2020b; O'Callaghan-Gordo et al., 2020).

Somewhat counterintuitively, the percentage attributed to pathways involving PA and BMI was low in the residential greenness-QUI-positive association. There are several possible explanations for the weak mediating effects of PA. First, our study population comprised approximately 65% of rural residents, and a higher quartile of greenness in residence is associated with a greater likelihood of living in rural areas. The level of greenness and its availability can differentially influence engagement in PA in green areas (An et al., 2019; Fong et al., 2018). Rural southwest China is covered by large-area natural vegetation (e.g., forestland) and agricultural lands without exercise facilities rather than more available meadows and well-organized parks, which have been reported to encourage PA (Coombes et al., 2010; Klompmaker et al., 2018). Therefore, the estimated mediating effect of PA may be diluted. Second, individual-dominated increases in PA levels may be more difficult to maintain compared to vegetation-dominated decreases in AAP. Another explanation may be that in our study, PA was assessed through a self-report questionnaire, which may have resulted in recall bias, and objective instruments such as relatively costly hip-worn accelerometers that are more suitable for small-scale studies were not used (Dewulf et al., 2016; James et al., 2017; Markevych et al., 2016). In the case of BMI, the BMI variable used in this study and its component measures (i.e., height and weight) obtained at baseline may only influence small short-term fluctuations in bone strength rather than long-term fluctuations. In addition, the weak inverse and indirect effects involving BMI likely resulted from reverse causality due to the intrinsic nature of cross-sectional data, which precluded the establishment of a temporal sequence between BMI and bone strength in SEM.

Notably, various unmeasured factors (e.g., heat, physical/mental stress, and biodiversity) may be impactful mediators (Chevalier et al., 2020; Markevych et al., 2017; Pisani et al., 2016; Villa et al., 2017). Because of data limitations, we could not investigate the mediating effects of these factors on the relationship between bone health and residential exposure to greenness.

4.3. Additional findings on greenness and bone strength

In stratified analyses, a stronger beneficial association between residential exposure to greenness and bone strength was identified in urban residents, men, the wealthy, drinkers, and smokers. These results are supported by our previous study (Wu et al., 2021), which found that participants living in urban areas were more vulnerable to the adverse effects of long-term AAP (including particulate matter and gaseous pollutants) exposure on bone health. Together with the mediation analyses, decreased AAP exposure may contribute to the beneficial effects of greenness on bone health, as it is commonly recognized that AAP inhalation is deleterious to human health (Greenwald et al., 2019).

Furthermore, males may inhale more air pollutants than females, likely because the minute ventilation of males is distinctly better than that of females (Edvardsen et al., 2013; Guenette et al., 2009; Löndahl et al., 2007). Therefore, males may bear more significant health hazards. Besides, men may be more sensitive to stress (Liu and Zhang, 2020), which can be diminished by exposure to greenness (Tsunetsugu et al., 2013). The smaller exposure-outcome linkage observed in females was non-negligible and of concern because females suffer from a much higher prevalence of osteoporosis fracture compared to males (Johnell and Kanis, 2006; Sozen et al., 2017). The positive correlation between greenness and female bone strength is supported by previous studies. As reported in European countries, living in greener areas is associated with a higher age at menopause and delayed reproductive decline in females (Triebner et al., 2019), which may help reduce osteoporosis (Icks et al., 2008). The disparity between lower (<20,000 yuan) and higher (≥20,000 yuan) annual family income groups may result from inequality in greenness availability, which is lower for individuals residing in lower-income areas (Astell-Burt et al., 2014), and higher socioeconomic status is associated with more exercise walking (Leslie et al., 2010). More positive associations were found in smokers and drinkers (current or ever), possibly because most subjects were men, and smoking/alcohol intake is a risk factor for low BMD and fracture (Pisani et al., 2016).

Unexpectedly, age and some chronic diseases affecting bone strength did not appear to affect the positive association between greenness and bone strength. There are several possible reasons for this. Although physiological changes caused by aging weaken bones, the magnitude of the greenness-bone association may diminish with increasing age. Whether active or passive, older people are more likely to spend more time exercising and enhancing social connections in parks, offsetting the age-specific variability in the linkage between greenness and bone. In addition, people with chronic conditions may be more inclined to change their unhealthy lifestyles (e.g., sedentary lifestyles) to counteract the adverse effects of chronic conditions on bone health. That is, the elderly who are more likely to have chronic diseases may be more physically active outdoors.

4.4. Strengths and limitations

Our study has several strengths. First, we included a large sample of Chinese adults with a broad age range, greenness exposure level, and air pollutant concentrations, first providing novel epidemiological evidence for the general population that supports the positive effects of residential greenness on bone health. Second, we explored the underlying mechanisms by which AAP ($PM_{2.5}$), PA, BMI, and even the serial PA-BMI path mediate the relationship between greenness and bone health, thus explaining the greenness-bone relationship. Third, multiple rigorous sensitivity analyses demonstrated the robustness of our results.

Nevertheless, this study also has several limitations. First, owing to the cross-sectional design, the causal relationship between greenness and bone strength should be cautiously interpreted. However, the exposure windows were pushed forward for three years to guarantee the exposure-outcome temporality as much as possible. Second, we did not explore the associations stratified according to a specific type of greenness. Third, exposure misclassification may occur because of a lack of proximity, quality, and use characteristics of greenness. Fourth, exposure to greenness and AAP may vary by time and location, decreasing the accuracy of the association estimations. Finally, in line with all cross-sectional studies involving retrospective surveys, the presence of residual confounding induced by measurement error and unmeasured confounding is inevitable.

5. Conclusion

This large population-based epidemiological study showed that living in districts with higher greenness levels is linked to higher bone strength, indicating that residential exposure to greenness appears to be a protective factor for bone health. This positive association may be partly mediated by the AAP, PA, BMI, and PA-BMI paths. Current observations provide new epidemiological evidence for refining strategies related to greenness planning, and green infrastructure interventions may be beneficial for preventing osteoporosis/attendant fractures. Further well-designed and more evidentiary longitudinal research are needed to confirm our findings.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.155393.

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