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Air pollution, genetic factors and the risk of osteoporosis: A prospective study in the UK biobank

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Purpose: To reveal relationship between air pollution exposure and osteoporosis (OP) risk.

Methods: Based on large-scale data from the UK Biobank, we evaluated the relationship between OP risk and several air pollutants. Then air pollution scores (APS) were constructed to assess the combined effects of multiple air pollutants on OP risk. Finally, we constructed a genetic risk score (GRS) based on a large genome-wide association study of femoral neck bone mineral density and assessed whether single or combined exposure to air pollutants modifies the effect of genetic risk on OP and fracture risk.

Results: $PM_{2.5}$, NO_2, NO_x, and APS were significantly associated with an increased risk of OP/fracture. OP and fracture risk raised with increasing concentrations of air pollutants: compared to the lowest APS quintile group, subjects in the highest quintile group had a hazard ratio (HR) (95% CI) estimated at 1.140 (1.072–1.213) for OP and 1.080 (1.026–1.136) for fracture. Moreover, participants with low GRS and the highest air pollutant concentration had the highest risk of OP, the HRs (95% CI) of OP were 1.706 (1.483–1.964), 1.658 (1.434–1.916), 1.696 (1.478–1.947), 1.740 (1.506–2.001) and 1.659 (1.442–1.908), respectively, for $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_2, and NO_x. Similar results were also observed for fractures. Finally, we assessed the joint effect of APS and GRS on the risk of OP. Participants with higher APS and lower GRS had a higher risk of developing OP. Similar results were observed in the joint effect of GRS and APS on fracture.

Conclusions: We found that exposure to air pollution, individually or jointly, could improve the risk of developing OP and fractures, and increased the risk by interacting with genetic factors.

KEYWORDS

osteoporosis, air pollution score, genetic risk score, genetic factor, air pollutant

1. Introduction

Osteoporosis (OP) is a systemic bone disease characterized by low bone mineral density (BMD), bone fragility, and devastation of the microstructure of bone tissue, which occurs when bone destruction exceeds new bone formation (1). As the population is aging, OP will develop dramatically, which will cause enormous social and economic stress. As a major cause of public health threats, long-term ambient air pollution exposure is related

to the increased risk of complex diseases (e.g., cardiovascular diseases, respiratory diseases, malignant tumors), and increased morbidity and mortality worldwide (2).

Previous studies have shown inconsistent associations between air pollution exposure and the risk of OP and fracture (Supplementary Table S1) (3–12). For example, a study using data from the UK Biobank confirmed that higher air pollution exposure was associated with lower eBMD levels and increased prevalence of osteoporosis (13). A cross-sectional study of 1,039 subjects showed no significant association between BMD with particulate matter (PM) exposure after correcting for age and sex (14), but some studies have reported an association of PM with an aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$) and PM with an aerodynamic diameter $\leq$10 μm (PM_{10}) exposure with bone health (4, 9). For each 1 $\mu g/m^3$ increase in $PM_{2.5}$, the prevalence of osteoporosis increased by 5% in all participants; per 1 $\mu g/m^3$ increase in PM_{10} corresponded with a 4% elevation in the risks of osteoporosis in the rural population (15). These inconsistent results may contribute to heterogeneity in the basic characteristics of subjects, study design, sample size, measurement of outcomes, and covariate correction during the analysis of various studies. Similarly, inconsistent findings exist for the relationship between air pollution exposure and fractures. A cross-sectional study of 44,602 Korean women aged 50 years or older showed a positive association between $PM_{2.5}$ exposure and osteoporotic fractures (7), while another cross-sectional study reported no significant association between PM exposure and forearm fractures in older adults (14).

Previous studies have typically focused on the association of a single air pollutant with disease risk, while largely ignoring the combined effects of various air pollutants (16, 17). It remains unclear whether combined exposure to various air pollutants could alter the associations between genetic factors and OP. Furthermore, previous studies, limited by cross-sectional studies and small sample designs, have only demonstrated associations and lacked cohort studies to confirm the relationship between air pollution and OP. More importantly, it is still unknown how air pollutants interact with genetic factors in determining the risk of OP. Therefore, it is necessary to conduct a large-scale cohort study to reveal the underlying relationship. Therefore, based on a large-scale cohort (UK Biobank) we conducted a systemic study to test associations between OP risk and exposure to environmental air pollutants ($PM_{2.5}$, PM_{10}, PM with diameters between 2.5 and 10 μm: $PM_{2.5-10}$, nitrogen dioxide: NO_2 and nitrogen oxide: NO_x) in either single or multiple patterns, and also to test the joint effects of air pollution and genetic factors on the risk of OP.

2. Materials and methods

2.1. Study design

For observational analysis, all individuals were used to assess the separate and joint effect of five types of air pollution on OP. For genetic analysis, around 296,790 European independent individuals were divided into a selection set ($N = 29,679$, 10%) and a validation set ($N = 267,111$, 90%). GRSs in different cut-offs were compared and best-performed GRS was finally selected in the selection set. All the other analyses were conducted in the validation set to avoid over-fitting. The overflow of our research was presented in Figure 1.

2.2. Data source

Between 2006 and 2010 the UK Biobanking Project recruited around 500,000 UK adults aged between 40 and 69 years, where ethical approval was certified by the Northwest Centre Research Ethics Committee, and informed consent was obtained from all participants. In our analysis, we included age (Field ID: 21022), gender (Field ID: 31), height (Field ID: 50), weight (Field ID: 21002), race (Field ID: 21000), eBMD (Field ID: 3084, 3148, 4105), eBMD T-score (Field ID: 77, 78, 4106), Fracture (Field ID: 6151), smoking status (Field ID: 20116), alcohol (Field ID: 20117), diet (Field ID: 100052), Townsend deprivation index (TDI) (Field ID: 189), International Classification of Diseases, Tenth Revision (ICD10).

2.3. Air pollution measurement

The researchers used the Land Use Regression (LUR) models, developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE) project, to calculate the estimated annual average concentrations of ambient air pollution ($PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, and NO_x) in UK Biobank (18, 19). Specifically, LUR models were used to assess variations of air pollutants concentrations at the residential address provided by the participants at baseline, and to estimate the individual exposure of the participants. Geographic Information System (GIS) variables were used as predictors (such as traffic intensity, population, topography, and land use) and a cross-validation procedure was used to assess model performance. Detailed processes for establishing LUR models for $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, and NO_x have been described elsewhere (18, 19). In final, $PM_{2.5}$, PM_{10}, NO_2 and NO_x had good model performance (cross-validation R^2 = 77, 88, 87 and 88%, respectively), while $PM_{2.5-10}$ had a relatively moderate model performance (cross-validation R^2 = 57%). Exposure data for $PM_{2.5}$, $PM_{2.5-10}$, and NO_x were collected in 2010, while annual concentration data for NO_2 and PM_{10} were within several years (NO_2 in 2005, 2006, 2007, and 2010; PM_{10} in 2007 and 2010). The average values of NO_2 and PM_{10} were calculated for further analysis. In addition, economic and cultural differences may lead to different exposures to air pollutants, so we included the TDI as a covariate in the subsequent analysis.

2.4. Measurements of OP

We considered three phenotypes for OP in our analysis, i.e., estimated bone mineral density (eBMD) (Field ID: 3084, 3148, 4105), the occurrence of OP, and fracture. Due to the lack of DXA (Dual Energy X-ray Absorptiometry)-BMD measurements in most participants in UK Biobank cohorts, we used eBMD which was measured for every subject as a measure of BMD, eBMD is BMD estimated by quantitative ultrasound of the heel (20). OP and

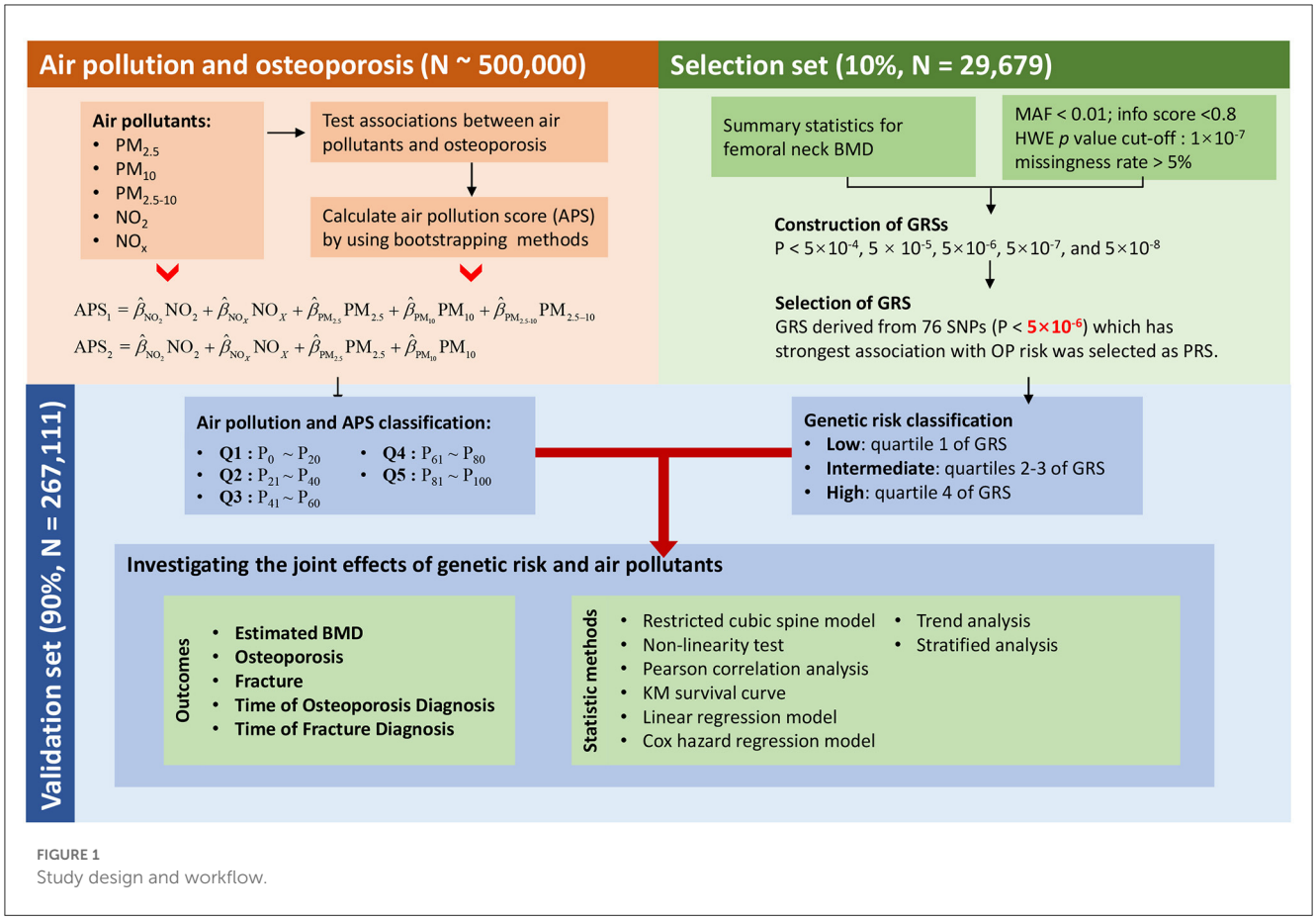

FIGURE 1
Study design and workflow.

fracture patients were defined by using ICD10 and the codes used in our analysis were presented as follows: OP (i.e., M80, M81, M82), fracture (i.e., M484, M485, M80, M843, M844, S12, S22, S32, S42, S52, S72, S82, Z8731, Z87310, Z87311). We excluded patients who were diagnosed before the baseline questionnaire was administered. We excluded individuals with unusual large or small eBMD value (eBMD < mean - 4.5SD (standard deviation) or eBMD > mean + 4.5SD). Furthermore, we applied strict quality control by using the following exclusion thresholds: SOS (speed of sound) (Male: [≤1,450 and ≥1,750 m/s], Female [≤1,455 and ≥1,700 m/s]) and BUA (broadband ultrasound attenuation) (Male: [≤27 and ≥138 dB/MHz], Female [≤22 and ≥138 dB/MHz]) for male and female subjects separately (20).

2.5. Calculation of APSs

According to previous research, we also created a weighted APS for OP by summing the weights of different air pollutants (17). Weights and corresponding confidence interval (CI) for different air pollutions are derived from the median and 2.5%, 75% of the bootstrapping distribution (21). In this procedure, we resampled the individuals with replacement, using the regenerated samples to assess the association between each air pollution and OP risk, with 1000 replications. Then the weighted APS was calculated through the combination of five air pollutants, weighted by the estimated coefficients on OP risk. Additionally, considering the weak association between $PM_{2.5-10}$ and OP risk, we further constructed APS_2 as a sensitivity analysis. The formulas of APS_1 and APS_2 were as follows:

$$APS_1 = \hat{\beta}_{NO_2} NO_2 + \hat{\beta}_{NO_x} NO_x + \hat{\beta}_{PM_{2.5}} PM_{2.5} + \hat{\beta}_{PM_{10}} PM_{10} + \hat{\beta}_{PM_{2.5-10}} PM_{2.5-10} \quad (1)$$

$$APS_2 = \hat{\beta}_{NO_2} NO_2 + \hat{\beta}_{NO_x} NO_x + \hat{\beta}_{PM_{2.5}} PM_{2.5} + \hat{\beta}_{PM_{10}} PM_{10} \quad (2)$$

2.6. Construction of GRS

To ensure quality, strict quality controls for induvial were conducted in genetic analysis: (1) failed genotyping samples were removed; (2) non-white British ancestry samples were removed; (3) samples without principal components calculations were removed; (4) genetically correlated individuals were removed; (5) individuals with sex chromosome aneuploid were removed. Finally, a total of 335,198 white British individuals were reserved for further analysis. Considering that the BMD of the femoral neck (FN-BMD) is the gold standard for diagnosing OP, we downloaded summary statistics for the largest GWAS of FN-BMD conducted by GEnetic Factors for OP Consortium (GEFOS, http://www.gefos.org), which is publicly available (22). The genotype of each SNP was obtained from the UK Biobank and the quality control of

SNPs was described elsewhere (23). A total of ~92 million variants were generated by imputation based on Haplotype Reference Consortium (HRC), 10 thousand individuals from the UK and 1000 Genomes reference panels. We removed low quality SNPs by following criteria: (1) minor allele frequency (MAF) < 0.01; (2) info score <0.8; (3) Hardy-Weinberg equilibrium (HWE) *p*-value cut-off was set to 1×10^{-7}; (4) and missingness rate > 5%. Finally, ~9,400,000 SNPs remained for further analysis. Lead SNPs for FN-BMD were determined by using the "–clump" procedure in PLINK software (24) at different thresholds ($p < 5\times10^{-4}$, 5×10^{-5}, 5×10^{-6}, 5×10^{-7}, 5×10^{-8}), containing 1498, 252, 76, 38 and 24 SNPs, respectively. The equation could be expressed as: $GRS_i = \sum_{k=1}^{K} G_{ik}\hat{\theta}_k$, where $\hat{\theta}_k$ is the SNP estimated effect for the k^{th} SNP, and G_{ik} is the genotypes (0, 1, 2) of the k^{th} SNP on i^{th} individual. Finally, we compared these five GRSs generated in different thresholds in the selection set after adjusting for age, sex, TDI, genotyping chip (UKB vs. BiLEVE), and top 10 genetic principal components (PCs). Finally, best-performed GRS ($p < 5\times10^{-6}$) with the highest effect on OP was chosen to represent genetic components (Supplementary Table S2). And the SNPs identified at the significance of 5×10^{-6} used for the construction of GRS were presented in Supplementary Table S3.

2.7. Statistical analysis

Pearson correlation was used to assess the relationship between air pollutants, and linear regression models were used to assess the associations between air pollutants and eBMD. A multivariable cox regression model was used to evaluate the association and hazard ratios (HR) were calculated with 95% CI after adjusting for several covariates. The restricted cubic spline (RCS) method was used to evaluate non-linear relationships between air pollutants and OP risk. Trend analysis was performed by Cochran-Armitage trend test with the "DescTools" package (25). It was noted that, for observational analysis, age, gender, genotyped batch, TDI, height, weight, and smoking status were used as covariates. For GRS analysis, age, gender, TDI, smoking status, genotyped batch, height, weight, and top 10 PCs were used as covariates. For sensitivity analysis, batch, center, age, sex, race, Townsend deprivation index, height, weight, smoking status, alcohol, physical activity, diet, CKD, T2D, cancer, and deprivation were used as covariates. To better evaluate the diseases risk among participants with different genetic risks, we divided GRS selected into different groups: low genetic risk (bottom quintile of GRS), intermediate genetic risk (quintiles 2 to 4), and high genetic risk (top quintile). All statistical analysis was performed in *R* 3.6.1 and the statistical significance was set to two-side $P < 0.05$.

3. Result

3.1. Basic information

In this study, a total of 13,291 OP cases and 19,695 fracture cases were recorded among 430,120 participants. The baseline characteristics of the study participants are presented in Table 1. Participants who had OP or fracture were older, predominantly female, had higher smoking rates, and with lighter weight and shorter height compared with those without OP or fracture. The mean of estimates of $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_2 and NO_x were 9.98 $\mu g/m^3$, 19.28 $\mu g/m^3$, 6.42 $\mu g/m^3$, 29.12 $\mu g/m^3$ and 43.86 $\mu g/m^3$.

3.2. Relationship between air pollution and OP risk

Five air pollutants were involved in our analyses: $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_2 and NO_x. The concentration of $PM_{2.5}$, PM_{10}, NO_2 and NO_x were significantly correlated with the decrease of eBMD even after Bonferroni adjustment (Supplementary Table S4). Similar results were obtained from sensitivity analysis (Supplementary Table S5). Then we used RCS model to assess the associations between each air pollutant with OP and fracture risk (Figure 2). As shown in Supplementary Table S6, $PM_{2.5}$, NO_2 and NO_x were significantly associated with an increased risk of OP. The HR of OP occurring in subjects were estimated to be 1.046 (95% CI = 1.027–1.066, $P = 2.31\times10^{-6}$), 1.029 (95% CI = 1.008–1.049, $P = 0.005$) and 1.029 (95% CI = 1.011–1.048, $P = 0.002$) for $PM_{2.5}$, NO_2 and NO_x, respectively. However, we did not observe a significant association between PM_{10} (HR = 1.009, 95% CI, 0.990–1.028, $P = 0.357$) or $PM_{2.5-10}$ (HR = 1.007, 95% CI, 0.990–1.024, $P = 0.431$) and risk of OP. Sensitivity analysis did not have a significant impact on the results (Supplementary Table S7). RCS method was then used to explore the linear relationships between each air pollutant and OP risk, we observed non-linear relationships for PM_{10}, NO_2, NO_x and a linear relationship for $PM_{2.5}$, $PM_{2.5-10}$. Supplementary Table S8 shows the associations between individual air pollutants and fracture. $PM_{2.5}$ (HR = 1.018, 95% CI = 1.003–1.034, $P = 0.020$), NO_2 (HR = 1.022, 95% CI = 1.005–1.039, $P = 0.009$), and NO_x (HR = 1.023, 95% CI = 1.007–1.038, $P = 0.003$) concentrations were interrelated with an increased risk of fracture. In addition, we observed a non-significant effect on risk of fracture with the increases in PM_{10} (HR = 0.987, 95% CI = 0.971–1.002, $P = 0.087$) and $PM_{2.5-10}$ (HR = 0.994, 95% CI = 0.980–1.009, $P = 0.443$). Sensitivity analysis showed that $PM_{2.5}$ no longer increased the risk of fracture (HR = 1.009, 95% CI, 0.993–1.025, $P = 0.275$) (Supplementary Table S9). For fracture risk, we observed a non-linear relationship for NO_2 and linear relationships for $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_x by using RCS model. Then the stratified analyses were also conducted, detailed results were presented in Supplementary Tables S10, S11.

3.3. Relationship between APSs and OP risk

We constructed APSs by combining different air pollutants with the bootstrapping procedure, and correlations between APSs and five air pollutants were shown in Supplementary Figure S1. The RCS model was used to evaluate the relationship between APS and the risk of OP and fracture. As shown in Figure 3, the spline analysis showed a significant relationship between APS and the risk of OP and fracture (*P* for non-linear was 0.409 and 0.057,

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TABLE 1 Baseline characteristics of the study subjects in the UK Biobank cohort.

Variables	Levels	Overall	No OP	OP	No Fracture	Fracture
		N = 430,120	*N* = 416,829 (96.9%)	*N* = 13,291 (3.1%)	*N* = 410,425 (95.4%)	*N* = 19,695 (4.6%)
Age [mean (SD)]		56.54 (8.09)	56.38 (8.09)	61.48 (6.13)	56.40 (8.09)	59.45 (7.46)
Sex (%)	female	233,356 (54.3)	222,217 (53.3)	11,139 (83.8)	220,401 (53.7)	12,955 (65.8)
	male	196,764 (45.7)	194,612 (46.7)	2,152 (16.2)	190,024 (46.3)	6,740 (34.2)
Height [mean (SD)]		168.54 (9.26)	168.71 (9.25)	163.13 (8.08)	168.62 (9.26)	166.96 (9.12)
Weight [mean (SD)]		78.06 (15.86)	78.32 (15.82)	69.87 (14.73)	78.15 (15.84)	76.17 (16.00)
TDI [mean (SD)]		−1.38 (3.02)	−1.39 (3.02)	−1.13 (3.15)	−1.39 (3.02)	−1.18 (3.12)
Race (%)	White	406,601 (94.5)	393,771 (94.5)	12,830 (96.5)	387,412 (94.4)	19,189 (97.4)
	Asian	8,484 (2.0)	8,279 (2.0)	205 (1.5)	8,273 (2.0)	211 (1.1)
	Black	6,809 (1.6)	6,723 (1.6)	86 (0.6)	6,718 (1.6)	91 (0.5)
	Mixed	8,226 (1.9)	8,056 (1.9)	170 (1.3)	8,022 (2.0)	204 (1.0)
Smoking status (%)	Never	235,616 (54.8)	228,677 (54.9)	6,939 (52.2)	225,503 (54.9)	10,113 (51.3)
	Previous	150,216 (34.9)	145,367 (34.9)	4,849 (36.5)	142,940 (34.8)	7,276 (36.9)
	Current	44,288 (10.3)	42,785 (10.3)	1,503 (11.3)	41,982 (10.2)	2,306 (11.7)
eBMD [mean (SD)]		0.55 (0.14)	0.55 (0.14)	0.45 (0.12)	0.55 (0.14)	0.49 (0.13)
No_x [mean (SD)]		43.86 (15.59)	43.84 (15.58)	44.55 (15.94)	43.84 (15.57)	44.36 (16.01)
NO_2 [mean (SD)]		29.12 (9.19)	29.11 (9.18)	29.53 (9.33)	29.11 (9.18)	29.33 (9.27)
PM_{10} [mean (SD)]		19.28 (1.95)	19.28 (1.95)	19.32 (1.93)	19.28 (1.95)	19.27 (1.94)
$PM_{2.5}$ [mean (SD)]		9.98 (1.06)	9.98 (1.06)	10.05 (1.07)	9.98 (1.06)	10.02 (1.08)
$PM_{2.5-10}$ [mean (SD)]		6.42 (0.90)	6.42 (0.90)	6.43 (0.89)	6.42 (0.90)	6.42 (0.89)

OP, osteoporosis; NO_x, nitrogen oxides; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; eBMD, estimated bone mineral density; TDI, Townsend deprivation index; SD, standard deviation.

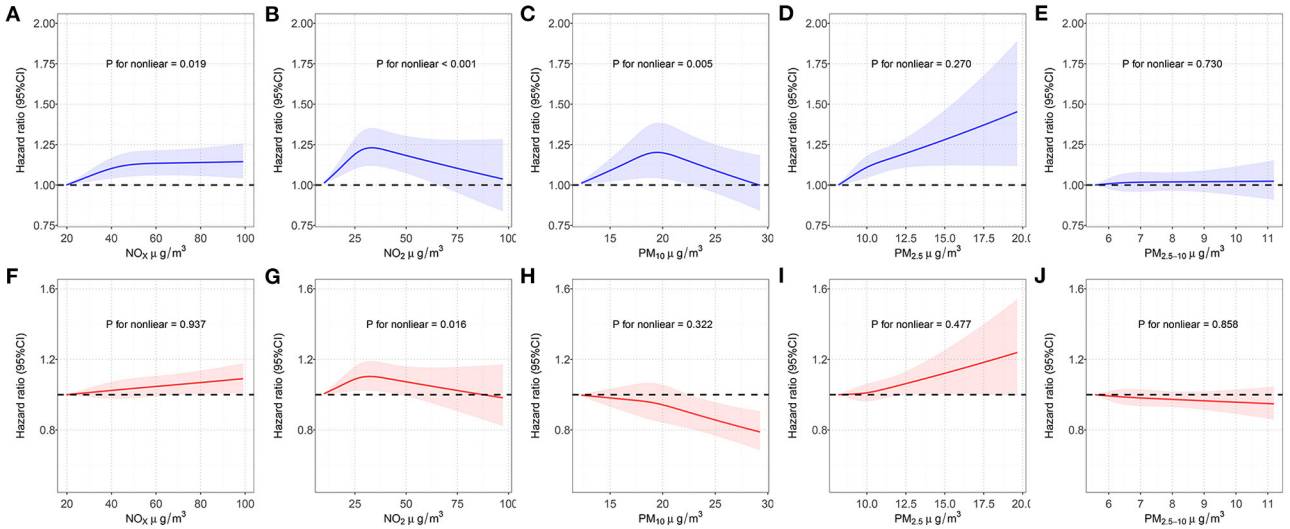

FIGURE 2
Restricted cubic spline models for the relationship between air pollution and OP and fracture risk. **(A)** NO_x concentration and OP risk; **(B)** NO_2 concentration and OP risk; **(C)** PM_{10} concentration and OP risk; **(D)** $PM_{2.5}$ concentration and OP risk; **(E)** $PM_{2.5-10}$ concentration and OP risk; **(F)** NO_x concentration and fracture risk; **(G)** NO_2 concentration and fracture risk; **(H)** PM_{10} concentration and fracture risk; **(I)** $PM_{2.5}$ concentration and fracture risk; **(J)** $PM_{2.5-10}$ concentration and fracture risk. Associations were adjusted for age, sex, genotyped batch, Townsend deprivation index, height, weight, and smoking status. OP, osteoporosis; NO_x, nitrogen oxides; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 m; $PM_{2.5-10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; CI, confidence interval.

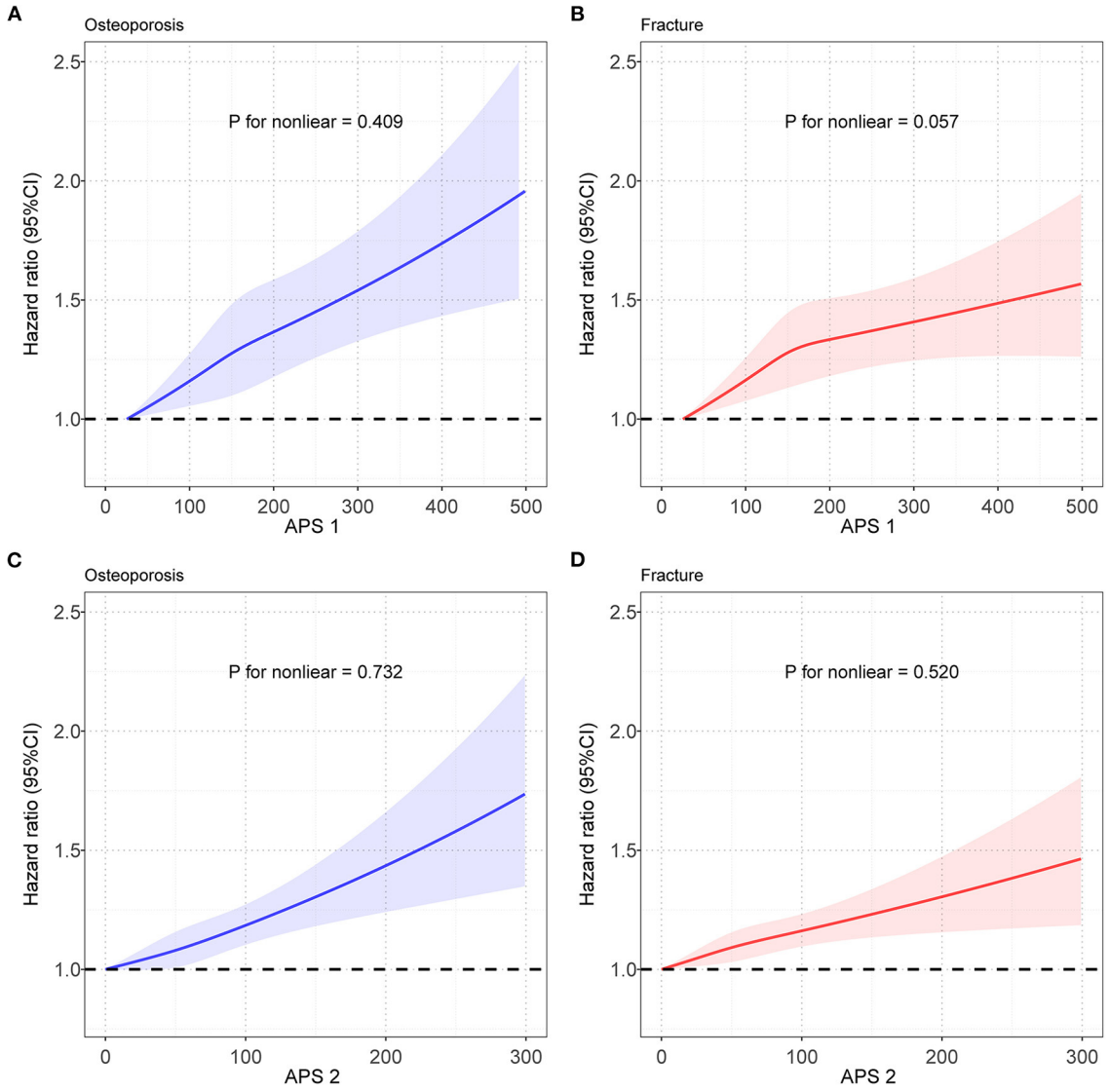

FIGURE 3
Restricted cubic spline models for the relationship between APS and OP and fracture risk. **(A)** Relationship between APS_1 and OP risk; **(B)** Relationship between APS_1 and fracture risk; **(C)** Relationship between APS_2 and OP risk; **(D)** Relationship between APS_2 and fracture risk. Note: Associations were adjusted for age, sex, genotyped batch, Townsend deprivation index, height, weight, and smoking status. OP, osteoporosis; APS, air pollution score; CI, confidence interval.

respectively, in the OP and fracture group). Similar results between APS without $PM_{2.5-10}$ and the risk of OP and fracture (*P* for nonlinear was 0.732 and 0.520, respectively, in the OP and fracture group) were observed (Figure 3). The relationships between APS and OP and fracture were shown in Supplementary Table S12. We found that higher levels of APSs were associated with a higher risk of developing OP. From the first quintile (Q1) of APS to the fifth quintile (Q5) of APS, we found an incremental trend in OP risk. The HRs (95% CI) of OP occurring in subjects with higher quintile groups compared to those with the lowest quintile of the APS were estimated to be 1.027 (0.967–1.090), 1.049 (0.988–1.115), 1.094 (1.030–1.161), and 1.140 (1.072–1.213). After excluding $PM_{2.5-10}$ in the APS, the result did not change appreciably. The HRs (95% CI) of OP were estimated to be 1.082 (1.019–1.149), 1.016 (0.956–1.080), 1.121 (1.056–1.190), and 1.173 (1.103–1.247) in higher quintile groups, when compared with Q1 of the APS. Similar results were observed in the relationship between APS and fracture. APSs were associated with an increased risk of fracture in a dose-response relationship. Compared with the lowest quintile of the APS, the HRs (95% CI) of fracture were estimated to be 1.005 (0.956–1.055), 1.040 (0.990–1.092), 1.064 (1.013–1.117), and 1.080 (1.026–1.136) for the higher quintile groups. Similarly, the removal of $PM_{2.5-10}$ in the APS did not significantly affect the results. The HRs (95% CI) of fracture for those exposed to the higher quintile groups were estimated to be 1.004 (0.956–1.055), 1.042 (0.992–1.094), 1.071 (1.020–1.125), and 1.077 (1.024–1.132), respectively. Sensitivity analysis did not have a significant impact on the results (Supplementary Table S13).

3.4. The joint effect of air pollution and genetic risk scores on OP risk

To further explore the joint effect of genetic and environmental factors on OP, we constructed a BMD-based GRS (detailed information was provided in Methods). The histograms show that the GRS of BMD is normally distributed and well stratified in osteoporosis/fracture patients and controls (Supplementary Figures S2A, B). And the RCS curves showed a significant negative linear relationship between GRS and osteoporosis/ fracture risk, respectively (Supplementary Figures S2C, D). Therefore, we believed that GRS could well represent the genetic component of the osteoporosis phenotype.

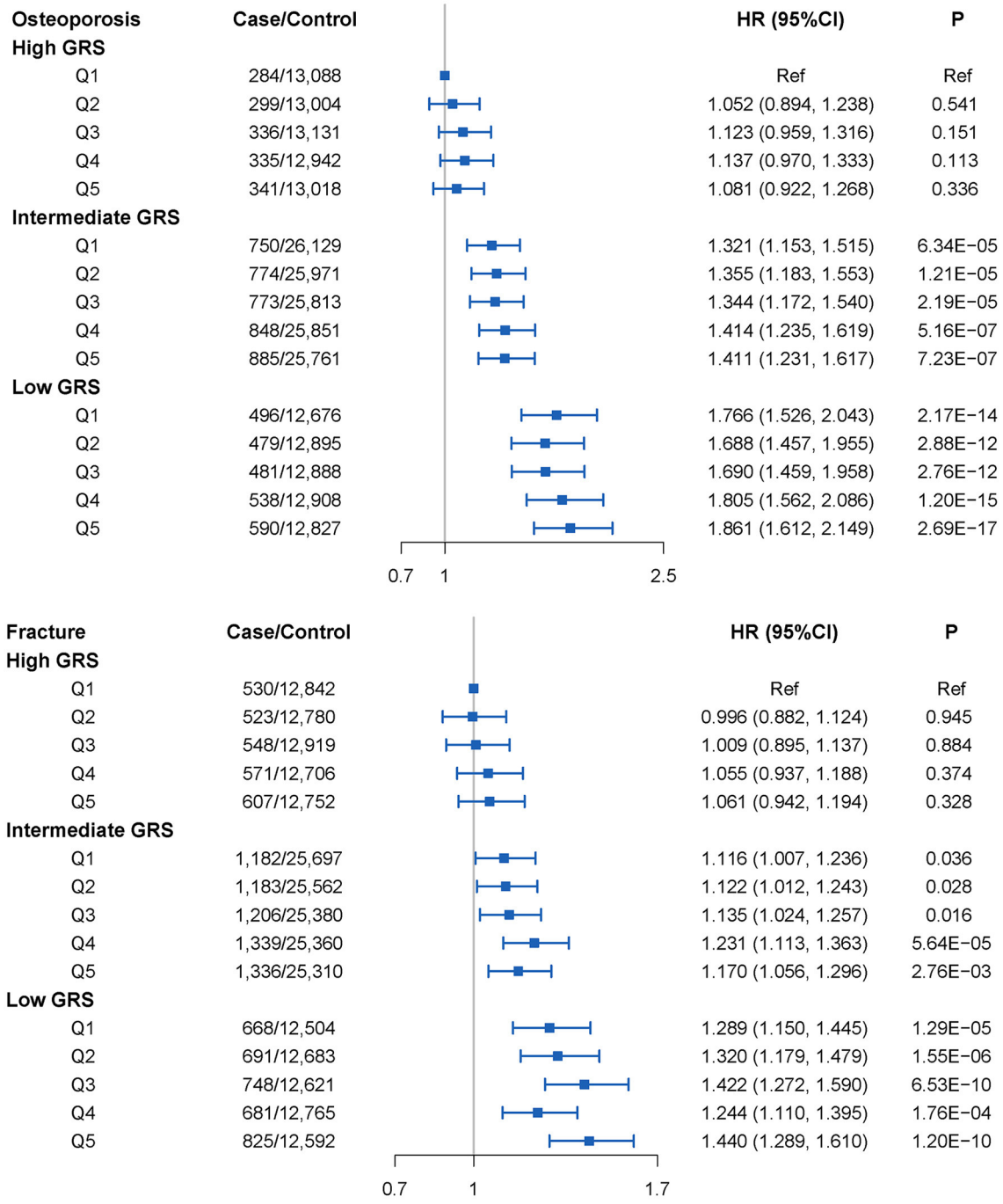

FIGURE 4
OP and fracture risks in the subgroups stratified by genetic risk and air pollution scores (APS_1) concentrations (vs. participants with the lowest concentration of APS_1 in the highest genetic risk group) in the UKB cohort. Note: Associations were adjusted for age, sex, genotyped batch, Townsend deprivation index, height, weight, smoking status, and the first 10 principal components of ancestry. CI, confidence interval; HR, hazard ratio; GRS, genetic risk score.

As the concentration of different air pollutant rises, the risk of OP in participants who has the intermediate GRS and low GRS increases significantly. We also found that participants with low GRS and the highest air pollutant concentration had the highest risk of OP, the HRs (95% CI) of $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_2, and NO_x on OP risk were estimated to be 1.706 (1.483–1.964), 1.658 (1.434–1.916), 1.696 (1.478–1.947), 1.740 (1.506–2.001) and 1.659 (1.442–1.908), respectively. In addition, the risk of OP was higher in the low GRS group than in the intermediate GRS group at equal concentrations of single air pollutants, while no such results were observed in the high GRS group. Similar results were also observed in the fracture individuals (Supplementary Figure S3).

We next assessed the joint association of APS and GRS on the risk of developing OP. As shown in Figure 4, the joint effect of intermediate GRS or low GRS and APS increased the risk of developing OP, and from Q1 to Q5, we also found an approximate gradient increase in OP risk. However, these were not observed in the high GRS group. We also found that participants with high APS and low GRS had the highest risk of developing OP, 86.1% (95% CI = 61.2–114.9%) greater than participants with low APS and high GRS. Similar results were observed in the joint effect of GRS and APS on fracture. Participants with high APS and low GRS had a 44.0% (95% CI = 28.9–61.0%) higher fracture risk than those with low APS and high GRS. Similar results were obtained from sensitivity analysis (Supplementary Table S14). After excluding $PM_{2.5-10}$ in the APS, the result did not change appreciably (Supplementary Figure S4 and Supplementary Table S15).

4. Discussion

This study observed the significant associations between an increased OP and fracture risk and the exposure to various ambient air pollutants, including $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_2, and NO_x. We then constructed APSs to evaluate the combined effect of various ambient air pollutants and found significant associations with the risk of developing OP and fracture. Moreover, we investigated the joint effects of genetic risk and air pollutants and found that low genetic risk and high APSs synergistically increased the risk of developing OP and fractures. In conclusion, this study performed a systemic study to disclose the associations between air pollution exposure and OP risk and highlighted the combined effects of multiple air pollutants and their interaction effects with genetic factors on OP risk.

In this large-scale prospective study, $PM_{2.5}$ was significantly associated with the risk of OP and fracture, which is consistent with previous epidemiology studies. An OP sub-study of the population-based Oslo Health Study showed that total body BMD was negatively associated with both $PM_{2.5}$ (3). Two studies in China and Italy found significant associations between OP and $PM_{2.5}$ (9, 11). Furthermore, a study conducted in Korea showed that $PM_{2.5}$ was associated with fracture (7). The association between PM_{10} and OP and fracture is inconsistent in previous studies (6, 7, 11), while our study identified adverse effects of PM_{10} on bone metabolism. In our analysis, we detected a significant effect of raised PM_{10} concentration on eBMD, but no significant association with OP and fracture risk. Our study found a nonlinear relationship between PM_{10} and OP risk using the RCS method, which may be one of the reasons for the inconsistent findings between BMD and OP. Additionally, the inconsistent results between $PM_{2.5}$ and PM_{10} may be because $PM_{2.5}$ has a larger specific surface area compared to PM_{10} and can adsorb more compounds and metals (26), which could affect the balance of bone metabolism. We also confirmed that NO_2 and NO_x were significant air pollutants related to the risk of OP and fracture, which was consistent with previous studies. Mazzucchelli et al. (5) found that hip fracture incidence was associated with SO_2, NO, and NO_2 (5). Retrospective cohort studies in Asia showed that NO_2 was associated with an increased risk of OP (4, 9). In addition, NO, NO_2 and NO_x were found negatively associated with BMD T-scores in a cross-sectional study (6).

The importance of assessing exposure to multiple ambient air pollutants has been recognized in recent years. Air pollution is a complex mixture composed of many substances (27), and synergistic effects may exist among various air pollutants. It is difficult to sort out the effects of a single component on humans. Therefore, APS enables a better assessment of combined exposure to air pollutants. As we expected, this study found more stable and robust associations between APS and the risk of OP and fracture, when compared to single pollutants. Similar methods have been used in previous studies. Lin et al. (6) found that the joint effects of SO_2 and NO_2, CO, and NO_x on OP were more significant than individual air pollutants (6). Moreover, similar methods have been used to evaluate the joint effects of other environmental risks (28, 29) and dietary factors (30).

The biological mechanisms underlying the effects of ambient air pollutants on OP risk have not been clearly explained, however, previous studies have presented several possible mechanisms for the relationship between air pollutants and OP. Air pollutants could lead to oxidative stress and inflammation (31, 32). Oxidative stress causes DNA damage and cellular aging which disrupts the balance between bone resorption and osteogenesis (33, 34). It has been demonstrated that exposure to air pollutants such as NO_2 and PM can lead to the production of free radicals, and then cause inflammatory processes (35–39). Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and IL-17 can affect the differentiation and function of osteoblasts and osteoclasts during bone metabolism (40–42), thus bring out the imbalance in the bone homeostasis and decrease bone density. For example, TNF-α drives RANK expression in monocytes and stimulates monocytes' conversion into osteoclast precursors, in addition to promoting RANKL expression in stromal cells (43). Air pollutants can also induce immune responses. Chronic exposure to PM has significant effects on innate and adaptive immune cell populations in the lung, lymphatic, and systemic immune populations have been previously reported. Chemicals attached to PM such as polycyclic aromatic hydrocarbons (PAH) can enhance T helper (Th)17 lymphocyte differentiation (44). Air pollutants can affect vitamin D synthesis by increasing levels of parathyroid hormone (45, 46), this hormone also facilitates the differentiation of T cells into Th17 cells (47). IL-17 is secreted by Th17 and can induce osteoblast production by promoting the release of RANKL from osteoblasts and osteocytes, and has an important role in bone metabolism. IL-17 also enhances RANKL sensitivity by regulating RANK expression, leading to increased osteoclast numbers and bone resorption (48). In addition, some indirect factors, such as vitamin D deficiency, can also link air pollution and OP. Prolonged

exposure to high air pollution levels increases the risk of vitamin D deficiency (49). For example, benzo [a] pyrene carried by $PM_{2.5}$ could promote the catabolism of vitamin D_3 (50). Environmental air pollutants such as PM and ozone can block ultraviolet light from the earth's surface (51), and that severe air pollution may also reduce the frequency of outdoor activities, which is detrimental to vitamin D synthesis.

We hypothesize that multiple air pollutants may influence OP risk through similar biological mechanisms such as oxidative stress and inflammation. In addition, studies have demonstrated interactions and synergistic effects between CO and NO_x, as well as SO_2 and NO_2 on BMD, which then reduces the efficiency of O_2 transport and the reversible (NO) or irreversible (CO) inhibition of mitochondrial oxidative phosphorylation by binding to hemoglobin. or irreversible (CO) inhibition of mitochondrial oxidative phosphorylation by reversible binding to the heme aa3 site of cytochrome c oxidase (52). Therefore, we hypothesized that NO_x exacerbates CO-induced hypoxia and exacerbates OP risk. NO_2 can promote sulfate formation, which, due to hygroscopicity, can form aqueous layers on mineral oxide particles, leading to further adsorption of and reaction with other pollutants, including SO_2 (53). Therefore, we hypothesize that the synergistic effect of SO_2 and NO_2 may be a risk factor for OP by promoting the adsorption of other pollutants.

The novelty of this study is the prospective design and the large sample size. The present study is based on a large-scale UK Biobank cohort including approximately 500,000 participates and therefore has good statistical power. In addition, we assessed the role of air pollutants in the association between genetic factors and OP, allowing us to accurately determine the effects of air pollutants on populations with different susceptibility levels. Furthermore, cross-validation analyses were performed in this study and the air pollutant models were found to perform well, demonstrating the robustness of our findings. However, there also exist some limitations: First, due to the big cost of performing DXA-BMD measurements in cohorts with a large sample size, eBMD instead of BMD was used as an indicator of bone strength. Although the previous study has shown the high consistency between genetic determined using ultrasound-derived BMD measurements and those using DXA-derived BMD, some significant differences still exist (54). Second, although we have comprehensively considered a variety of air pollutants, some previously reported air pollutants such as O_3, SO_2, and CO are not present in the UK Biobank. Third, we constructed the APS by treating air pollutants as linear indicators, and although consistent results were shown across phenotypes, possible non-linear relationships between individual air pollutants and OP could interfere with the true association. Finally, the participants in the UK Biobank are predominantly of European origin. The applicability of the findings obtained from this study to other ethnic groups and regions requires further investigation.

5. Conclusion

In conclusion, we found that chronic exposure to air pollution, assessed with APS, played an important role in improving the risk of developing OP and fractures, and increased the adverse effects of genetic risk. Our findings emphasize that improving air quality can reduce the risk of developing OP and fracture, which has important implications for the development of environmental health policies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

F-YD, S-FL, and X-HY conceived the design of the study. X-HY and LB obtained the data. X-HY cleared up the datasets. X-HY and H-WC mainly performed the data analyses. F-YD, S-FL, X-HY, and H-WC drafted and revised the manuscript. All authors approved the manuscript and provided relevant suggestions.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1119774/full#supplementary-material

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