Original article

Associations between osteoporosis and exposure to air pollution: Results from a cross-sectional study on 45,483 adults in Italy

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Abstract. *Background and aim of the work:* Osteoporosis is a disease characterized by the chronic deterioration of bone tissue, leading to an increased risk of fractures, hospitalization and mortality. Recent studies highlighted that exposure to air pollution may represent a risk factor for osteoporosis. This study aimed to investigate the association between air pollution exposure and osteoporosis in a sample of 45,483 Italian adults. *Research design and Methods:* Osteoporosis Data were extracted from a nationwide survey conducted by the Italian National Institute of Statistics in 2019. A logistic regression model was employed to analyze the association between osteoporosis and self-reported levels of air pollution in residential areas. The model was adjusted by sociodemographic characteristics, comorbidities, and lifestyle factors. The Benjamini–Hochberg procedure was applied to multiple comparisons occurring in multivariable analysis to control the false discovery rate. Gender stratified analyses were also performed. *Results*: Higher odds of osteoporosis were found in individuals living in areas reported as 'very polluted' (OR = 1.35, 95%CI = 1.17–1.57, q <0.001), as 'quite polluted' (OR = 1.28, 95%CI = 1.15–1.43, q <0.001), and as 'scarcely polluted' (OR = 1.10, 95%CI = 1.00–1.22, q = 0.0872), compared to those living in areas reported as 'not polluted'. The gender stratified analysis showed that this association was present in females, but not in males. *Conclusions:* Due to the limitations of the cross-sectional design of this study, further research is needed to confirm the results and fully understand the explanatory mechanisms of the association between air pollution and osteoporosis. (www.actabiomedica.it)

Key words: osteoporosis, air pollution, air quality, cross-sectional, survey

Introduction

Osteoporosis is a systemic disease characterized by reduced Bone Mineral Density (BMD) and deterioration of bone microarchitecture, with a consequent increase in bone fragility and susceptibility to fracture after low-level or low-energy trauma, typically affecting the spine, hip, distal forearm and proximal humerus (1). Osteoporotic fractures represent a major risk of hospitalization, long-term disability, loss of independence, and overall impaired quality of life (QoL) increased mortality (2–4). According to the World Health Organization, osteoporosis affects around 200 million women worldwide, with a higher prevalence in Northern America and Europe (22.1% of women and 6.6% of men over 50-years-old), being Italy the most affected country (4,5). The worldwide economic burden of osteoporotic hip fractures is projected to reach $131.5 billion by 2050 (6), while the direct cost of osteoporotic fractures in Italy was estimated to be €9.4 billion in 2019 (5). Several risk factors for the development of osteoporosis have been identified, including family history of osteoporosis; age; female gender; low socioeconomic status (SES); smoking; excessive alcohol consumption; lack of physical activity (PA); low calcium ingestion (7,8); chronic diseases, i.e., chronic obstructive pulmonary disease (COPD), peptic ulcer and diabetes; long-term treatment with corticosteroids or chemotherapy (9–11); and, more recently, air pollution. Specifically, a study performed in Taiwan demonstrated a significant reduction of BMD in women with long-term exposure to $PM_{2.5}$ (12), while another study from South Korea reported an increased risk of osteoporotic fractures in elderly exposed to higher levels of sulfur dioxide (SO_2) (13). The pathogenetic mechanisms underlying the association between air pollution and bone damage are not fully understood (14,15). The aim of this cross-sectional study was to analyze the association between the exposure to air pollution and the development of osteoporosis in a large representative sample of Italian adults.

Methods

Data sources

Data were extracted from the 2019 survey '*Aspects of Daily Life*', part of an integrated system of social surveys conducted by the Italian National Institute of Statistics (Istat) named 'Multi-Purpose Surveys on Families' (16), administered to 20,000 families equally distributed in about 800 Italian municipalities of different population sizes. Families are randomly extracted by Istat using a sampling strategy aimed at achieving a statistically representative sample of Italy's resident population. Individuals are interviewed using a sequential computer-assisted web-based interview mixed with paper interviews every year between March and May. The questionnaires investigate various aspects of social and daily life to determine individual, family and community health, wealth, interactions and functioning in relation with public services, productive and leisure activities by assessing people behaviors, motivations, and opinions. The study was designed following STROBE guidelines (17).

Study variables

Each study variable corresponded to a survey question. The outcome binary variable was the diagnosis of osteoporosis as reported by the patient (0 for 'not affected' and 1 for 'affected'). Exposure to air pollution was assessed using self-reported residential air quality levels codified as *'very polluted'*, *'quite polluted'*, *'scarcely polluted'*, and *'not polluted'*. Covariates included in the analysis were gender, age, educational level, citizenship, macro-region area of residence, PA, body mass index (BMI), vegetable consumption, smoking habit, and presence of the following conditions: diabetes, heart diseases, asthma, COPD, gastric/duodenal ulcer, and cancer. All variables were self-reported by the study participants. Age categories are derived by self-reported age and divided in "Young" for individuals younger than 65 and "Elderly" for individuals aged 65 or older. BMI categories are derived by self-reported height and body weight.

Statistical analysis

Baseline demographic and clinical characteristics were described as mean ± standard deviation, median and interquartile range, or as absolute values and percentages, as appropriate. The normal distribution of numerical variables was confirmed by the Shapiro–Wilk test and Q–Q plot analysis. The association between osteoporosis and each variable was investigated using *t*-test for continuous variables, and chi-square test or Fisher's exact test for categorical variables. Logistic regression analysis was employed to assess the association between air pollution and osteoporosis. The first model (Model 0) provided the unadjusted odds ratio (OR) and 95% confidence interval (CI) for this association, while the second and final model (Model 1) provided the adjusted OR and 95% CI by including all confounding variables as covariates. The set of confounding variables was determined based on the statistical significance of crude associations and previous scientific evidence. Model 1 was also stratified by gender in order to analyze gender differences in the relationship between air pollution and osteoporosis. The reference category for perceived air pollution was set at the lowest level of exposure ('not polluted'). Due to the presence of missing data for various covariates, multiple imputation by chained equations (MICE) was used to create and analyze 30 multiply imputed datasets. Incomplete variables, including the outcome variable, were imputed under fully conditional specification (18). The parameters of interest were separately estimated in each imputed dataset, then combined using Rubin's rules (19) to obtain pooled results. A sensitivity analysis performed using weighted regression estimates to test for local departures from the missing-at-random assumption gave results similar to those obtained under missing-at-random multiple imputation (data not shown) (20). Because such analysis could not confirm the missing-completely-at-random assumption, MICE was performed only on covariates with <25% of missing data to avoid estimation bias (21,22). Therefore, PA, with 36.3% of missing records, was not included in the final list of covariates. However, since PA is recognized as a major protective factor against osteoporosis, a sensitivity analysis was conducted by categorizing the variable into three levels (i.e., active, sedentary, and missing) that were incorporated into the logistic regression models to assess their robustness and stability. All tests were two-sided. The significance level was set as $p < 0.05$. The Benjamini–Hochberg procedure was applied to multiple comparisons occurring in multivariable analysis to control the false discovery rate (23). As a consequence, the *p*-values resulting from Model 1 were presented as *q*-values, i.e., adjusted *p*-values. All analyses were carried out using R-Studio statistical software (RStudio, PBC, Boston, MA, USA) (19).

Results

Study population

The main characteristics of the 45,483 subjects included in the Istat sample are summarized in Table 1. A number of 23,527 (51.7%) individuals were females and 21,956 (48.3%) were males. A total of 34,201 (75.2%) individuals were younger than 65 years, and 11,282 (24.8%) were 65 or older. A total of 5,938 (13.1%) had a university degree, 14,281 (31.4%) a high school degree, 12,438 (27.3%) a middle school degree, and 9,926 (21.8%) an elementary school degree.

Table 1. Population characteristics.

	N	%
Gender		
Male (ref.)	21,956	48.3
Female	23,527	51.7
Age		
Elderly (>65yo)	11,282	24.8
Young (<65yo) (ref.)	34,201	75.2
Educational level		
University degree (ref.)	5,938	13.1
High school degree	14,281	31.4
Middle school degree	12,438	27.3
Elementary school degree	9,926	21.8
Missing	2900	6.4
Citizenship		
Italian (ref.)	42,792	94.1
Foreign	1,633	3.6
Missing	1,058	2.3
Region		
North-west	9,940	21.9
North-east (ref.)	9,711	21.4
Center	8,238	18.1
South	12,912	28.4
Isles	4,648	10.2
Missing	34	0.1
Osteoporosis		
No	39,003	85.8
Yes	3,998	8.8
Missing	2,482	5.5
Air quality		
Very polluted	4,303	9.5
Quite Polluted	10,619	23.3
Scarcely polluted	17,151	37.7
Not polluted at all (ref.)	11,958	26.3
Missing	1,452	3.2
Physical Activity		
Active (ref.)	6,437	14.2
Sedentary	22,547	49.6
Missing	16,499	36.3
BMI		
Underweight	1,104	2.4
Normal weight (ref.)	19,317	42.5

Table 1 (*Continued*)

	N	%
Overweight	13,676	30.1
Obese	4,281	9.4
Missing	7,105	15.6
Vegetables consumption		
More than once a day	5,486	12.1
Once a day	13,619	29.9
A few times a week	19,769	43.5
Less than once a week	3,569	7.8
Never	1,155	2.5
Missing	1,885	4.1
Smoking habit		
Smoker	7,201	15.8
Quitter	9,368	20.6
Non-smoker	24,319	53.5
Missing	4,595	10.1
Diabetes		
no	40,350	88.7
yes	2, 846	6.3
Missing	2,287	5.0
Heart disease		
no	41,259	90.7
yes	1,535	3.4
Missing	2,689	5.9
COPD		
no	41,034	90.2
yes	1,824	4.0
Missing	2,625	5.8
Asthma		
no	41,016	90.2
yes	1,776	3.9
Missing	2,691	5.9
Ulcer		
No	41,551	91.4
Yes	1,222	2.7
Missing	2,710	6.0
Cancer history		
No	41,571	91.4
yes	1,259	2.8
Missing	2,653	5.8

Abbreviation: ref. = reference category.

The vast majority hold Italian citizenship (94.1%). Air quality at residential places was reported as very polluted by 4,303 (9.5%), quite polluted by 10,619 (23.3%), scarcely polluted by 17,151 (37.7%), and not polluted by 11,958 (26.3%). A diagnosis of osteoporosis was reported by 3,998 (8.8%) subjects. Overall, 13,488 (29.7%) records were incomplete. The percentage of missing values varied between 0.0% and 15.6% across the 17 variables included in the regression models, except for PA that was burdened by 36.3% of missing data (see 'Methods' section).

Regression analysis

Complete results from logistic regression models are reported in Table 2. The crude analysis showed a significant association between air pollution and osteoporosis, with the prevalence of osteoporosis being significantly higher in very polluted areas (OR = 1.26, 95% CI = 1.12–1.42, p <0.001) than in not polluted areas. This significant association was confirmed in the adjusted model (OR = 1.35, 95% CI = 1.17–1.57, q <0.001), according to which the rate of osteoporosis was also higher among those living in quite polluted areas (OR = 1.28, 95% CI = 1.15–1.43, q <0.001), but not in scarcely polluted areas (OR = 1.10, 95% CI = 1.00–1.22, q = 0.0872), as compared to those living in not polluted areas.

Female gender, older age, obesity, presence of comorbidities, lower educational level, foreign citizenship, and living in central, southern or insular Italy were also significantly associated with higher rates of osteoporosis (Table 2).

As reported in Table 3, higher odds of osteoporosis were identified in females exposed to higher levels of air pollution (OR = 1.37, 95% CI = 1.18–1.60, q <0.001), but not in males (OR = 1.12, 95% CI = 0.83–1.50, q = 0.210).

Lastly, the introduction of PA in the analysis did not significantly change the model estimates (Supplementary Table S1).

Discussion

This cross-sectional study performed on 45,483 subjects residing in Italy supports the hypothesis of air

Table 2. Logistic regressions results.

	Adjusted model				Unadjusted model		
	OR	95% CI	p-value	q-value	OR	95% CI	p-value
Air pollution							
Not polluted	—	—			—	—	
Scarcely polluted	1.1	1.00, 1.22	0.052	0.072	1.02	0.94, 1.11	0.643
Quite Polluted	1.28	1.15, 1.43	**<0.001**	**<0.001**	1.14	1.04, 1.25	**0.013**
Very polluted	1.35	1.17, 1.57	**<0.001**	**<0.001**	1.26	1.12, 1.42	**<0.001**
Gender							
Male	—	—					
Female	7.73	6.93, 8.63	**<0.001**	**<0.001**			
Age							
Young	—	—					
Elderly	8.01	7.31, 8.77	**<0.001**	**<0.001**			
Educational level							
University degree	—	—					
High school degree	1.27	1.09, 1.48	**0.002**	**0.003**			
Middle school degree	1.41	1.21, 1.64	**<0.001**	**<0.001**			
Elementary school degree	1.55	1.34, 1.80	**<0.001**	**<0.001**			
Citizenship							
Italian	—	—					
Foreign	0.61	0.44, 0.84	**0.003**	**0.004**			
Macro-region							
North-East	—	—					
North-West	1.11	0.98, 1.25	0.111	0.148			
Center	1.38	1.22, 1.57	**<0.001**	**<0.001**			
South	1.67	1.49, 1.88	**<0.001**	**<0.001**			
Islands	1.95	1.68, 2.26	**<0.001**	**<0.001**			
BMI							
Normal weight	—	—					
Underweight	0.94	0.74, 1.19	0.609	0.656			
Overweight	1.10	1.01, 1.20	**0.038**	0.056			
Obesity	1.18	1.05, 1.34	**0.007**	**0.011**			
Vegetables Consumption							
Never	—	—					
Less than once a week	1.07	0.78, 1.47	0.693	0.718			
A few times a week	1.16	0.87, 1.55	0.297	0.347			
Once a day	1.20	0.90, 1.61	0.210	0.267			
More than once a day	1.20	0.89, 1.61	0.243	0.295			

Table 2 (*Continued*)

	Adjusted model				Unadjusted model		
	OR	95% CI	p-value	q-value	OR	95% CI	p-value
Smoking history							
Non-smoker	—	—					
Quitter	1.03	0.93, 1.14	0.599	0.656			
Smoker	0.99	0.87, 1.12	0.834	0.834			
Diabetes							
No	—	—					
Yes	1.63	1.45, 1.84	**<0.001**	**<0.001**			
Heart Disease							
No	—	—					
Yes	2.20	1.88, 2.57	**<0.001**	**<0.001**			
COPD							
No	—	—					
Yes	2.59	2.24, 3.00	**<0.001**	**<0.001**			
Asthma							
No	—	—					
Yes	1.70	1.43, 2.01	**<0.001**	**<0.001**			
Gastric/duodenal ulcer							
No	—	—					
Yes	4.11	3.48, 4.85	**<0.001**	**<0.001**			
Cancer							
No	—	—					
Yes	2.65	2.25, 3.12	**<0.001**	**<0.001**			

Note: the q value is derived from the Benjamini & Hochberg correction for multiple testing.

pollution as a potential risk factor for osteoporosis. Previous studies performed in large population-based cohorts reported a significant decrease in BMD coupled with a significant increase in osteoporosis in people exposed to high levels of air pollutants, including $PM_{2.5}$, PM_{10} and NO_x (24–26). Another study demonstrated higher levels of urinary polycyclic aromatic hydrocarbons (PAHs) in patients with osteoporosis (27). Moreover, higher levels of exposure to $PM_{2.5}$ were associated with higher risk of osteoporotic fractures (28,29). Although the exact pathogenesis remains to be established, several mechanisms linking chronic exposure to air pollution to osteoporosis have been postulated. First, air pollution has been demonstrated to trigger inflammatory pathways and oxidative stress involved in pathogenesis of osteoporosis (30,31). Pro-inflammatory cytokines and other inflammatory mediators may contribute to the disruption of bone tissue and reduce BMD (32,33). RANK-RANKL-OPG pathway is primarily involved in the pathogenesis of osteoporosis. RANK binding to RANKL, a member of the tumor-necrosis-factor family of ligands placed on the surface of osteoclasts, activates their differentiation, thus stimulating bone resorption (34). Osteoprotegerin (OPG) binds to RANKL and prevents its interaction with RANK, thus inhibiting osteoclastogenesis. The RANKL/OPG ratio has a crucial role in maintaining bone homeostasis. In osteoporosis, a relative increase in RANKL and decrease in OPG results in the increase of osteoclastic activity (34). Inflammation increases the production of RANKL, activating the RANK pathway, and, consequently, stimulates osteoclast activation and bone resorption (35,36), ultimately increasing the risk of osteoporotic

Table 3. Gender stratified logistic regressions.

	Males				Females			
	OR	95% CI	p-value	q-value	OR	95% CI	p-value	q-value
Air pollution								
Not polluted	—	—			—	—		
Scarcely polluted	1.07	0.88, 1.31	0.506	0.711	1.09	0.98, 1.21	0.043	0.065
Quite Polluted	1.19	0.95, 1.49	0.377	0.598	1.32	1.17, 1.48	**<0.001**	**<0.001**
Very polluted	1.12	0.83, 1.50	0.101	0.210	1.37	1.18, 1.60	**<0.001**	**<0.001**
Age								
Young	—	—			—	—		
Elderly	4.86	4.02, 5.87	**<0.001**	**<0.001**	9.08	8.24, 10.0	**<0.001**	**<0.001**
Educational level								
University degree	—	—			—	—		
High school degree	1.11	0.81, 1.54	0.656	0.768	1.29	1.10, 1.53	**0.002**	**0.003**
Middle school degree	1.24	0.91, 1.71	0.233	0.420	1.43	1.21, 1.68	**<0.001**	**<0.001**
Elementary school degree	1.70	1.25, 2.35	**0.010**	**0.024**	1.50	1.28, 1.77	**<0.001**	**<0.001**
Citizenship								
Italian	—	—			—	—		
Foreign	0.88	0.38, 1.74	0.230	0.42	0.55	0.39, 0.77	**0.004**	**0.006**
Macro-region								
North-East	—	—			—	—		
North-West	0.99	0.75, 1.31	0.366	0.598	1.10	0.96, 1.25	0.141	0.182
Center	1.42	1.08, 1.87	**0.010**	**0.024**	1.33	1.16, 1.53	**<0.001**	**<0.001**
South	2.05	1.61, 2.62	**<0.001**	**<0.001**	1.63	1.44, 1.85	**<0.001**	**<0.001**
Islands	1.78	1.31, 2.42	**<0.001**	**<0.001**	2.00	1.71, 2.34	**<0.001**	**<0.001**
BMI								
Normal weight	—	—			—	—		
Underweight	0.93	0.33, 2.24	0.427	0.640	0.87	0.68, 1.10	0.741	0.741
Overweight	1.09	0.84, 1.39	0.067	0.150	1.08	0.98, 1.19	0.061	0.086
Obesity	0.99	0.77, 1.27	0.962	0.965	1.23	1.08, 1.41	**<0.001**	**<0.001**
Vegetables Consumption								
Never	—	—			—	—		
Less than once a week	0.79	0.47, 1.40	0.566	0.728	1.22	0.84, 1.78	0.393	0.443
A few times a week	0.82	0.52, 1.36	0.868	0.937	1.33	0.96, 1.88	0.211	0.248
Once a day	0.74	0.46, 1.24	0.682	0.768	1.41	1.01, 2.00	0.096	0.129
More than once a day	0.81	0.48, 1.39	0.965	0.965	1.38	0.98, 1.97	0.149	0.182
Smoking history								
Non-smoker	—	—			—	—		
Quitter	1.14	0.95, 1.36	0.628	0.768	1.06	0.95, 1.19	0.506	0.546
Smoker	1.22	0.96, 1.53	0.526	0.711	0.95	0.83, 1.09	0.646	0.671

Table 3 (*Continued*)

	Males				Females			
	OR	**95% CI**	**p-value**	**q-value**	**OR**	**95% CI**	**p-value**	**q-value**
Diabetes								
No	—	—			—	—		
Yes	2.19	1.81, 2.64	**<0.001**	**<0.001**	1.43	1.26, 1.64	**<0.001**	**<0.001**
Heart Disease								
No	—	—			—	—		
Yes	2.05	1.64, 2.56	**<0.001**	**<0.001**	2.34	1.96, 2.80	**<0.001**	**<0.001**
COPD								
No	—	—			—	—		
Yes	2.44	1.93, 3.06	**<0.001**	**<0.001**	2.48	2.09, 2.95	**<0.001**	**<0.001**
Asthma								
No	—	—			—	—		
Yes	2.36	1.83, 3.04	**<0.001**	**<0.001**	1.40	1.15, 1.68	**<0.001**	**<0.001**
Gastric/duodenal ulcer								
No	—	—			—	—		
Yes	3.51	2.76, 4.44	**<0.001**	**<0.001**	4.46	3.65, 5.44	**<0.001**	**<0.001**
Cancer								
No	—	—			—	—		
Yes	2.54	1.98, 3.25	**<0.001**	**<0.001**	2.95	2.44, 3.55	**<0.001**	**<0.001**

Note: the q value is derived from the Benjamini & Hochberg correction for multiple testing.

fractures (37). High levels of air pollution may also indirectly promote osteoporosis by significantly reducing PA, lowering the willingness to practice outdoor physical exercise in individuals living in highly polluted areas (38). In addition, air pollution has been linked to decreased lung function and increased rates of respiratory symptoms, which may reduce the ability to engage in PA and participate in activities requiring high levels of aerobic fitness (39,40). Furthermore, air pollution may contribute to reducing vitamin D levels by lowering the amount of solar UVB radiation, especially in people living in highly polluted areas (41,42), which represents a primary risk factor for osteoporosis. Specifically, particulate matter absorbs UVB radiation and reduces the amount that reaches the earth's surface (43), while other pollutants like ozone and sulfur dioxide could scatter UVB radiation (44). A 2019 cohort study found an association between air pollution exposure and vitamin D deficiency in pregnant women (45). Finally, some components of particulate matter may act as endocrine-disruptors and negatively impact on bone health (46) by interfering with estrogen activity directly (i.e., PAHs and polychlorinated biphenyls (PCBs) (47–49)), and indirectly via RANK-RANKL pathway (50), disrupting the function of the hypothalamic-pituitary-adrenal (HPA) axis, a key endocrine system involved in the regulation of stress and metabolism (51,52), with consequent decrease in BMD and increased risk of osteoporosis (53–55). Our gender-stratified analysis suggests the existence of gender differences in the association between air pollution and osteoporosis. The underlying mechanisms explaining these gender differences are not fully understood yet. However, the endocrine effects of pollutants, as well as lifestyle and environmental exposure pathway differences between men and women, may play a role in explaining these results (56). Moreover, the prevalence of osteoporosis is lower in males, resulting in a decreased statistical power in this sub-sample. Further research is needed to confirm these results. This study also confirms the significant increase of osteoporosis in elderly and females (49), as well as in subjects with an obesity condition, in agreement with the most recent research (57–59). Indeed, as suggested by previous studies (60), fat mass could exert protective effects on bone health, but this may not be sufficient to counteract the negative effects of obesity secondary, for example, to chronic low-grade systemic inflammation, which increases bone marrow adipogenesis and bone resorption, and reduces bone formation (61). Moreover, all comorbidities included in the adjusted model resulted associated with osteoporosis, confirming previous studies (7,10,62). The most important underlying pathogenic mechanism appears to be chronic inflammation, typical of diabetes, cardiovascular diseases, but also COPD and cancer, leading also to the increase of osteoporotic fractures (10, 11, 62–64). The results of this study also found an association between higher risk of osteoporosis and lower education. This association may be the result of a multifactorial mechanism, with education also acting as a proxy variable for socioeconomic status. Low education and deprived socioeconomic status may represent barriers to the access to health information, and to the adoption of healthy lifestyle (i.e., buy healthy food and practice physical activity) (65–70). Moreover, socioeconomic status may influence the access to healthcare interventions aimed at preventing osteoporosis and associated comorbidities (71,72). The higher osteoporosis rates in people living in southern regions and islands could be a direct consequence of a lower availability of health services (73,74). Moreover, higher prevalence of osteoporosis in southern and insular regions may be related to the higher prevalence of vitamin D deficiency since childhood reported in the literature (75). This study findings are coherent with the 2019 geographical distribution of the use of osteoporosis treatments in Italy (76). Smoking habit and low vegetable consumption were not associated with an increased risk of osteoporosis, although they are generally considered known risk factors (77–80). These results may depend on selection bias, reverse causality, or self-report bias affecting studies with a cross-sectional design (81). The results also showed that individuals with foreign citizenship had a lower likelihood of reporting a diagnosis of osteoporosis compared to those with Italian citizenship. The underlying reasons are multifactorial and may be difficult to fully understand. One of the potential explanatory mechanisms may be that the prevalence of many pathologies, including osteoporosis, in the foreign population is underestimated due to difficulties accessing healthcare (82). Migrants and non-native speakers may face language and cultural barriers in accessing the health system, which may prevent these individuals from seeking medical attention and getting an accurate diagnosis (83). In addition, a nationwide study in Sweden showed that foreigners had lower risk of osteoporotic fractures compared to Swedish citizens (84), suggesting that explanations on this association may be linked also to shared individuals' characteristics, and not only to societal determinants. The main strength of this study is the large sample size, which provides sufficient statistical power to assess the association between perceived air pollution and osteoporosis, and to assess the impact of other endogenous and exogenous factors. On the other hand, some limitations should be acknowledged. First, the cross-sectional design limits causal inferences. Moreover, residual confounding can not be excluded. Second, osteoporosis, air pollution and all the other determinants included in the analysis were self-reported. While self-assessment can be a useful tool for collecting data, it is subject to biases and errors that may affect the accuracy and reliability of the results. For example, participants may not accurately remember or report their behavior or attitudes or may be influenced by social desirability biases. Additionally, self-assessment relies on the assumption that participants are capable of accurately evaluating their own characteristics, which may not always be the case. Although it is not the ideal choice of diagnosis assessment method, self-reported prevalence of osteoporosis was reported as acceptable in terms of accuracy (85). On the other hand, self-reported levels of exposure to air pollution were found to be associated with objectively measured exposure levels to air pollutants (86). Third, the self-reported diagnosis of osteoporosis was the only outcome variable analyzed in this study. Hence, associations between air pollution and osteoporosis severity or staging, or clinical complications, such as fractures, remain to be investigated. Fourth, data were collected at supra-regional level, which means that it is not possible to analyze and draw conclusions on the association between osteoporosis and air pollution for smaller geographical areas or specific municipalities within each region, which could, instead, present significant differences in terms of air pollution. To conclude, this study found an association between self-reported osteoporosis and higher perceived air pollution at the participants' area of residence. It was also found that people living in the central, southern and insular regions of Italy had a higher probability of having osteoporosis. Age, gender, educational level, body weight and specific comorbidities also resulted as determinants of osteoporosis. However, these findings are not conclusive and further studies are needed to confirm and expand upon them. Because of the complexity of osteoporosis pathogenesis, large prospective harmonized cohorts of patients living in different countries and evaluated with standardized tools are strongly required to assess the impact of air pollution and other environmental and social determinants. Understanding the underlying mechanisms by which environmental exposures and demographic factors may contribute to osteoporosis could lead to the development of targeted prevention and treatment strategies. Overall, this study adds to the growing body of research on osteoporosis and highlights the need for continued investigation in this important area of biomedical research.

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ANNEX

Table S1. Sensitivity analysis.

	Adjusted model			
	OR	95% CI	p-value	q-value
Air pollution				
Not polluted	—	—		
Scarcely polluted	1.11	1.01, 1.23	**0.037**	0.056
Quite Polluted	1.29	1.16, 1.44	**<0.001**	**<0.001**
Very polluted	1.36	1.17, 1.58	**<0.001**	**<0.001**
Gender				
Male	—	—		
Female	7.43	6.65, 8.30	**<0.001**	**<0.001**
Age				
Young	—	—		
Elderly	7.24	6.59, 7.96	**<0.001**	**<0.001**
Educational level				
University degree	—	—		
High school degree	1.21	1.04, 1.41	**0.014**	**0.022**
Middle school degree	1.29	1.11, 1.51	**0.001**	**0.002**
Elementary school degree	1.42	1.22, 1.66	**<0.001**	**<0.001**
Citizenship				
Italian	—	—		
Foreign	0.57	0.41, 0.79	**<0.001**	**0.001**
Macro-region				
North-East	—	—		
North-West	1.08	0.95, 1.22	0.251	0.302
Center	1.32	1.16, 1.50	**<0.001**	**<0.001**
South	1.53	1.36, 1.72	**<0.001**	**<0.001**
Islands	1.8	1.55, 2.09	**<0.001**	**<0.001**
BMI				
Normal weight	—	—		
Underweight	1.33	0.73, 1.18	0.540	0.578
Overweight	1.07	0.98, 1.17	0.128	0.175
Obesity	1.13	1.00, 1.27	0.057	0.082
Vegetables Consumption				
Never	—	—		
Less than once a week	1.06	0.77, 1.46	0.711	0.711
A few times a week	1.16	0.87, 1.55	0.299	0.345
Once a day	1.22	0.91, 1.63	0.181	0.226
More than once a day	1.23	0.91, 1.66	0.176	0.226

Smoking history				
Non-smoker	—	—		
Quitter	1.04	0.94, 1.15	0.467	0.519
Smoker	1.37	0.86, 1.10	0.674	0.697
Diabetes				
No	—	—		
Yes	1.61	1.43, 1.81	**<0.001**	**<0.001**
Heart Disease				
No	—	—		
Yes	2.19	1.87, 2.56	**<0.001**	**<0.001**
COPD				
No	—	—		
Yes	2.54	2.20, 2.94	**<0.001**	**<0.001**
Asthma				
No	—	—		
Yes	1.71	1.44, 2.02	**<0.001**	**<0.001**
Gastric/duodenal ulcer				
No	—	—		
Yes	4.03	3.42, 4.76	**<0.001**	**<0.001**
Cancer				
No	—	—		
Yes	2.66	2.26, 3.13	**<0.001**	**<0.001**
Physical activity				
Active	—	—		
Sedentary	1.21	1.08, 1.35	**<0.001**	**0.002**
Missing	1.02	0.71, 7.38	0.761	0.819

Note: the q value is derived from the Benjamini & Hochberg correction for multiple testing.