npj Primary Care Respiratory Medicine

Article in Press

https://doi.org/10.1038/s41533-026-00490-w

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Received: 29 September 2025

Accepted: 3 February 2026

Cite this article as: Gao, Y., Li, Z., Wu, J. *et al.* The risk of osteoporosis in COPD: An analysis of sex differences and mediating effects based on NHANES. *npj Prim. Care Respir. Med.* (2026). https://doi.org/10.1038/s41533-026-00490-w

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The Risk of Osteoporosis in COPD: An Analysis of Sex Differences and Mediating Effects Based on NHANES

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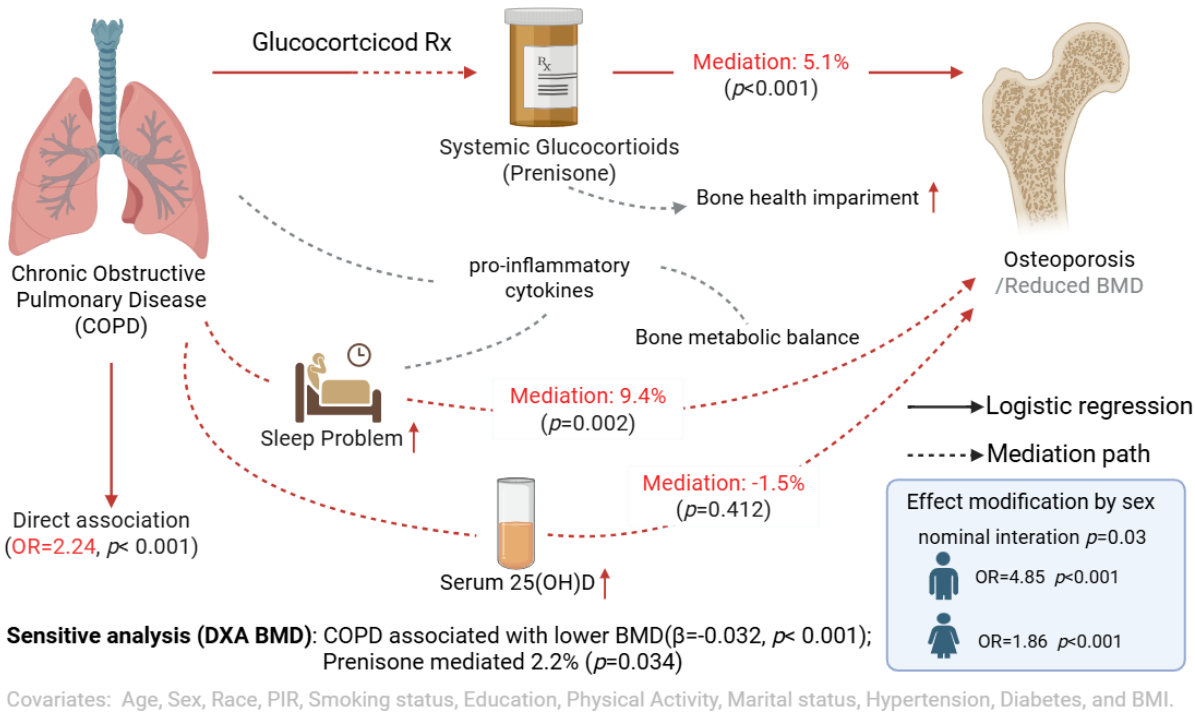
Graphical Abstract



Number of figures: 3; Number of tables:6; Number of appendix: 1

Abstract

Background: Chronic obstructive pulmonary disease (COPD) and osteoporosis are significant public health concerns, often co-occurring due to shared risk factors such as ageing, smoking, and systemic inflammation, as well as treatment-related factors such as long-term glucocorticoid use. However, large-scale studies exploring these associations, their sex-specific effects, and mediating factors remain limited.

Methods: A total of 8,274 participants aged ≥50 years from NHANES cycles 2005-2018 were included. COPD and osteoporosis were identified based on self-reported diagnoses, with Bone Mineral Density (BMD), measured by Dual-energy X-ray Absorptiometry (DXA), used as a sensitivity outcome. Weighted logistic regression analyzed the association between COPD and osteoporosis. Interaction and stratified analyses explored effect modification by sex, BMI, prednisone use, vitamin D, and race. Exploratory mediation analysis examined the indirect effects of prednisone, sleep problems, and vitamin D.

Results: COPD was significantly associated with osteoporosis risk (OR = 2.24, P < 0.001). A nominal sex interaction was observed (unadjusted P = 0.03), with a stronger association in males (adjusted OR = 4.85, 95% CI: 2.49-9.42, P < 0.001) than females (adjusted OR = 1.86, 95% CI: 1.30-2.65, P < 0.001).

Exploratory mediation analyses suggested that prednisone use (mediated 5.1%) and sleep problems (mediated 9.3%) accounted for portions of the association, while vitamin D level did not show meaningful mediation. Sensitivity analyses confirmed an association between COPD and lower BMD ($\beta = -0.032$, $P < 0.001$), with significant mediation by prednisone (2.2%, $P = 0.034$).

Conclusions: COPD is significantly associated with osteoporosis, with a stronger relative effect observed in males. Exploratory findings suggest potential mediation by prednisone use and sleep disorders. These results highlight the importance of integrated bone health management in COPD patients, with particular attention to sex-specific risks and modifiable factors such as glucocorticoid exposure and sleep quality.

Keywords: chronic obstructive pulmonary disease; osteoporosis; glucocorticoids; sleep problems; mediation analysis

1 Introduction

Chronic Obstructive Pulmonary Disease (COPD), marked by progressive airflow obstruction, remains a critical global health challenge. Current estimates indicate nearly 400 million affected individuals worldwide, with projections suggesting it will rank as the third-leading cause of death by 2030 [1,2]. Beyond respiratory impairment, COPD heightens vulnerability to multiple comorbidities, amplifying healthcare burdens and mortality. Osteoporosis—a skeletal disorder featuring compromised bone mass and microarchitectural deterioration—elevates fracture susceptibility, particularly in older adults [3]. Annual osteoporosis-attributable fractures approach 9 million globally, profoundly diminishing life quality and escalating costs[4].

Notably, COPD elevates osteoporosis susceptibility[5] and low-trauma fracture readmissions [6]. Among the multiple pathways linking COPD to impaired bone health, long-term systemic glucocorticoid use, sleep disturbance and vitamin D status are of particular interest. Glucocorticoids are a recognized cause of secondary osteoporosis and are widely used in COPD management; sleep disorders, including obstructive sleep apnea (OSA) and insomnia, are common in COPD and may exacerbate systemic inflammation and physical inactivity; and 25-hydroxyvitamin D [25(OH)D] is essential for bone mineralization and may be altered by reduced outdoor activity and supplementation practices in COPD. These variables are routinely measured in NHANES and thus provide an opportunity to explore their potential mediating roles[6-8]. While androgen decline may accelerate bone loss in males, estrogen deficiency contributes to higher baseline osteoporosis rates in females [9,10]. However, prior studies suffer from methodological constraints: predominantly single-center designs with inadequate examination of mediating factors (e.g., sleep, prednisone) or sex-stratified effects, and insufficient population-based evidence.

Our investigation harnesses the NHANES database (2005-2010, 2013-2014, 2017-2018) to rigorously examine the COPD-osteoporosis relationship. We specifically quantify mediating roles of sleep disturbances, prednisone use, and serum 25(OH)D, while assessing sex-based effect modification. Using survey-weighted regression and causal mediation frameworks, supplemented by bone mineral density (BMD) sensitivity analyses, this work provides evidence to optimize clinical screening protocols.

2. Materials and Methods

2.1 Data Source

Data originated from the nationally representative National Health and Nutrition Examination Survey (NHANES), conducted by Centers for Disease Control and Prevention (CDC)/ National Center for Health Statistics (NCHS) using stratified multistage probability sampling. Cycles 2011-2012 and 2015-2016 were excluded due to incomplete prednisone/BMD data. All participants provided written informed consent under NCHS-approved protocols.

2.2 Study Population

From 50,463 participants across five NHANES cycles, we excluded individuals aged <50 years and those with missing values for COPD, osteoporosis, BMD, or key covariates used in the fully adjusted model. The final analytic sample comprised 8,274 adults (Figure 1).

To evaluate potential selection bias due to missing data, we compared baseline characteristics between participants included in the analytic sample and those excluded because of missing exposure, outcome or covariate values (Supplementary Table S1). Excluded individuals were slightly older and had less favorable cardiometabolic and socioeconomic profiles than those included, indicating that missingness was not completely at random.

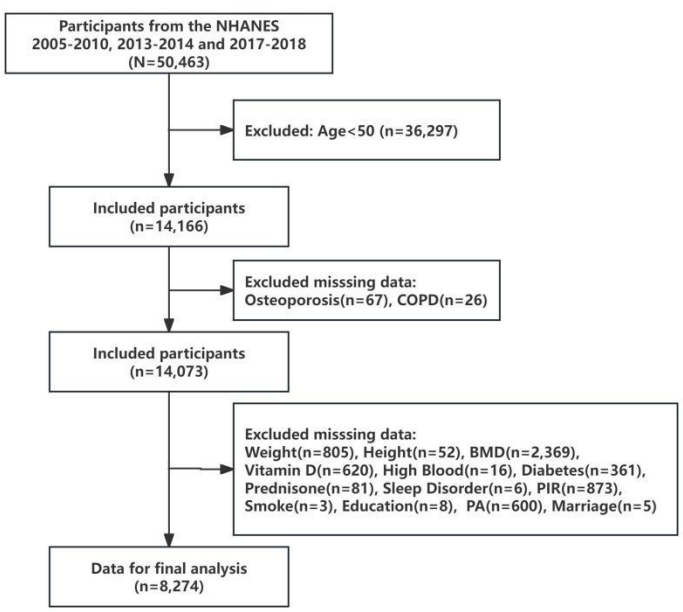


Figure 1. Flowchart of the study population

2.3 Outcome Variables

The primary outcome was osteoporosis, defined by affirmative responses to the NHANES question: "Has a doctor ever told you that you have osteoporosis?"

The Secondary outcome was Total femur bone mineral density (BMD; g/cm²) measured by dual-energy X-ray absorptiometry (DXA). Per NHANES protocol: Eligible participants: Aged ⩾8 years; Exclusions: Pregnancy, Recent radioactive contrast use (⩽7 days), Nuclear medicine examinations (⩽3 days), Weight >300 lbs (136 kg), Scanning sequence: Left hip preferred; right hip if left unavailable; exclusion if bilateral abnormalities.

2.4 Exposure Variables

COPD exposure was operationalized through self-reported diagnoses based on positive responses to any of: "Ever told you had chronic bronchitis", "Ever told you had COPD", "Ever told you had emphysema", and "Ever told you had COPD, emphysema, ChB" . Responses were aggregated into a COPD variable in this study.

2.5 Covariates

To explore the association between COPD and osteoporosis, this study selected common risk factors related to both conditions, including:

Demographic Factors: Age, Sex (Male/Female), Race/Ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race - Including Multi-Racial), Marital status (Married or living with a partner, Single (widowed/divorced/separated), Never married).

Socioeconomic Factors: Education (Less than high school, high school or equivalent, college or above), Poverty-Income Ratio (PIR; higher values indicate greater family income relative to the poverty threshold).

Comorbidities: Hypertension (ascertained by "Ever told you had high blood pressure"), Diabetes (ascertained by "Doctor told you have diabetes"). Only participants answering definitively "Yes" or "No" were included; others were excluded.

Behavioral & Lifestyle Factors: Body Mass Index (BMI; kg/m², calculated from measured height and weight), Physical activity (MET-min/week; categorized as low (<500) or high (≥500)[11]), Smoking (classified as Smoker or Non-smoker based on serum cotinine levels, using a cut-point of 3 ng/mL[12]).

2.6 Mediating Factors

Three mediators were assessed: **Sleep problems**("Ever told a doctor about trouble sleeping?"), **Prednisone use** ("Ever taken prednisone or cortisone daily for ⩾30 days?"), **Vitamin D** (Serum 25-hydroxyvitamin D [25(OH)D] level (nmol/L), summing $25(OH)D_2 + 25(OH)D_3$).

2.7 Causal Structure Assumptions and Directed Acyclic Graph (DAG)

To guide the selection of covariates and clarify the assumed temporal and causal relationships between variables, we constructed a DAG (Figure 2) based on prior clinical knowledge and the existing literature[7,13-18].

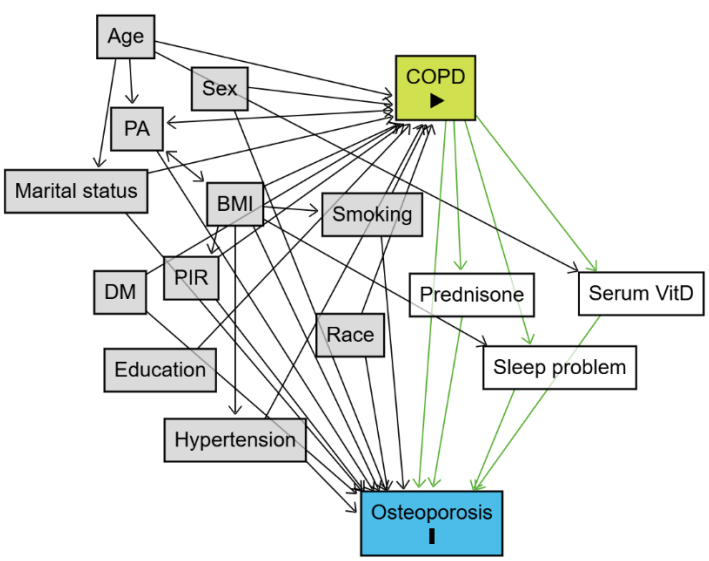


Figure 2. DAG Illustrating Hypothesized Causal Pathways Among Variables.

2.8 Statistical Analysis

All analyses incorporated NHANES sampling weights using R 4.3.3. Continuous variables are reported as weighted mean ± standard error (SE) with comparisons by weighted t-tests; categorical variables as weighted percentages with chi-square tests.

Guided by this DAG, we estimated four nested logistic regression models for the association between COPD and osteoporosis : Model 1 (unadjusted); Model 2 (adjusted for pre-exposure confounders: age, sex, race); Model 3 (extended pre-exposure model: further adjusted for education, smoking, PA, marital status, PIR, BMI, hypertension, and diabetes); Model 4 (full model: additionally adjusted for potential mediators - prednisone use, sleep disorders, and serum vitamin D). The extended pre-exposure model (Model 3) was considered the primary model for estimating the total association. The full model (Model 4) was included for completeness but interpreted cautiously, as adjustment for post-exposure mediators may attenuate the association and reflect non-mediated (direct) effects. Interaction, stratified, and mediation analyses were based on the extended pre-exposure model to preserve the total effect. Interaction analysis was evaluated via survey-weighted generalized linear models (quasi-binomial family) testing interactions between COPD and BMI categories, sex (Male, Female), prednisone use (Yes, No), vitamin D levels (tertiles: Low, Medium, High), and race/ethnicity (Mexican-American, Other-Hispanic, White, Black, Other). To avoid collinearity, BMI was excluded from the covariate list when BMI was analyzed as an effect modifier; the same as Sex. Significant interactions ($P<0.05$) underwent stratified analysis. As multiple interactions were tested, we applied the Benjamini-Hochberg procedure to control the False Discovery Rate (FDR), reporting adjusted P-values for interaction. Causal mediation effects of prednisone use, sleep problems, and serum 25(OH)D were estimated using the R with 1,000 nonparametric bootstraps replications, reporting indirect effects and proportion mediated. Sensitivity analyses repeated all models using continuous total femur BMD as the outcome. In sensitivity analyses, Age was modelled as a continuous linear term in primary analyses. In sensitivity analyses, age was additionally modelled using restricted cubic splines with 4 knots placed at the default Harrell quantiles.

To further explore group differences in vitamin D status, we conducted post-hoc analyses focusing on self-reported supplement intake (calculated as the average "Vitamin D (D2 + D3) Total Dietary Supplements"). Specifically, group comparisons were performed using Welch's two-sample t-tests, while a two-way analysis of variance (ANOVA) was used to assess the main effects of osteoporosis status and sex, as well as their interaction.

3 Results

3.1 Baseline Characteristics

A total of 8,274 participants aged ≥50 years were included, with a weighted mean age of 64.64±9.39 years; 4,290 (51.8%) were men and 3,984 (48.2%) were women. Overall, 759 participants (weighted prevalence 9.2%) reported a diagnosis of COPD, and 879 (weighted prevalence 10.6%) reported osteoporosis.

Baseline characteristics stratified by COPD status are presented in Table 1. Compared with participants without COPD, those with COPD were slightly older (66.13 vs. 64.49 years, SMD = 0.18), had lower socioeconomic status (lower poverty-income ratio: 2.20 vs. 2.81, SMD = -0.39; lower proportion with college or above education: 44.8% vs. 51.0%), and were more likely to be current or former smokers (70.6% vs. 48.6%, SMD = 0.45). COPD participants also exhibited a higher burden of comorbidities, including hypertension (59.9% vs. 51.7%) and diabetes (26.6% vs. 18.7%).

Notably, individuals with COPD had significantly lower total femur bone mineral density (0.89 vs. 0.93 g/cm², SMD = -0.28) and a nearly two-fold higher prevalence of osteoporosis (18.8% vs. 9.8%, SMD = 0.26). Potential mediating factors were more prevalent in the COPD group: long-term prednisone use (17.7% vs. 4.7%, SMD = 0.43) and self-reported sleep disorders (49.3% vs. 27.3%, SMD = 0.46).

Table 1. Descriptive Analysis of Variables by COPD

Variable	Non-COPD	COPD	SMD	P-value
Age (Mean±SD)	64.49 ± 9.38	66.13 ± 9.35	0.18	<0.001
BMI (Mean±SD)	28.53 ± 5.50	29.14 ± 6.60	0.10	0.014
BMD (Mean±SD)	0.93 ± 0.16	0.89 ± 0.17	-0.28	<0.001
VitD (Mean±SD)	69.75 ± 28.65	71.90 ± 31.63	0.07	0.072

PIR(Mean±SD)	2.81 ± 1.62	2.20 ± 1.48	-0.39	<0.001
Sex				0.012
Male	3930 (52.3%)	360 (47.4%)	-0.10	
Female	3585 (47.7%)	399 (52.6%)	0.10	
Race				<0.001
Mexican American	1020 (13.6%)	54 (7.1%)	-0.22	
Other Hispanic	655 (8.7%)	43 (5.7%)	-0.12	
Non-Hispanic White	3765 (50.1%)	490 (64.6%)	0.30	
Non-Hispanic Black	1423 (18.9%)	121 (15.9%)	-0.08	
Other Race - Including Multi-Racial	652 (8.7%)	51 (6.7%)	-0.08	
Education				0.005
Less than high school	1912 (25.4%)	215 (28.3%)	0.07	
high school or equivalent	1769 (23.5%)	204 (26.9%)	0.08	
college or above	3834 (51.0%)	340 (44.8%)	-0.13	
Marital status				<0.001
Married or living with a partner	4742 (63.1%)	388 (51.1%)	-0.24	
Single (widowed/divorced/separated)	2322 (30.9%)	309 (40.7%)	0.21	
Never married	451 (6.0%)	62 (8.2%)	0.09	
Smoke				<0.001
Yes	3652 (48.6%)	536 (70.6%)	0.45	
No	3863 (51.4%)	223 (29.4%)	-0.45	
PA				<0.001
Low physical activity	3279 (43.6%)	384 (50.6%)	0.14	
High physical activity	4236 (56.4%)	375 (49.4%)	-0.14	
Hypertension				<0.001
Yes	3882 (51.7%)	455 (59.9%)	0.17	
No	3633 (48.3%)	304 (40.1%)	-0.17	
DM				<0.001
Yes	1402 (18.7%)	202 (26.6%)	0.19	
No	6113 (81.3%)	557 (73.4%)	-0.19	
Prednisone				<0.001
Yes	355 (4.7%)	134 (17.7%)	0.43	
No	7160 (95.3%)	625 (82.3%)	-0.43	
Sleep problem				<0.001
Yes	2048 (27.3%)	374 (49.3%)	0.46	
No	5467 (72.7%)	385 (50.7%)	-0.46	
Osteoporosis				<0.001
Yes	736 (9.8%)	143 (18.8%)	0.26	
No	6779 (90.2%)	616 (81.2%)	-0.26	

3.2 Weighted Logistic Regression

Weighted logistic regression models assessed the association between chronic obstructive pulmonary disease (COPD) and osteoporosis (Table 2). In the unadjusted Model 1, COPD was significantly associated with increased odds of osteoporosis (Odds Ratio [OR] = 2.55, 95% Confidence Interval [CI]: 1.92-3.39, P < 0.001). After adjusting for age, sex, and race in Model 2, this association remained significant (OR = 2.36, 95% CI: 1.68-3.33, P < 0.001). In the extended pre-exposure Model 3, COPD remained significantly associated with osteoporosis (OR = 2.23, 95% CI: 1.58-3.15, P < 0.001). In the full Model 4, which additionally adjusted for potential mediators (prednisone use, sleep disorders, and vitamin D), the association was slightly attenuated but still significant (OR = 1.96, 95% CI: 1.39-2.78, P < 0.001).

Table 2. Weighted Logistic Regression Results for Osteoporosis

	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
COPD	2.55(1.92, 3.39)	<0.001	2.36(1.68, 3.33)	<0.001	2.23 (1.58,3.15)	<0.001	1.96 (1.39,2.78)	<0.001

OR, odds ratio; CI, confidence interval;
Model 1 was an unadjusted model. Model 2: Model1 + Age, Sex, Race. Model 3: *Model 2 + education, smoking, PA, marital status, PIR, BMI, hypertension, diabetes. Model 4: Model 3+prednisone use, sleep disorders, and serum vitamin D.*

3.3 Interaction and Stratified Analysis

Interaction analyses were performed to explore potential effect modification by BMI category, sex, prednisone use, vitamin D level, race, and age group (50-64, 65-74, and ≥75 years) (Table 3). P-values for all interaction terms were adjusted for multiple comparisons using the Benjamini-Hochberg procedure to control the false discovery rate. After adjustment, none of the tested interactions reached statistical significance. The unadjusted p-value for the sex interaction term was 0.03(Table S2), suggesting possible heterogeneity by sex. Therefore, as an exploratory analysis, we conducted sex-stratified logistic regression models adjusted for the same covariates (Table 4 & Supplementary Figure S1). COPD was significantly associated with increased odds of osteoporosis in both men (adjusted OR = 4.85, 95% CI: 2.49-9.42, P < 0.001) and women (adjusted OR = 1.86, 95% CI: 1.30-2.65, P < 0.001). The magnitude of the association was greater in men than in women, consistent with the nominal

interaction finding, although this difference was not statistically significant after correction for multiple testing.

Table 3. Interaction Analysis of COPD and Osteoporosis by Effect Modifiers

Effect Modifier	Subgroup	OR (95% CI)	Adjusted P-value (FDR)
BMI	Normal	0.29 (0.07-1.20)	0.27
	Overweight	0.51 (0.13-2.06)	0.42
	Obese	0.29 (0.08-1.05)	0.27
Sex	Female	0.43 (0.20-0.91)	0.27
Prednisone	Yes	0.56 (0.21-1.44)	0.41
Vitamin D	Medium	0.69 (0.31-1.51)	0.42
	High	0.74 (0.37-1.48)	0.42
Race	Other-Hispanic	0.33 (0.09-1.26)	0.27
	White	0.77 (0.28-2.16)	0.62
	Black	0.61 (0.20-1.84)	0.42
	Other	2.75 (0.30-24.90)	0.42
Age	65-74 years	0.52 (0.25-1.09)	0.27
	≥75 years	0.57 (0.26-1.21)	0.31

The controls for each effect modifier are as follows: Underweight [BMI], Male [Sex], No [Prednisone], Low [Vitamin D], Mexican-American [Race],50-64 years[Age].

Table 4. Sex-Stratified Analysis of COPD and Osteoporosis

	OR（95%CI）	P
Male	4.85(2.49-9.42)	<0.001
Female	1.86(1.30-2.65)	<0.001

Odds ratios are derived from survey-weighted logistic regression models adjusted for age, race, education, marital status, BMI, PIR, smoking status, PA, hypertension and diabetes. Sex was not included as a covariate in the sex-stratified models.

3.4 Causal Mediation Analysis

Causal mediation analysis was conducted to explore the potential mediating roles of prednisone use, sleep problems, and serum vitamin D levels in the relationship between COPD and osteoporosis.

Mediation models and pathways are shown in Table 5 and Figure 3, with COPD as the independent variable, osteoporosis as the dependent variable, and prednisone use, sleep problems, and vitamin D levels as mediators. Results indicated that prednisone use partially mediated the relationship between COPD and osteoporosis, with an indirect effect of 0.005 (95% CI: 0.004, 0.015, P < 0.001), accounting for 5.1% (P < 0.001) of the total effect (Figure 3, A). Similarly, sleep problems partially mediated this relationship with an indirect effect of 0.009 (95% CI: 0.001, 0.010, P = 0.002), accounting for 9.3% (P = 0.002) of the total effect (Figure 3, B). However, vitamin D did not demonstrate significant mediation (P = 0.412) (Figure 3, C).

Table 5. Mediation analysis of Prednisone, Sleep Disorders, Vitamin D in the association between COPD and Osteoporosis.

	Effect Decomposition	Coefficient (95%CI)	P
Prednisone	Total Effect	0.091(0.043,0.112)	<0.001
	ACME	0.005(0.004,0.015)	<0.001
	ADE	0.086(0.035,0.103)	<0.001
	Proportion of mediation	0.051(0.045,0.222)	<0.001
Sleep Problems	Total Effect	0.095(0.044,0.115)	<0.001
	ACME	0.009(0.001,0.010)	0.002
	ADE	0.086(0.040,0.108)	<0.001
	Proportion of mediation	0.094(0.016,0.146)	0.002
Vitamin D	Total Effect	0.094(0.045,0.114)	<0.001
	ACME	-0.001 (-0.003,0.001)	0.412
	ADE	0.095(0.046,0.115)	<0.001
	Proportion of mediation	-0.015(-0.039,0.018)	0.412

All mediation models are survey-weighted and adjusted for age, sex, race/ethnicity, education, marital status, PIR, smoking status, PA, BMI, hypertension and diabetes.

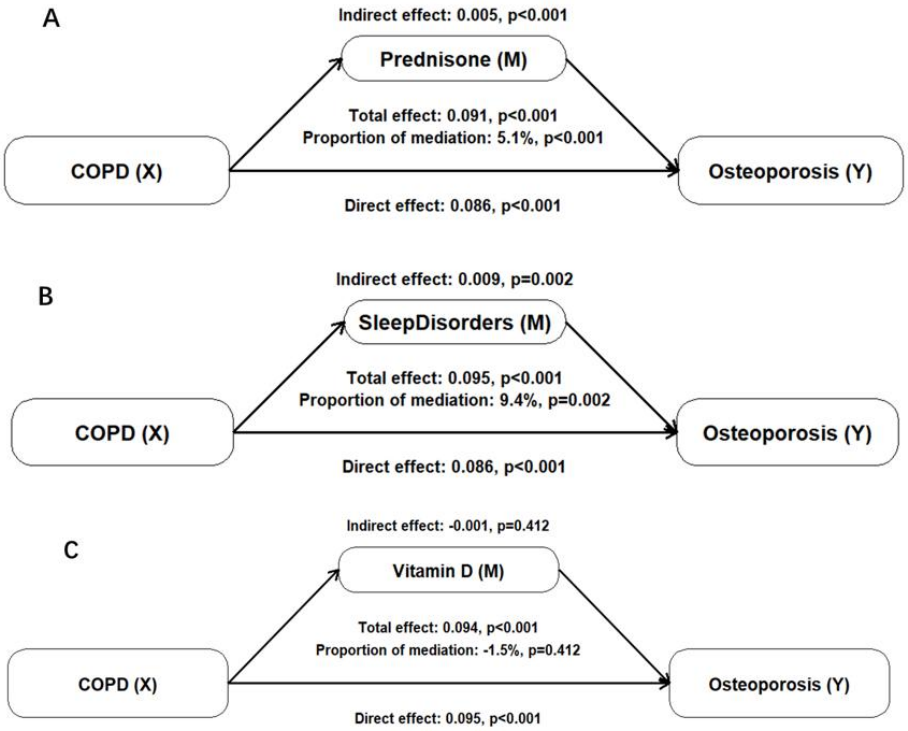


Figure 3. Mediation Path Diagram

3.5 Sensitivity Analysis

Restricted cubic spline analysis revealed a significant non-linear relationship between age and osteoporosis risk (non-linear Wald P = 0.0003). However, substituting restricted cubic splines for linear age did not materially alter the COPD – osteoporosis association. For parsimony and interpretability, we retained the linear age term in the main models (Figure S2).

Sensitivity analyses using bone mineral density (BMD) as the outcome confirmed a significant negative association with COPD (adjusted $\beta = -0.028$, $P < 0.001$ in Model 3; Table S3). Interaction analyses indicated a significant interaction only by sex ($\beta = -0.024$, $P = 0.047$, Table S4). Stratified analysis by sex revealed a significant negative association among women ($\beta = -0.038$, $P < 0.001$), but no significant association among men ($\beta = -0.017$, $P = 0.085$, Table S5). Mediation analysis indicated a small mediating effect of prednisone use (2.2%, P = 0.034), while sleep problems and vitamin D showed no significant mediation (Table S6).

3.6 Post-hoc analyses

As the "Vitamin D supplement intake" variable had a high proportion of missing data, only 1,382 individuals were ultimately included in the post-hoc analysis examining its relationship with osteoporosis. Individuals with self-reported osteoporosis had significantly higher vitamin D supplement intake than those without osteoporosis (P = 0.015). Two-way ANOVA confirmed a significant main effect of osteoporosis status (P = 0.017) and sex (P < 0.001), but no significant osteoporosis-by-sex interaction (P = 0.667) (Table 6).

Table 6. Vitamin D Supplement Intake by Osteoporosis Status and Sex

Group		N	Mean ± SD(μ g/day)	P[a]
Osteoporosis		210	23.0 ± 17.2	
	Male	28	20.0 ± 16.6	
	Female	182	23.4 ± 17.3	
Non-Osteoporosis		1172	19.8 ± 17.9	
	Male	584	17.3 ± 16.1	
	Female	588	22.3 ± 19.3	
Osteoporosis status main effect				0.017
Sex main effect				< 0.001
Osteoporosis status × Sex				0.667

[a] Two-way ANOVA analysis

4 Discussion

The slight attenuation observed in the full model (OR = 1.96) compared to the extended pre-exposure model (OR = 2.23) is consistent with partial mediation by prednisone use and sleep disorders, as quantified separately. Although formal testing did not reveal significant effect modification after adjusting for multiple comparisons, exploratory sex-stratified analyses indicated a stronger positive association between COPD and osteoporosis in men (OR = 4.85) compared to women (OR = 1.86). This observation is hypothesis-generating and may reflect differences in disease severity, bone metabolism, or residual confounding between sexes. Future studies with larger samples are needed to confirm whether this association truly differs by sex. Our mediation analyses quantitatively establish that prednisone use and sleep problems account for 5.1% and 9.3% of this association, respectively, while

serum vitamin D demonstrated no significant mediation role. These observations were robustly confirmed through BMD sensitivity analyses[19,20]. Although COPD was more strongly associated with osteoporotic diagnosis in men than in women, the BMD-based sensitivity analyses showed statistically significant associations only in women. This apparent discrepancy likely reflects differences in how bone fragility is captured by dichotomous versus continuous measures, as well as sex-specific BMD distributions and diagnostic thresholds. In women, relatively small decrements in BMD may more readily cross the T-score threshold used to define osteoporosis, while in men a larger absolute reduction is often required to meet diagnostic criteria. In addition, the smaller number of men with both COPD and DXA measurements may have limited statistical power to detect modest BMD differences. Taken together, these findings suggest that while COPD-related bone health impairment is evident in both sexes, the way it is expressed in BMD and clinical diagnosis may differ between men and women.
The identified risk elevation aligns with existing literature indicating a 1.5-2 fold increase in osteoporosis incidence among COPD populations, where BMD reduction correlates with disease severity[19]. The association between COPD and osteoporosis may occur through multiple mechanisms. COPD patients experience chronic low-grade inflammation in the lungs and systemically, with elevated pro-inflammatory cytokines (such as TNF-α, IL-6, IL-1β) creating an inflammatory microenvironment that disrupts bone metabolic balance[20,21]. These cytokines influence bone metabolism via complex signaling networks: TNF-α downregulates Runx2 expression and induces Wnt antagonists DKK1 and SOST, blocking the Wnt/β-catenin pathway and inhibiting osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs)[22-25]. IL-1β and IL-18 induce BMSC death via the NLRP3/Caspase-1/GSDMD pyroptosis pathway, reducing osteogenic differentiation capacity[26,27]. IL-6 exhibits dual effects: it negatively regulates osteogenic differentiation through SHP2/MEK2 and SHP2/AKT2 pathways[28], while the IL-6-sIL-6R complex positively increases ALP activity[29,30]. In osteoclasts, TNF-α and IL-1β upregulate RANKL, activate NF-κB and AP-1 signaling, and reduce OPG secretion, promoting osteoclast differentiation[23,31-40]. IL-6, IL-17, and IL-18 enhance bone resorption by inducing T cells (especially Th17 cells) to secrete RANKL and M-CSF[20,40-46]. Macrophages and osteocytes release inflammatory cytokines via NLRP3/Caspase-1/GSDMD, exacerbating osteoclastogenesis[47-50]. In ovariectomized (OVX) models, inhibiting NLRP3 or estrogen therapy alleviates bone resorption, indicating inflammation-driven osteoporosis and further promoting osteoclastogenesis[51-54].

Exploratory mediation analysis suggests that sleep problems may account for approximately 9.3% of the association between COPD and osteoporosis. Studies have reported a U-shaped relationship between sleep duration and the risk of developing osteoporosis[55], and sleep deprivation has been shown to elevate systemic inflammatory markers[56]. Among COPD patients, OSA represents a common subtype of sleep disorders[57]. In a cohort study, the risk of osteoporosis among OSA patients was approximately twice that of the control group[15]. Additionally, both OSA and insomnia may increase susceptibility to acute exacerbations of COPD (AECOPD)[58]. These findings support the potential role of sleep disturbances as a mediating pathway in this study; however, their directionality and COPD-specific effects require further validation through longitudinal cohort studies.

Glucocorticoid use (particularly prednisone) emerged as a key mediator in this study, as glucocorticoids are commonly used in COPD treatment and are a known cause of glucocorticoid-induced osteoporosis (GIOP)[59]. Research shows that cumulative glucocorticoid doses ≥5400 mg increase risk approximately 2.5 times compared to <675 mg, with fracture risk 17.1 times higher in patients over 50 years, though fracture risk decreases significantly months after discontinuation[60]. Glucocorticoids impair bone health through multiple mechanisms, including inhibition of Wnt and BMP signaling, reduced Runx2 expression, and promotion of osteoblast apoptosis[14,61-63], as well as increased RANKL/OPG ratio to enhance osteoclast activity, disrupting bone homeostasis[10]. Additionally, glucocorticoids suppress IGF-1 transcription and disrupt calcium homeostasis, indirectly exacerbating bone loss and leading to rapid bone mass reduction and increased fracture risk[64,65]. The emerging gut-bone axis concept provides a new perspective for studying COPD-osteoporosis relationships, where gut microbiota influence bone metabolism via metabolites, immune regulation, and nutrient absorption[66]. Studies confirm that Lactobacillus paracasei LC 86 enhances bone and cartilage structure, increases beneficial bacteria, reduces pathogens, and improves bone structure in osteoporosis models[67]. Given that COPD-related inflammation may alter gut microbiota, future research should explore the gut-bone axis as a potential therapeutic target for COPD-associated osteoporosis.

This study also found higher serum 25-hydroxyvitamin D (25(OH)D) levels in the osteoporosis group compared to the non-osteoporosis group, contradicting the typical association of low vitamin D with osteoporosis[13]. Post-hoc analyses further revealed that participants with self-reported osteoporosis had significantly higher vitamin D supplement intake, supporting the hypothesis of reverse causation:

diagnosed patients are more likely to receive and adhere to recommendations for vitamin D supplementation as part of bone health management, potentially leading to higher reported intake and elevated serum 25(OH)D levels. Two-way ANOVA confirmed independent main effects of osteoporosis status and sex on supplement intake, with no significant interaction, indicating that the association between osteoporosis diagnosis and higher supplementation was consistent across sexes and not driven solely by sex differences. We propose the following possible explanations for this unexpected finding: osteoporosis patients may exhibit higher 25(OH)D levels due to vitamin D supplementation post-diagnosis. NHANES data relies on self-reported osteoporosis diagnoses, and diagnosed patients may be more attentive to bone health, adhering to clinical guidelines (e.g., American College of Rheumatology recommendations) for vitamin D supplementation, resulting in higher serum 25(OH)D levels than undiagnosed non-osteoporosis individuals. Notably, the osteoporosis group had a higher proportion of females—a reflection of the substantially higher baseline risk of osteoporosis in women, primarily driven by postmenopausal estrogen deficiency and rapid bone loss. Consistent with this, women in our cohort had significantly higher vitamin D supplement intake than men in both the osteoporosis and non-osteoporosis groups. Women are also more likely to undergo bone health screening and receive preventive or therapeutic interventions, including vitamin D supplementation. Additionally, patients with COPD may be advised to supplement vitamin D due to long-term glucocorticoid use, which increases the risk of glucocorticoid-induced osteoporosis[68]. Furthermore, NHANES data spans 2005-2018, during which the U.S. (e.g., National Bone Health and Osteoporosis Foundation) promoted vitamin D-fortified foods and supplements, potentially elevating 25(OH)D levels in osteoporosis patients. However, the lack of significant vitamin D mediation (P = 0.41) suggests that higher 25(OH)D levels may not effectively translate into bone-protective effects. This could be due to COPD-related chronic inflammation (TNF-α, IL-6, etc.) counteracting vitamin D benefits by inhibiting osteoblast differentiation and promoting osteoclastogenesis. Additionally, higher 25(OH)D levels may reflect compensatory mechanisms, such as elevated parathyroid hormone (PTH) promoting 1,25(OH)2D production, indirectly affecting 25(OH)D metabolism[69].

This study found that male COPD patients had a significantly higher osteoporosis risk (OR = 4.85) than females (OR = 1.86), with a stronger COPD-osteoporosis association in males, a finding with important clinical implications. Traditionally, females are considered at higher osteoporosis risk due to

postmenopausal estrogen decline[3]. However, our results suggest that in the COPD context, males may face greater bone health risks. This may relate to factors such as longer smoking histories and more severe lung function impairment in male COPD patients[70]; testosterone promotes osteoblast activity and inhibits bone resorption, contributing to higher peak bone mass [9]. Yet, chronic inflammation and glucocorticoid use may suppress testosterone levels[71,72], accelerating bone loss. Cytokine-driven systemic inflammation from macrophages can downregulate the hypothalamic-pituitary-gonadal axis, reducing testosterone secretion[73]. In contrast, this study's predominantly postmenopausal females (mean age 64.64 years) may benefit from hormone replacement therapy or other estrogen-deficiency interventions via the RANKL/OPG pathway, potentially slowing bone loss[10]. The necessity of adopting sex-specific strategies in COPD bone health management, particularly the urgency of enhancing osteoporosis screening and intervention in male patients.

Strengths of this study include the use of a large, nationally representative NHANES sample, rigorous adjustment for confounders, and comprehensive mediation and sensitivity analyses. Weighted logistic regression and complex survey design ensure generalizability to the U.S. population. However, several limitations of this study should be acknowledged. First, the cross-sectional design of NHANES precludes definitive conclusions about temporality and causality; in some individuals, osteoporosis may have been diagnosed before COPD, and bidirectional relationships are possible. Longitudinal studies are needed to confirm the directionality of the observed associations. Second, both COPD and osteoporosis were ascertained by self-reported physician diagnosis, which may introduce recall bias and misclassification. Third, we lacked detailed information on COPD severity (e.g., spirometry results or exacerbation frequency), smoking intensity (e.g., pack-years), and other environmental exposures, all of which are relevant to both lung function and bone health. NHANES data do not allow reliable differentiation between emphysema-predominant and chronic bronchitis-predominant COPD phenotypes, which may exhibit differing systemic effects relevant to bone health; future studies with detailed phenotypic characterization are warranted. Consequently, residual confounding by disease severity, smoking burden, and unmeasured lifestyle or environmental factors is likely. Fourth, long-term prednisone use, sleep problems, and osteoporosis diagnoses may all be influenced by healthcare utilization, raising the possibility of healthcare use bias and diagnostic surveillance effects. Although negative control outcome analyses would be useful to probe this bias, the available NHANES variables

did not allow us to define a robust negative control that met the necessary assumptions; we highlight this as an important direction for future work. It is important to note that long-term prednisone use in NHANES likely reflects more severe COPD and frequent exacerbations. Therefore, the observed mediating role of prednisone may partly capture confounding by disease severity and healthcare utilization, rather than a purely pharmacologic effect. Although we adjusted for several comorbidities and behavioral factors, we lacked detailed spirometry and exacerbation data and could not fully disentangle these pathways. Fifth, the unexpected elevation in vitamin D levels in the osteoporosis group warrants further investigation into supplementation patterns and their impact on bone health. Sixth, inflammatory markers such as C-reactive protein and white blood cell count could not be robustly evaluated as mediators due to high missingness, which limited statistical power and risked selection bias in complete-case analyses. Finally, a further limitation is that a sizeable number of participants were excluded because of missing information. These excluded individuals tended to be older and to have poorer overall health profiles, including higher prevalence of both COPD and osteoporosis. As a result, our complete-case sample may represent a somewhat healthier subset of older adults, and the observed COPD-osteoporosis associations are likely to be conservative rather than exaggerated. Nevertheless, some selection bias cannot be ruled out and our findings should be interpreted in this context.
Our mediation analyses rely on strong, unverifiable assumptions of no unmeasured confounding between COPD, mediators and osteoporosis, which are unlikely to be fully satisfied in cross-sectional survey data. Therefore, these results should be viewed as hypothesis-generating. Future work integrating Mendelian randomization, which uses genetic variants as instruments for COPD, bone traits and relevant mediators, would be valuable for strengthening causal inference around the pathways suggested here. Future research should employ longitudinal designs to establish causality and integrate microbiomics, metabolomics, and proteomics to explore the complex networks of COPD-related osteoporosis. The gut-bone axis, as an emerging therapeutic target, merits in-depth study.

5 Conclusion

This cross-sectional NHANES analysis shows that COPD is associated with an increased odd of osteoporosis in older US adults, with a stronger association observed in men than in women. Prednisone

use and sleep problems appear to account for a modest proportion of this association, whereas serum 25(OH)D did not show a clear mediating role. These findings highlight the importance of considering bone health in COPD management, particularly in male patients and in those receiving long-term glucocorticoid therapy or reporting sleep disturbance. However, given the observational design and potential residual confounding, these pathways should be interpreted as hypotheses-generating and require confirmation in longitudinal and mechanistic studies.

Declarations

Acknowledgements
We would like to express our sincere thanks to all participants in the NHANES survey.

Ethics approval and consent to participate
The NCHS Research Ethics Review Committee and the NHANES both examined and approved the research that involved human subjects. To take part in this study, the patients/participants gave their written informed consent. This study utilized de-identified, publicly available NHANES secondary data. All personally identifiable information (including names, identification numbers, and other direct identifiers) was removed through standardized de-identification procedures in compliance with ethical requirements for human subject data protection. In accordance with prevailing research ethics guidelines, secondary analysis of such pre-approved, de-identified public datasets qualifies for exemption from additional institutional review, a standard this study rigorously followed. Additionally, our institution has also conducted an ethical review and agreed to exempt the study from ethical review.

Consent for publication
Not applicable.

Data Availability Statement
This study used publicly available data from the National Health and Nutrition Examination Survey (NHANES). The datasets analysed are available from the NHANES website (https://www.cdc.gov/nchs/nhanes/) following the survey's data-use guidelines.

Competing interests
All authors declare no financial or non-financial competing interests.

Funding
This research was supported by the 2024 Shantou Science and Technology Plan Medical and Health Project (Grant No: 240506186498668, 240922169602002).

Author Contributions

YG: Conceptualization, Data curation, Formal Analysis, Visualization, Software, Writing - original draft, Writing - review & editing. JW: Data curation, Software, Visualization, Writing - review & editing. ZL: Data curation, Writing - review & editing. LD: Data curation, Conceptualization, Writing - review & editing. MM: Methodology, Supervision , Writing - review & editing. LL: Conceptualization, Methodology, Writing - review & editing. XC:Methodology, Writing - review & editing. ZZ: Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing. SC: Project administration, Methodology, Supervision, Funding acquisition, Writing - review & editing.

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