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Chronic obstructive pulmonary disease and allied conditions is a strong independent risk factor for osteoporosis and pathologic fractures: a population-based cohort study

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Summary

Background: Chronic obstructive pulmonary disease and allied conditions (COPD) is frequently associated with various comorbidities. This study examined the association between osteoporosis and pathologic fractures in a sample of patients with COPD.

Methods: In this cohort study, claims data from the National Health Insurance Research Database of Taiwan were used to evaluate the risk between COPD and osteoporosis. Using data from the Longitudinal Health Insurance Database 2000, we conducted a retrospective cohort study by investigating patients aged 20 years and older who were newly diagnosed with COPD and comparing them with controls without COPD during 2000–2010. In addition, we used univariable and multivariable Cox proportional hazards regression models to measure the association between COPD and the risk of osteoporosis.

Results: Our results revealed that COPD was significantly associated with a high risk of osteoporosis, regardless of whether the patients with COPD were corticosteroid users and irrespective of age and sex. After adjustment for covariates, the COPD patients exhibited a 1.54-fold higher risk of developing osteoporosis (hazard ratio 1.54, 95% confidence interval 1.44–1.64). COPD was a stronger risk factor for osteoporosis in men. Moreover, patients with severe COPD had a higher risk of osteoporosis or pathologic fractures.

Conclusion: This study revealed that COPD, which shares the characteristics of inflammatory diseases, is associated with a higher risk of osteoporosis after adjustment for comorbidities.

Introduction

Patients with chronic obstructive pulmonary disease and allied conditions (COPD) are frequently associated with an increased risk of comorbidities, such as cardiovascular diseases, peptic ulcer/gastroesophageal reflux disease, metabolic syndrome, diabetes, lung cancer and osteoporosis.[1,2] Osteoporosis is more common in elderly and female populations. Studies have identified risk factors for osteoporosis prevalence, such as old age, a low body mass index, calcium and vitamin D intake, physical activity level and a history of smoking.[1–4] A previous study reported that systemic corticosteroids have the greatest impact on secondary osteoporosis, which both directly and indirectly affects the skeleton.[5] However, a comprehensive literature review revealed that the effects of long-term corticosteroid exposure on bone mineral density (BMD) remain debatable.

The major risk factor for osteoporosis in patients with COPD is the male sex and an older age; however, the relationship between COPD severity and glucocorticoids (GCs) in affecting osteoporosis remains unclear.[6] Therefore, this retrospective study examined the relationship between COPD and osteoporosis. We used medical insurance claims health care databases to evaluate the association between osteoporosis and fracture among patients with COPD and the relationship between osteoporosis and COPD severity.

Materials and methods

Data source

A single-payer and compulsory National Health Insurance (NHI) program was implemented in Taiwan in 1995 and covers nearly 99% of the population in Taiwan; moreover, the NHI program has established contracts with 97% of the hospitals and clinics throughout Taiwan (http://www.nhi.gov.tw/english/index.aspx). The National Health Insurance Research Database (NHIRD) is a research database developed and managed by the National Health Research Institutes (NHRI) and confidentiality is maintained according to the directives of the Bureau of NHI. The NHIRD contains comprehensive information regarding clinical visits, including prescription details and diagnostic codes based on the Interactional Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Longitudinal Health Insurance Database 2000 (LHID2000) comprises a random sample of 1 million patients from the NHIRD, which provides longitudinally linked data for the 1996–2011 period. The NHRI attests that no statistical differences in age, sex and health care costs exist between the LHID2000 data and those of all enrollees. In the LHID2000, the original identification number for each patient was encrypted for privacy; however, all data sets can be linked together through unique and anonymous identifiers created by the NHRI. This study was approved by the Institutional Review Board of China Medical University and China Medical University Hospital (CMU-REC-101-012).

Study population

Figure 1 shows the selection procedure for the study cohort. By referring to the data from the LHID2000, we conducted a retrospective cohort study of patients aged 20 years and older who were newly diagnosed with COPD (Chronic Obstructive Pulmonary Disease And Allied Conditions, ICD-9-CM codes: 490–496) between 1 January 2000 and 31 December 2010. The initial diagnosis date was set as the index date for each patient. Patients younger than 20 years of age ($n=19.557$) and those with a history of osteoporosis (ICD-9-CM codes: 733.0 and 733.1; $n=4322$) before the index date or with incomplete demographic information ($n=11$) were excluded. For each patient with COPD, one control was randomly selected from the pool of patients without COPD or osteoporosis at baseline and frequency matched according to index date, age (span of every 5 year) and sex. The exclusion criteria for the patients with COPD were also applied to the controls.

Study endpoint and comorbidities

We observed all study patients until osteoporosis diagnosis, death, disenrollment from the NHI system, or 31 December 2011. The examined risk factor comorbidities were diabetes (ICD-9-CM code: 250), hyperlipidemia (ICD-9-CM code: 272), hypertension (ICD-9-CM codes: 401–405), coronary artery disease (ICD-9-CM codes: 410–414), depression (ICD-9-CM codes: 296.2, 296.3, 300.4 and 311), chronic kidney disease (ICD-9-CM code: 585), stroke (ICD-9-CM codes: 430–438), cancer (ICD-9-CM codes: 140–208) and pneumonia and influenza (ICD-9-CM codes: 480–488). We used prednisolone, the most used corticosteroid in Taiwan, as the target agent of GC for analysis. Use with GCs and inhaled corticosteroids (ICS) were also examined in the study period. The cumulative defined daily dose (cDDD) was calculated as the total prescribed defined daily dose (DDD) for prednisolone users.

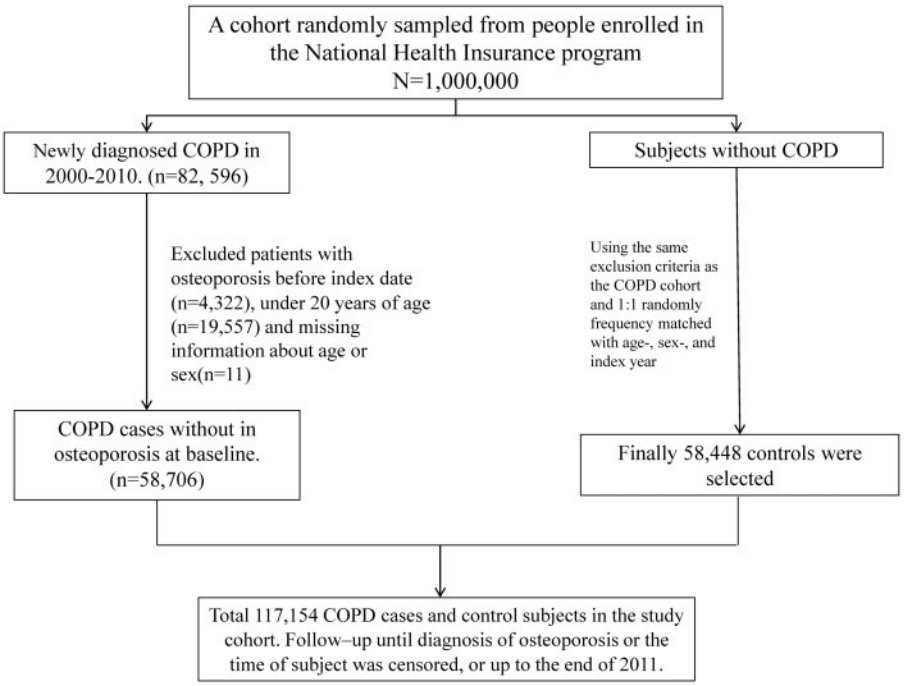

Figure 1. The selection procedure of study participants.

Statistical analysis

We compared demographic factors, including sex, age, baseline comorbidities and medications, between the COPD cohort and the comparison cohort by conducting a χ^2 test for categorical variables and a *t* test for continuous variables. We calculated the incidence density rates of osteoporosis according to the demographic characteristics subsequent to COPD. We used univariable and multivariable Cox proportional hazards regression models to measure the association of COPD with osteoporosis risk. We simultaneously adjusted the multivariable models for sex, age, baseline comorbidities and medication and we estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) in the Cox models. Further analysis was performed to verify the impact of COPD severity on osteoporosis. To estimate the cumulative incidence of osteoporosis, we performed a survival analysis of both cohorts using the Kaplan–Meier method, assessing the significance of the results using the log-rank test. All statistical analyses were performed using the SAS package (Version 9.3 for Windows; SAS institute, Inc., Cary, NC). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Table 1 lists the distribution of demographic characteristics, revealing a similar age and sex distribution in both cohorts. The mean age was 51.0 17.3 years in the COPD cohort and 50.1 17.2 years in the comparison cohort. Patients with COPD exhibited a greater prevalence of all baseline comorbidities as well as corticosteroid and ICS use compared with the comparison cohort ($P < 0.001$). The mean follow-up time was 6.67 years (standard deviation [SD] = 3.54) and 6.74 years (SD = 3.45) for the COPD and comparison cohorts, respectively.

The overall incidence of osteoporosis in the COPD cohort was higher than that in the comparison cohort (7.05 vs. 4.63 per 1000 person years, crude HR = 1.53, 95% CI = 1.44–1.62), with an adjusted HR of 1.54 (95% CI = 1.44–1.64; Table 2). Figure 2 shows the cumulative osteoporosis incidence curve for the two cohorts. The COPD incidence curve was significantly higher than that of the comparison cohort (log-rank $P < 0.001$). The osteoporosis incidence was greater in women than in men in both cohorts. The adjusted HR for osteoporosis in the sex-specific COPD cohort was significant for both women (HR = 1.43, 95% CI = 1.32–1.54) and men (HR = 1.77, 95% CI = 1.58–1.97) compared with the comparison cohort. The incidence increased with age in both cohorts. The adjusted HR for osteoporosis in the age-specific COPD cohort compared with the comparison cohort was significant for all age groups (HR = 1.63, 95% CI = 1.36–1.96 in the group with patients aged ≤49 year; HR = 1.64, 95% CI = 1.47–1.84 in the group with patients aged 50–64 year; HR = 1.49, 95% CI = 1.37–1.62 in the group with patients

Table 1 Comparisons in demographic characteristics and comorbidities in patient with and without COPD

	COPD		*P*-value
	No (*N* = 58 448)	Yes (*N* = 58 706)	
Gender			0.49
Women	27 286(46.7)	27 287(46.5)	
Men	31 162(53.3)	21 419(53.5)	
Age stratified			0.62
20–34	12 646(21.6)	12 646(21.5)	
35–49	16 690(28.6)	16 690(28.4)	
50–64	15 011(25.7)	15 011(25.6)	
≥65	14 101(24.1)	14 359(24.5)	
Age, mean SD[a]	50.1(17.2)	51.0(17.3)	<0.001
Follow-up years, mean SD[a]	6.74(3.45)	6.67(3.54)	<0.001
Comorbidity			
Diabetes	4241(7.26)	6012(10.2)	<0.001
Hypertension	12 735(21.8)	18 946(32.3)	<0.001
Hyperlipidemia	6800(11.6)	10 430(17.8)	<0.001
Coronary artery disease	4573(7.82)	8923(15.2)	<0.001
Depression	1332(2.28)	2482(4.23)	<0.001
CKD	2148(3.68)	4131(7.04)	<0.001
Stroke	1424(2.44)	3285(5.60)	<0.001
Cancer	1105(1.89)	1539(2.62)	<0.001
Pneumonia and influenza	9889(16.9)	19518(33.3)	<0.001
Medication			
Prednisolone use	10 733(18.4)	16 506(28.1)	<0.001
ICS	60(0.10)	7497(12.8)	<0.001

χ^2 test.
[a]*t* test.

aged ≥ 65 year). Patients with COPD were associated with a significantly higher risk of osteoporosis compared with the control patients, regardless of whether they had a comorbidity. Table 3 shows the associations between osteoporosis and the number of emergency department (ED) visits for acute exacerbation of COPD (AECOPD). COPD with hospitalization was associated with a significantly increased risk of osteoporosis with pathologic fracture (HR = 2.57, 95% CI = 1.98–3.34) and osteoporosis without fracture (HR = 1.61, 95% CI = 1.46–1.77). AECOPD resulting in more than two ED visits was associated with a significantly higher risk of pathologic fractures compared with the comparison cohort (HR = 13.0, 95% CI = 4.69–36.0).

Table 4 lists the effects of prednisolone and ICS on osteoporosis risk. Patients with COPD undergoing prednisolones treatment had a significantly lower risk of osteoporosis (HR = 0.61, 95% CI = 0.53 − 0.69) compared with patients without COPD and those not undergoing prednisolone treatment. Among the patients with COPD, compared with the non-prednisolone users, the osteoporosis risk was lower in patients who were administered >20 cDDD of prednisolone (HR = 0.50, 95% CI, 0.45–0.57), followed by those who were administered ≤20 cDDD of prednisolone (HR = 0.66, 95% CI, 0.59–0.74). Compared with patients without COPD, patients with COPD undergoing ICS treatment exhibited a significantly lower risk of osteoporosis (HR = 0.88, 95% CI = 0.88–1.02).

Discussion

Our study determined the association between COPD and osteoporosis. The overall incidence rate of osteoporosis was higher in the COPD cohort (HR = 1.54) than in the non-COPD cohort after adjustment for age, sex, medical comorbidities and GCs. Male adults with COPD also appeared to have a higher risk. A reduced incidence was observed in the group with GCs and ICS use, a

Table 2 Comparison of incidence densities of osteoporosis and HR between with and without COPD by demographic characteristics

	COPD							
	No			Yes				
	Event	PY	Rate[a]	Event	PY	Rate[a]	Crude HR (95% CI)[b]	Adjusted HR[c] (95% CI)
All	1823	39 4078	4.63	2762	391 537	7.05	1.53(1.44, 1.62)***	1.54(1.44, 1.64)***
Gender								
Women	1289	186 216	6.92	1804	185 477	9.73	1.41(1.31, 1.51)***	1.43(1.32, 1.54)***
Men	534	207 862	2.57	958	206 059	4.65	1.81(1.63, 2.01)***	1.77(1.58, 1.97)***
Age								
20–49	200	212 623	0.94	366	218 110	1.68	1.79(1.50, 2.12)***	1.63(1.36, 1.96)***
50–64	546	100 888	5.41	899	98 429	9.13	1.69(1.52, 1.87)***	1.64(1.47, 1.84)***
≥65	1077	80 567	13.4	1497	74 998	20.0	1.49(1.38, 1.61)***	1.49(1.37, 1.62)***
Comorbidity[d]								
No	635	242 053	2.62	500	156 296	3.20	1.22(1.09, 1.37)***	1.68(1.49, 1.90)***
Yes	1188	152 025	7.81	2262	235 240	9.62	1.24(1.15, 1.33)***	1.48(1.38, 1.59)***

[a]Rate, incidence rate, per 1000 person-years.
[b]Crude HR, relative HR.
[c]Adjusted HR adjusted for sex, age and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, depression, chronic kidney disease, stroke, cancer and pneumonia and influenza and medication of prednisolone use and ICS.
[d]Comorbidity: Only to have one of comorbidities (including diabetes, hypertension, hyperlipidemia, coronary artery disease, depression, chronic kidney disease, stroke, cancer and pneumonia and influenza) classified as the comorbidity group.

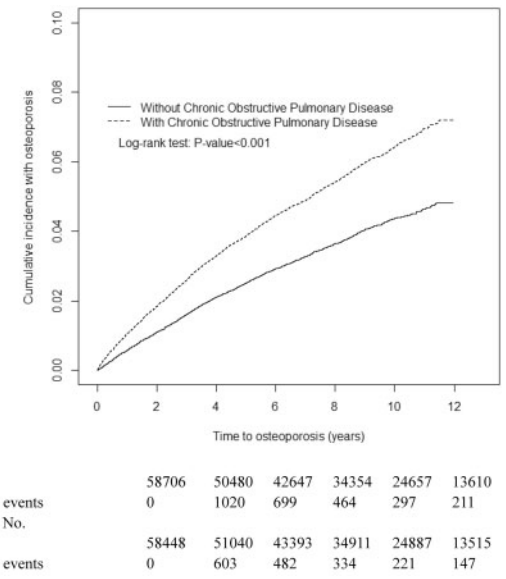

Figure 2. Cummulative incidence comparison of osteoporosis between with and without chronic obstructive pulmonary disease.

phenomenon that is consistent with the results of COPD with anti-inflammation medications. Therefore, we suggest that COPD increases the risk of developing osteoporosis.

A previous study verified that COPD involves local and systemic chronic inflammation[7] and might lead to a high prevalence of systemic complications.[8] A literature review revealed that the prevalence of osteoporosis varied between 9% and 69% in patients with chronic lung diseases.[9] Moreover, the results of a previous study were identical to our results of the HRs between patients with and without COPD; these results indicate that the severity of osteoporosis is correlated with that of COPD.[10] Similarly, the same effect was apparent in the impact of COPD, which exacerbates osteoporosis.[11] However, the aforementioned studies involved small sample sizes, whereas our study is the first to use a population database to explore the association between osteoporosis and COPD. The prevalence of COPD varied among countries; the estimated prevalence was 5.4% in Taiwan. The average prevalence in Asian-Pacific countries, the United States and the United Kingdom was 6.3, 4.8 and 5.0%, respectively.[12] Similarly, the prevalence of COPD was ~5.49–7.15% in the our database.

GCs, potent anti-inflammatory agents, are essential for treating inflammatory disorders, including acute diseases (e.g. acute bronchitis, urticaria, allergic diseases and acute gouty arthritis) and chronic

Table 3 Comparisons of HRs between patients with and without COPD for different outcomes (osteoporosis and pathologic fracture)

Variables(ICD-9-CM)	Event	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)
Outcome: osteoporosis without fracture (ICD-9-CM 733.0)				
Without COPD	1660	4.21	1(Reference)	1(Reference)
Outpatient COPD	1863	5.48	1.31(1.22, 1.40)***	1.40(1.31, 1.50)***
Inpatient COPD	626	12.1	2.81(2.57, 3.09)***	1.61(1.46, 1.77)***
Number of emergency room visits per year due to COPD with AE				
≤1	2486	6.36	1.51(1.42, 1.61)***	1.54(1.44, 1.64)***
≥2	3	8.43	1.73(0.56, 5.38)	1.38(0.44, 4.28)
Outcome: osteoporosis with pathologic fracture (ICD-9-CM 733.1)				
Without COPD	163	0.41	1(Reference)	1(Reference)
Outpatient COPD	166	0.49	1.18(0.95, 1.46)	1.24(0.99, 1.55)
Inpatient COPD	107	2.07	5.03(3.94, 6.42)***	2.57(1.98, 3.34)***
Number of emergency room visits per year due to COPD with AE				
≤1	269	0.69	1.66(1.37, 2.02)***	1.54(1.25, 1.90)***
≥2	4	11.2	27.3(10.1, 73.9)***	13.0(4.69, 36.0)***

[a]Rate, incidence rate, per 1000 person-years.
[b]Crude HR, relative HR.
[c]Adjusted HR adjusted for sex, age and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, depression, chronic kidney disease, stroke, cancer and pneumonia and influenza and medication of prednisolone use.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 4 Comparisons of HRs between patients with and without prednisolone use for osteoporosis

Variables	*N*	Event	PY	Rate[a]	Crude HR[c] (95% CI)	Adjusted HR[d] (95% CI)
Non-COPD						
Without prednisolone use	47 715	1561	302 345	5.16	1(Reference)	1(Reference)
With prednisolone use	10 733	262	91733	2.86	0.58(0.50, 0.66)***	0.61(0.53, 0.69)***
COPD						
Without prednisolone use	42 200	2153	26 280	8.21	1.59(1.49, 1.70)***	1.64(1.53, 1.76)***
With prednisolone use	16 506	609	129 257	4.71	0.94(0.86, 1.03)	0.95(0.86, 1.04)
COPD						
Without prednisolone use					1(Reference)	1(Reference)
Prednisolone use						
≤20 cDDD[b]	8155	321	64 090	5.01	0.63(0.56, 0.71)***	0.66(0.59, 0.74)***
>20 cDDD	8351	288	65 167	4.42	0.56(0.49, 0.63)***	0.50(0.45, 0.57)***
Non-COPD	58 448	1823	394 078	4.63	1(Reference)	1(Reference)
COPD						
Without ICS	51 209	2548	337 927	7.54	1.63(1.54, 1.73)***	1.54(1.44, 1.64)***
With ICS	7497	214	53 610	3.99	0.87(0.75, 1.00)	0.88(0.77, 1.02)

[a]Rate, incidence rate, per 1000 person-years.
[b]Associated with Cumulative Daily Defined Dose (DDD) Use of prednisolone.
[c]Crude HR, relative HR.
[d]Adjusted HR adjusted for sex, age and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, depression, chronic kidney disease, stroke, cancer and pneumonia and influenza and medication of prednisolone use and ICS.
**$P < 0.01$, ***$P < 0.001$.

diseases (e.g. autoimmune diseases, nephritis, lymphoma, inflammatory bowel diseases and endocrine diseases). Table 1 shows that the GCs use in the COPD and non-COPD groups was 28.1 and 18.4%, respectively; these data might indicate the general GC use for COPD. Moreover, the adjusted HR of incidence densities of osteoporosis were higher according to the sex, age and comorbidity among the patient with COPD (Table 2). Previous studies have shown that the risk of fracture attributed to the long-term use of GCs may lead to osteoporosis and an increased risk of fragility fractures[13,14]; in addition, the risk of fracture is often asymptomatic and might occur in ~30 −50% of patients.[15]

Although Langhammer *et al*.[16] reported that patients with COPD have a high risk of osteoporosis attributable to using high doses of oral corticosteroids and ICSs, this finding may have been confounded by the disease severity. Mathioudakis *et al*.[17] reported that the effect of 4-year use of low-dose ICSs slowed BMD loss. A previous study demonstrated the effects of GCs on bone modeling and calcium metabolism.[5] These effects might induce autophagy in osteocytes when patients are exposed to low doses of GCs and trigger the regulation of apoptosis when patients are exposed to high doses of GCs or prolonged GCs use.[18] In our study, we use cDDD to calculate the dose-related impact of GCs in osteoporosis. Table 4 shows that both COPD and non-COPD cohorts with GCs use had lower adjusted HRs for osteoporosis. Because COPD plays a critical role in systemic inflammation and contributes to numerous comorbidities, we hypothesize that GCs may reduce the inflammatory process and the risk of osteoporosis in patients with COPD. However, further study is required to clarify the research question.

ICS use in patients with COPD indicated that osteoporosis is highly prevalent, even though no significant difference between the sexes was observed.[19] This result is similar to our findings regarding a higher risk of osteoporosis that does not differ between the sexes. Price *et al*.[20] reported that indiscriminate use of ICSs by patients with COPD may increase the risk of side effects such as pneumonia and osteoporosis. In addition, a Cochrane Review[21] showed that long-term ICS use did not exert a major effect on fracture and BMD and suggested that ICS use might be evaluated according to improvement in quality of life. Similarly, our study showed that COPD patients with ICS use have lower HRs (adjusted HR = 0.88, 95% CI: 0.77–1.02).

The increased incidence was associated with the group experiencing a high frequency of osteoporosis exacerbations, consistent with the results observed in the severe COPD group.[22] We alternatively compared the severity of COPD in the inpatient group and outpatient group. Table 3 shows that the HRs (adjusted HR = 13.0, 95% CI 4.69–36.0) for patients with osteoporosis, pathologic fracture and AECOPD were high. Although the indexes of COPD severity, such as pulmonary function, symptom severity and daily-life activity, were are unavailable in our database, we demonstrated that the severity of COPD was associated with severe complications of osteoporosis with fracture. Overall, the results of this population-based cohort study revealed that COPD, which shares the characteristics of inflammatory diseases, might be a strong independent risk factor for osteoporosis.

Theoretically, the impact of osteoporosis depends on multiple factors such as age, race, lifestyle and medical conditions and treatments. Despite being a population-based cohort study, this study had several limitations. First, calcium and vitamin D supplementation data were lacking, and a history of smoking might have altered the calcium metabolism in bone mass. Second, the NHIRD does not provide data on patient characteristics such as smoking status, body mass index and physical activity level, all of which may be confounding factors. Third, the NHIRD claims were not verified for analysis and are entirely based on declarations of NHI fees. Moreover, we were unable to confirm adherence to steroid use. However, all insurance claims from the NHI program are scrutinized by medical reimbursement specialists and subject to peer review. Thus, the diagnoses for patients with COPD and osteoporosis are relatively reliable.

Conclusion

In conclusion, this nationwide retrospective cohort study demonstrated that COPD is associated with a higher risk of developing osteoporosis after adjustment for age, sex and comorbidities. Higher frequencies of AECOPD could be used to predict a higher risk of osteoporosis with fracture. The detailed pathophysiology may require further clarification in future prospective studies. Preventing the development of COPD and effectively treating COPD to prevent the development of osteoporosis is crucial. Prospective randomized controlled trials are required to confirm our findings and researchers might consider investigating confounding factors such as medical interventions and medication adherence.

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