OPEN

The Risk of Erectile Dysfunction in Chronic Obstructive Pulmonary Disease

A Population-Based Cohort Study in Taiwan

Te-Chun Shen, MD, Wen-Chi Chen, MD, PhD, Cheng-Li Lin, MS, Chia-Hung Chen, MD, Chih-Yen Tu, MD, Te-Chun Hsia, MD, Chuen-Ming Shih, MD, PhD, Wu-Huei Hsu, MD, and Fung-Chang Sung, PhD, MPH

Abstract: The prevalence of erectile dysfunction (ED) in patients with chronic obstructive pulmonary disease (COPD) seemed high; however, large scale of population-based study was absent.

We conducted a retrospective cohort study using data from the National Health Insurance system of Taiwan. The cohort included 29,042 male patients who were newly diagnosed with COPD. Patients were recruited between 2000 and 2011, and the date of diagnosis was defined as the index date. Each patient was randomly matched with 1 male person from the general population without COPD according to age and the index year. The occurrence of ED was followed up until the end of 2011. The hazard ratios of ED were estimated using the Cox proportional hazard model after adjusting for age, index year, comorbidities, and medications.

The overall incidence of ED was 1.88-fold greater in the COPD cohort than in the non-COPD cohort (24.9 vs 13.3/1000 person-years, 95% confidence interval [CI] = 1.61–2.18). Compared with non-COPD patients, the hazard ratio increased with the number of emergency room visits and admissions for COPD from 1.51 (95% CI 1.29–1.77) to 5.46 (95% CI 3.03–9.84) and from 1.50 (95% CI 1.28–1.76) to 11.5 (95% CI 5.83–22.6), respectively.

Patients with COPD are at a significantly higher risk of developing ED compared with the general population regardless of age and presence of comorbidity. The results also support that poor control of COPD status is a key factor affecting ED development.

(*Medicine* 94(14):e448)

Abbreviations: anti-HTN = antihypertensive agent, BZD = benzodiazepine, CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, ED = erectile dysfunction, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, KD = kidney disease, LHID 2000 = Longitudinal Health Insurance Database 2000, NSAID = nonsteroidal anti-inflammatory drug, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, PAD = peripheral artery disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, treatable, and preventable disease characterized by persistent airflow limitation caused by the long-term exposure to harmful particles or gases. Cigarette smoking is thought to be the greatest risk factor for the development of this disease. Increased inflammatory response in the airway is a typical feature in patients with COPD, although inflammation is not limited to the lungs and has systemic impact.[1] Comorbidities such as cardiovascular diseases, lung cancer, osteoporosis, diabetes and metabolic syndromes, anxiety, depression, and various infections have all been associated with COPD.[2]

Erectile dysfunction (ED) is a condition of inability to persistently reach and/or maintain an erection sufficient to have satisfactory sexual activity.[3] Aging, vascular insufficiency, psychogenic and neural disorders, systemic illness such as diabetes mellitus, hormonal derangement, and side-effects of medications may result in ED.[4] ED has a profound negative impact on the quality of life and men's self-esteem. But, clinical practices may often underestimate this important problem.

Several studies have reported ED as a common comorbidity in patients with COPD. Fletcher and Martin[5] first reported erectile impotence in 30% (6/20) of COPD patients. Köseoğlu et al[6] reported a much higher ED prevalence of 75.5% (40/53) in COPD patients with various degrees of ED. The observed moderate-to-severe ED is 2.8-fold more prevalent in COPD patients than in controls (57% [54/95] vs 20% [6/30]).[7] Collins et al also reported that 74% (67/90) of patients with moderate-to-severe COPD had at least 1 sexual dysfunction, with ED

Editor: Jingyun Yang.
Received: August 27, 2014; revised: December 3, 2014; accepted: December 17, 2014.
From the Graduate Institute of Clinical Medicine Science (T-CS, C-HC, F-CS), College of Medicine; Division of Pulmonary and Critical Care Medicine (T-CS, C-HC, C-YT, T-CH, C-MS, W-HH), Department of Internal Medicine, China Medical University Hospital, Taichung; Division of Pulmonary and Critical Care Medicine (T-CS), Department of Internal Medicine, Chu Shang Show Chwan Hospital, Nantou; Department of Urology (W-CC); Management Office for Health Data (C-LL), China Medical University Hospital, Taichung, Taiwan.
Correspondence: Fung-Chang Sung, Graduate Institute of Clinical Medicine Science, College of Medicine, China Medical University, No. 91 Hsueh-Shih Road, Taichung 404, Taiwan; Wen-Chi Chen, Department of Urology, China Medical University Hospital, China Medical University, No. 2 Yude Road, Taichung 404, Taiwan (. e-mail: fcsung.tw@gmail.com; wgchen@mail.cmuh.org.tw).
W-CC and F-CS contributed equally to this article.
T-CS and W-CC contributed to the conception and design of the study; T-CH, C-MS, and W-HH provided administrative support; all of the authors were responsible for the collection and assembly of data and final approval of the article; C-LL, C-HC, and F-CS contributed to data analysis and interpretation; T-CS, C-LL, C-YT, W-CC, and F-CS were responsible for article writing.
This work was supported by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW103-TDU-B-212-113002). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000448

being the most common (72%, 48/67).[8] A recent Turkey study has also confirmed lower testosterone levels in COPD patients with ED than non-COPD subjects with ED.[9]

Nevertheless, most of previous studies were performed either as a passive questionnaire or with small study samples. The present study attempts to determine the risk of ED in patients with COPD by conducting a nationwide population-based retrospective cohort study in Taiwan with data using the National Health Insurance Research Database (NHIRD) of Taiwan.

MATERIALS AND METHODS

Data Sources

In March 1995, the Taiwanese government officially started a National Health Insurance (NHI) program to provide a comprehensive, unified, and universal health insurance to all citizens of Taiwan (http://www.nhi.gov.tw/english/index.aspx). The NHIRD is a nationwide database of reimbursement claim data of the NHI program, and is maintained by the National Health Research Institutes (NHRI). We obtained the NHRI a subdataset of the Longitudinal Health Insurance Database 2000 (LHID 2000), which comprises a random sample of 1 million subjects with longitudinally linked data available from 1996 to 2011. The NHRI states that no statistical differences in age, sex, and health care costs exist between LHID 2000 and NHIRD. The NHRI has encrypted all patient identification numbers for the protection of privacy and provides researchers with anonymous numbers to link the relevant claim information, such as patient sex, birth date, medical claims, and types of care, including medication prescriptions. Diseases in the claims data were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). An ad hoc committee was established for the insurance system to randomly sample claims to verify the diagnoses and related cares for accuracy to prevent violations. This study was approved by the Institutional Review Board of China Medical University in central Taiwan (CMU-REC-101-012).

Study Population

Male patients with newly diagnosed COPD (ICD-9-CM 491, 492, and 496) were identified for the period of 2000 to 2011 from the dataset of LHID 2000. Subjects who had at least 2 diagnoses of COPD within a year with medication were eligible for inclusion in the COPD cohort. The first diagnosis date was defined as the index date of COPD. COPD patients with an ED history before the index date, aged <20 years, and with incomplete information on demographics were excluded. Comparison patients were selected from people without COPD or an ED history in the file of LHID 2000. For each identified COPD patient, 1 comparison person was randomly identified and frequency-matched with age (each 5-year span) and year of index date for the non-COPD cohort. Subjects <20 years of age were excluded.

Outcome Measurements, Comorbidities and Medications

All study subjects were followed from the index date to until the date with ED diagnosed (ICD-9-CM code 302.72 and 607.84),[10] date of withdrawal from the NHI program, or the end of 2011, whichever was reached first. The baseline comorbidities considered in this study included coronary artery disease (CAD) (ICD-9-CM code 410–414), peripheral artery disease (PAD) (ICD-9-CM code 443.81, 443.9, 440.2, 444.2, and 444.89), asthma (ICD-9-CM 493), stroke (ICD-9-CM code 430–438), kidney disease (KD) (ICD-9-CM code 580–589), hypertension (ICD-9-CM code 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), depression (ICD-9-CM code 296.2, 296.3, 300.4, and 311), and anxiety (ICD-9-CM code 300.00). Medications that may be associated with ED were also evaluated, including antihypertensive agents (anti-HTNs), benzodiazepines (BZDs), and nonsteroidal anti-inflammatory drugs (NSAIDs). Anti-HTNs included calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, α-blocker, β-blocker, and diuretics.

Statistical Analysis

The baseline characteristics and comorbidities of the COPD cohort and non-COPD cohort were compared. Chi-square and *t* tests were used to test the difference of categorical and continuous variables, respectively, between the 2 cohorts. The overall, sex-, age-, and comorbidity-specific incidence rates (per 10,000 person-years) of ED were calculated for each cohort. Univariable and multivariable Cox proportional hazards regression analyses were used to assess the hazard ratio (HR) and 95% confidence interval (CI) of ED development associated with COPD, compared with the non-COPD cohort. In the multivariable analysis, the model was adjusted for age and comorbidities of CAD, PAD, asthma, stroke, KD, hypertension, diabetes, hyperlipidemia, depression, anxiety, medications of anti-HTNs, BZDs, and NSAIDs, and all of which showed a significant difference (Table 1). The joint effect for ED between COPD and comorbidity was also assessed. The relationship between ED and the annual number of visits to the emergency room and admissions for COPD were also assessed. The cumulative incidence of ED between the COPD cohort and the non-COPD cohort was analyzed using the Kaplan–Meier method, and the difference was examined by log-rank test. The SAS software (version 9.2 for Windows; SAS Institute Inc, Cary, NC) was used for all data analyses. A P value <0.05 was considered statistically significant.

RESULTS

Overall, 57,928 subjects were selected for this retrospective cohort study, including 29,042 COPD patients and 28,886 non-COPD controls. The age distribution was similar in both cohorts, with the mean age slightly higher in the COPD cohort than in the non-COPD cohort (61.0 [SD = 15.8] vs 59.9 [SD = 15.8] years) but statistically significant. Compared with non-COPD subjects, COPD patients were more prevalent with comorbidities, including CAD, PAD, asthma, stroke, KD, hypertension, diabetes, hyperlipidemia, depression, and anxiety (all $P < 0.001$, Table 1). All of medications were more prevalent in the COPD cohort at the baseline (all $P < 0.001$, Table 1), compared with the non-COPD cohort. After 12 years of follow-up, the cumulative incidence of ED in the COPD cohort was approximately 1.29% higher than that in the non-COPD cohort ($P < 0.001$, Figure 1).

Overall, COPD patients had a 1.88-fold higher incidence of ED than non-COPD patients had (24.9 vs 13.3/1000 person-years, 95% CI 1.61–2.18) (Table 2). After adjusting for age and comorbidities of CAD, PAD, asthma, stroke, KD, hypertension, diabetes, hyperlipidemia, depression, and anxiety, COPD patients had an adjusted HR of 1.52 (95% CI 1.30–1.79) for ED, compared with non-COPD patients. COPD patients had approximately similar hazards to develop organic and

TABLE 1. Comparisons in Demographic Characteristics and Comorbidities Between Cohorts With and Without COPD

	COPD		
Variable	**No N = 28886**	**Yes N = 29042**	***P* Value***
Age, y‡			0.84
20–49	7301 (25.3)	7301 (25.1)	
50–59	5197 (18.0)	5190 (17.9)	
60–69	6608 (22.9)	6615 (22.8)	
≥70	9780 (33.9)	9936 (34.2)	
Mean ± SD†	59.9 (15.8)	61.0 (15.8)	<0.001
Comorbidity			
CAD	4249 (14.7)	7864 (27.1)	<0.001
PAD	248 (0.86)	419 (1.44)	<0.001
Asthma	562 (1.95)	4110 (14.2)	<0.001
Stroke	1472 (5.10)	2698 (9.29)	<0.001
KD	2116 (7.33)	3401 (11.7)	<0.001
Hypertension	10265 (35.5)	14244 (49.1)	<0.001
Diabetes	2825 (9.78)	3506 (12.1)	<0.001
Hyperlipidemia	4796 (16.6)	6648 (22.9)	<0.001
Depression	672 (2.33)	1296 (4.46)	<0.001
Anxiety	902 (3.12)	1847 (6.36)	<0.001
Medication			
Anti-HTNs	8738 (30.3)	12121 (41.7)	<0.001
BZDs	5945 (20.6)	9749 (33.6)	<0.001
NSAIDs	10344 (35.8)	14642 (50.4)	<0.001

BZD = benzodiazepine, COPD = chronic obstructive pulmonary disease, CAD = coronary artery disease, KD = kidney disease, anti-HTN = antihypertensive agent, NSAID = nonsteroidal anti-inflammatory drug. PAD = peripheral artery disease,

* Chi-square test.

† *t* test.

‡ The age is partitioned into 4 segments (20–49 years, 50–59 years, 60–69 years, and ≥70 years) by quartile.

psychosexual EDs. The association between psychosexual ED and COPD was not significant, with a small number of patients.

The age-specific showed that the ED incidence was the highest for 50- to 59-year-old men in both cohorts. The COPD cohort to non-COPD cohort adjusted HR of ED was not significant for this age group, and was the lowest among age groups. The incidence of ED increased with the number of comorbidities in both cohorts. COPD, with or without comorbidity, was associated with a significantly higher risk of ED than non-COPD.

Table 3 shows not strong increase for the joint effect of developing ED between COPD and comorbidities. Depression had a stronger association with ED than COPD had. Lowered ED HR was observed for those with comorbid stroke. The association between ED and the annual number of emergency room visits and admissions for COPD is shown in Table 4. Compared with non-COPD patients, the HR increased with the number of these services for COPD from 1.51 (95% CI 1.29–1.77) to 5.46 (95% CI 3.03–9.84) and from 1.50 (95% CI 1.28–1.76) to 11.5 (95% CI 5.83–22.6), respectively.

DISCUSSION

To the best of our knowledge, this is the first nationwide population-based study evaluating the relationship between COPD and subsequent ED risk. A significant hazard of ED was identified among patients with COPD compared with the general population (adjusted HR 1.52, 95% CI 1.29–1.80). Meanwhile, those with more comorbidities were found to have an increased incidence of developing ED in both cohorts. In addition, this study showed that the risk of ED increased as COPD patients required more emergency room visits and admissions. These results support the notion that poor control of COPD status is a key factor affecting ED development.

The definitive mechanism of ED development in COPD patients remains unknown. First, hormonal imbalances should be considered. Androgen deficiency can induce depression, anxiety, anger, fatigue, and sleep disorders. Most important, hormonal imbalance decreases libido, ED, and reduces ejaculation output volume and speed.[11] Hypogonadism and lower testosterone levels have been reported in males with COPD.[9,12,13] Therefore, a link between gonadal status and sexual dysfunction in men with COPD is likely. Second, endothelial dysfunction and vascular insufficiency may play an important role. As is well known, cardiovascular disease is the major comorbidity of COPD, and is probably the most frequent and severe condition coexisting with COPD.[14] In aged patients, ED is most often due to organic causes, the most common factor being atherosclerosis.[15,16] Not surprisingly, COPD has thus been associated with ED development. Third, respiratory or general symptoms of COPD could also contribute to sexual dysfunction via somatophysical effects; dyspnea, cough, muscular weakness, and the associated reduction of physical activity can directly influence sexual activity in COPD patients.[7,17] In addition, chronic hypoxia is an important risk associated with pathological conditions, including ED. Recent trials have shown that inadequate oxygen supply impairs nitric oxide synthesis, which subsequently reduces the functional integrity of penile smooth muscles.[18,19] It has been suggested that ED in COPD may be due to persistent exposure to a hypoxic environment.[20]

In some studies, researchers found a correlation between COPD severity and ED risk.[5,6,9] In previous versions of the Global Initiative for Chronic Obstructive Lung Disease report, COPD treatment recommendations were based on spirometry only. However, the pulmonary function test is a poor descriptor of disease, and thus, the treatment strategy for COPD should also consider the patient's symptoms and further risk of exacerbations, and therefore, exacerbation history is considered in the evaluation of disease status in COPD.[21] In the present study, the number of emergency room visits and admissions per year for COPD has been considered to reflect, at least in part, the COPD control status. The results related to emergency room visits and admissions also supported the hypothesis that poor control of COPD status results in an increased risk of ED development.

With regards to relative risk, Karadag et al[7] reported a 1.05 HR of overall ED between moderate-to-severe COPD and controls, and a 2.85 HR of moderate and severe ED between moderate-to-severe COPD and controls. Kahraman et al[9] reported a 1.40 HR of overall ED between the COPD group and controls. Thus, the results were compatible to those presented herein (HR 2.17, 95% CI 1.84–2.56). With regards to ED prevalence, previous studies reported a 30% to 79% prevalence in overall COPD patients and a 53% to 87% prevalence in moderate-to-severe COPD patients.[5–9] The incidence reported herein was far less, probably due to the present study reflecting a relative ''real world'' scenario wherein the diagnosis of ED is due to a real medical consultation. Thus, the ED patients included were believed to have greater disease severity. In

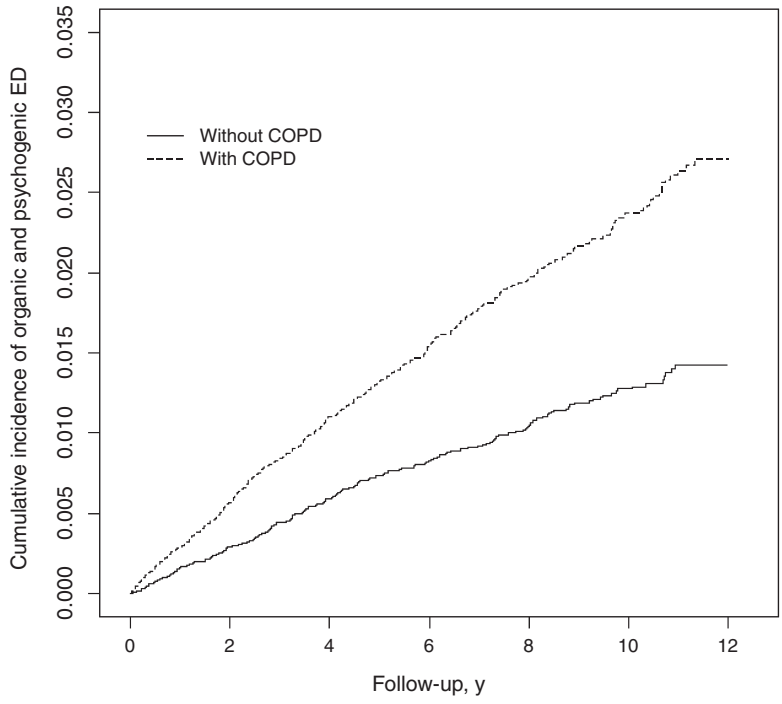

FIGURE 1. Cumulative incidence of ED in patients with (dashed line) or without (solid line) COPD. COPD = chronic obstructive pulmonary disease, ED = erectile dysfunction.

TABLE 2. Incidence of Organic and Psychogenic ED and Cox Method Estimated HR of ED for COPD Cohort Compared With Control Cohort by Demographic Characteristics and Comorbidity

	COPD							
	No			Yes				
Variables	Event	PY	Rate[†]	Event	PY	Rate[†]	Crude HR (95% CI)	Adjusted HR[#] (95% CI)
All[§]	258	194662	13.3	475	190993	24.9	1.88 (1.61, 2.18)***	1.52 (1.30, 1.79)***
Organic ED[§]	238		12.2	437		22.9	1.87 (1.60, 2.19)***	1.53 (1.29, 1.80)***
Psychosexual ED[§]	20		1.03	38		1.99	1.94 (1.13, 3.33)*	1.50 (0.85, 2.65)
Age[‖]								
20–49	43	54660	7.87	106	54841	19.3	2.46 (1.72, 3.50)***	1.74 (1.19, 2.54)**
50–59	71	36619	19.4	123	35833	34.3	1.77 (1.32, 2.37)***	1.30 (0.95, 1.78)
60–69	86	47355	18.2	144	45750	31.5	1.73 (1.32, 2.26)***	1.48 (1.12, 1.95)**
≥70	58	56029	10.4	102	54570	18.7	1.80 (1.30, 2.48)***	1.62 (1.16, 2.27)**
Number of comorbidities[¶]								
0	81	110037	7.36	104	62359	16.7	2.27 (1.70, 3.03)***	1.88 (1.39, 2.53)***
1	67	37020	18.1	117	48347	24.2	1.34 (0.99, 1.81)	1.28 (0.95, 1.74)
≥2	110	47606	23.1	254	80288	31.6	1.37 (1.10, 1.72)**	1.26 (1.01, 1.58)*

Anti-HTN = antihypertensive agent, BZD = benzodiazepine, CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, ED = erectile dysfunction, HR = hazard ratio, KD = kidney disease, NSAID = nonsteroidal anti-inflammatory drug, PAD = peripheral artery disease, PY = person-years.

[†] Rate, incidence rate per 1000 person-years.

[§] Adjusted HR was calculated by Cox proportional hazards regression and adjusted for age, comorbidities of CAD, PAD, asthma, stroke, KD, hypertension, diabetes, hyperlipidemia, depression, and anxiety, and medication of anti-HTNs, BZDs, and NSAIDs.

[‖] Adjusted HR was calculated by Cox proportional hazards regression stratified by age and adjusted for comorbidities of CAD, PAD, asthma, stroke, KD, hypertension, diabetes, hyperlipidemia, depression, and anxiety, and medication of anti-HTNs, BZDs, and NSAIDs.

[¶] Adjusted HR was calculated by Cox proportional hazards regression stratified by number of comorbidities and adjusted for age and sex.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

TABLE 3. Cox Proportional Hazard Regression Analysis for the Risk of Organic and Psychogenic ED Associated COPD With Joint Effect of Comorbidity

Variables		Participant N	Event n	Adjusted HR[†] (95% CI)	*P* Value
COPD	CAD				0.24
No	No	24637	196	1 (Reference)	
No	Yes	4249	62	1.47 (1.08, 1.99)*	
Yes	No	21178	300	1.58 (1.31, 1.90)***	
Yes	Yes	7864	175	2.04 (1.62, 2.58)***	
COPD	PAD				0.89
No	No	28638	255	1 (Reference)	
No	Yes	248	3	1.32 (0.42, 4.15)	
Yes	No	28623	466	1.53 (1.30, 1.79)***	
Yes	Yes	419	9	1.95 (0.99, 3.81)	
COPD	Asthma				0.41
No	No	28324	252	1 (Reference)	
No	Yes	562	6	1.14 (0.51, 2.57)	
Yes	No	24932	406	1.53 (1.30, 1.80)***	
Yes	Yes	4110	69	1.46 (1.11, 1.92)**	
COPD	Stroke				0.54
No	No	27414	252	1 (Reference)	
No	Yes	1472	6	0.44 (0.19, 1.00)	
Yes	No	26344	461	1.53 (1.30, 1.80)	
Yes	Yes	2698	14	0.59 (0.34, 1.01)	
COPD	KD				0.05
No	No	26770	221	1 (Reference)	
No	Yes	2116	37	1.79 (1.25, 2.56)**	
Yes	No	25641	398	1.61 (1.35, 1.91)***	
Yes	Yes	3401	77	1.98 (1.50, 2.62)***	
COPD	Hypertension				0.005
No	No	18621	133	1 (Reference)	
No	Yes	10265	125	1.25 (0.95, 1.65)	
Yes	No	14788	231	1.82 (1.46, 2.26)***	
Yes	Yes	14244	244	1.58 (1.23, 2.04)***	
COPD	Diabetes				0.02
No	No	26061	222	1 (Reference)	
No	Yes	2825	36	1.27 (0.88, 1.82)	
Yes	No	25536	423	1.61 (1.36, 1.90)***	
Yes	Yes	3506	52	1.33 (0.97, 1.83)	
COPD	Hyperlipidemia				0.07
No	No	24090	180	1 (Reference)	
No	Yes	4796	78	1.76 (1.33, 2.34)***	
Yes	No	22394	314	1.66 (1.37, 2.00)***	
Yes	Yes	6648	161	2.23 (1.76, 2.83)***	
COPD	Depression				0.045
No	No	28214	241	1 (Reference)	
No	Yes	672	17	2.52 (1.52, 4.16)***	
Yes	No	27746	440	1.59 (1.35, 1.87)***	
Yes	Yes	1296	35	2.32 (1.60, 3.37)***	
COPD	Anxiety				0.79
No	No	27984	247	1 (Reference)	
No	Yes	902	11	1.01 (0.55, 1.86)	
Yes	No	27195	435	1.53 (1.30, 1.81)***	
Yes	Yes	1847	40	1.56 (1.10, 2.23)*	

Anti-HTN = antihypertensive agent, BZD = benzodiazepine, CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, ED = erectile dysfunction, HR = hazard ratio, KD = kidney disease, NSAID = nonsteroidal anti-inflammatory drug, PAD = peripheral artery disease.

[†] Model was adjusted for age, other comorbidities, and medication of anti-HTNs, BZDs, and NSAIDs.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

TABLE 4. HR of ED Associated With the Number of Annual Emergency Room Visits and Admissions for Patients With COPD

	ED	HR (95% CI)	
	No. of Events	Crude*	Adjusted†
Controls	258	1 (Reference)	1 (Reference)
COPD cohort Emergency room visits			
≤1	463	1.85 (1.59, 2.15)***	1.51 (1.29, 1.77)***
≥2	12	5.43 (3.04, 9.70)***	5.46 (3.03, 9.84)***
P for trend		<0.001	<0.001
Admissions			
≤2	460	1.84 (1.58, 2.14)***	1.50 (1.28, 1.76)***
3–4	6	2.86 (1.27, 6.42)**	3.00 (1.32, 6.78)**
≥5	9	10.4 (5.33, 20.3)***	11.5 (5.83, 22.6)***
P for trend		<0.001	<0.001

Anti-HTN = antihypertensive agent, BZD = benzodiazepine, CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, ED = erectile dysfunction, HR = hazard ratio, KD = kidney disease, NSAID = nonsteroidal anti-inflammatory drug, PAD = peripheral artery disease.

* Crude HR, relative HR.

† Model was adjusted for age and comorbidities of CAD, PAD, asthma, stroke, KD, hypertension, diabetes, hyperlipidemia, depression, and anxiety, and medication of anti-HTNs, BZDs, and NSAIDs.

** $P < 0.01$.

*** $P < 0.001$.

addition, the participants in the previous studies passively received and answered a questionnaire. Not surprisingly, the prevalence of ED in the control group has been reported to be as high as 83%.[7] Nevertheless, we consider that ED is indeed a much underestimated problem in COPD patients. Clinical physicians should pay more attention to this group of individuals and provide appropriate support.

A major strength of the present study is its use of population-based data that are highly representative of the general population. However, the study has several limitations. First, the diagnoses selected from the ICD-9 code depend on the performance of clinical physicians; we were unable to check their validity. However, the NHI system of Taiwan has been used for various studies over several years.[22–24] Second, the NHIRD does not contain detailed information regarding smoking habits, body mass index, diet preference, drug use, and family history of systemic diseases, all of which may be associated risk factors for COPD development. In addition, several relevant clinical variables, such as laboratory data, imaging results, culture reports, and pathology findings, were unavailable for the patients. Physicians may not report some clinical conditions in the medical claims without inquiring of patients, such as sexual life after stroke. Stroke is a well-known risk impairing sexual function.[25] Our data shows that stroke is a protective factor of ED. It is likely that the ED conditions are underreported in our study population. The prevalence of stroke at the baseline was 1.8-fold higher in the COPD cohort than in the non-COPD cohort. Therefore, the protective association of stroke for COPD cohort in this study is misleading.

CONCLUSION

Patients with COPD are at a significantly higher risk of developing ED compared with the general population regardless of age and presence of comorbidity. The results also support that poor control of COPD status is a key factor affecting ED development.

REFERENCES

1. Karadag F, Ozcan H, Karul AB, et al. Sex hormone alterations and systemic inflammation in chronic obstructive pulmonary disease. *Int J Clin Pract.* 2009;63:275–281.
2. Sin DD, Anthonisen NR, Soriano JB, et al. Mortality in COPD: role of comorbidities. *Eur Respir J.* 2006;28:1245–1257.
3. NIH Consensus Conference Impotence. NIH consensus development panel on impotence. *JAMA.* 1993;270:83–90.
4. Lue TF. Erectile dysfunction. *N Engl J Med.* 2000;342:1802–1813.
5. Fletcher EC, Martin RJ. Sexual dysfunction and erectile impotence in chronic obstructive pulmonary disease. *Chest.* 1982;81:413–421.
6. Köseoğlu N, Köseoğlu H, Ceylan E, et al. Erectile dysfunction prevalence and sexual function status in patients with chronic obstructive pulmonary disease. *J Urol.* 2005;174:249–252.
7. Karadag F, Ozcan H, Karul AB, et al. Correlates of erectile dysfunction in moderate-to-severe chronic obstructive pulmonary disease patients. *Respirology.* 2007;12:248–253.
8. Collins EG, Halabi S, Langston M, et al. Sexual dysfunction in men with COPD: impact on quality of life and survival. *Lung.* 2012;190:545–556.
9. Kahraman H, Sen B, Koksal N, et al. Erectile dysfunction and sex hormone changes in chronic obstructive pulmonary disease patients. *Multidiscip Respir Med.* 2013;8:66.
10. Blumentals WA, Gomez-Caminero A, Joo S, et al. Should erectile dysfunction be considered as a marker for acute myocardial infarction? Results from a retrospective cohort study. *Int J Impot Res.* 2004;16:350–353.
11. Hafez B, Hafez ES. Andropause: endocrinology, erectile dysfunction, and prostate pathophysiology. *Arch Androl.* 2004;50:45–68.

12. Laghi F, Antonescu-Turcu A, Collins E, et al. Hypogonadism in men with chronic obstructive pulmonary disease: prevalence and quality of life. *Am J Respir Crit Care Med.* 2005;171:728–733.
13. Turner HE, Wass JA. Gonadal function in men with chronic illness. *Clin Endocrinol (Oxf).* 1997;47:379–403.
14. Fabbri LM, Luppi F, Beghé B, et al. Complex chronic comorbidities of COPD. *Eur Respir J.* 2008;31:204–212.
15. Melman A, Gingell JC. The epidemiology and pathophysiology of erectile dysfunction. *J Urol.* 1999;161:5–11.
16. Meldrum DR, Gambone JC, Morris MA, et al. The link between erectile and cardiovascular health: the canary in the coal mine. *Am J Cardiol.* 2011;108:599–606.
17. Schönhofer B. Sexuality in patients with restricted breathing. *Med Klin (Munich).* 2002;97:344–349.
18. Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. *Int J Impot Res.* 1998;10:113–120.
19. Sáenz de Tejada I, Angulo J, Cellek S, et al. Physiology of erectile function. *J Sex Med.* 2004;1:254–265.
20. Verratti V, Di Giulio C, Berardinelli F, et al. The role of hypoxia in erectile dysfunction mechanisms. *Int J Impot Res.* 2007;19:496–500.
21. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available from: http://www.goldcopd.org/.
22. Shen TC, Lin CL, Chen CH, et al. Increased risk of chronic obstructive pulmonary disease in patients with rheumatoid arthritis: a population-based cohort study. *QJM.* 2014;107:534–543.
23. Shen TC, Lin CL, Chen CH, et al. Increased risk of chronic obstructive pulmonary disease in patients with systemic lupus erythematosus: a population-based cohort study. *PLoS One.* 2014;9:e91821.
24. Shen TC, Chung WS, Lin CL, et al. Does chronic obstructive pulmonary disease with or without type 2 diabetes mellitus influence the risk of lung cancer? Result from a population-based cohort study. *PLoS One.* 2014;9:e98290.
25. Jung JH, Kam SC, Choi SM, et al. Sexual dysfunction in male stroke patients: correlation between brain lesions and sexual function. *Urology.* 2008;71:99–103.