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The Impact of Lung Function on Extra-Pulmonary Diseases and All-Cause Mortality in US Adult Population with and without COPD

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Objective: Spirometric lung function is usually used to evaluate respiratory health. However, the impact of lung function on extra-pulmonary diseases and all-cause mortality has not been fully elucidated, especially in people without chronic obstructive pulmonary disease (COPD).

Patients and Methods: Participants aged ≥20 and underwent spirometry test from the US National Health and Nutrition Examination Surveys (NHANES) 2007–2012 were analyzed in this study. Multivariate logistic and Cox regressions were used to evaluate the impact of forced expiratory volume in 1 second percent of predicted (FEV_1% predicted) and forced vital capacity percent of predicted (FVC% predicted) on 14 extra-pulmonary diseases and all-cause morbidity after adjusting for multiple confounders.

Results: During 2007–2012, 1800 COPD patients and 11,437 non-COPD subjects were included. The prevalence of hypertension, diabetes mellitus (DM), dyslipidemia, metabolic syndrome (MS), congestive heart failure (CHF), coronary disease, stroke, chronic kidney disease (CKD), arthritis, cancer, underweight and osteoporosis in COPD patients was higher than that in the non-COPD population. After adjusting for confounders, the decrease of FEV_1 % predicted and FVC% predicted was related with higher odds of having hypertension, DM, obesity, MS, CHF, coronary disease and depression (OR > 1, P<0.05) in both the COPD and non-COPD populations. These 2 indices were also related with higher odds of dyslipidemia, CKD, arthritis and osteoporosis in the non-COPD population. The risk of stroke, anemia and cancer was not related with the decrease of lung function. In addition, the decrease of lung function was independent risk factors for the increase of all-cause mortality. These risks were gradually increased with the decrease of lung function.

Conclusion: The decrease of FEV_1% predicted and FVC% predicted was related with higher risk of multiple extra-pulmonary diseases and all-cause mortality in both the COPD and non-COPD population.

Keywords: lung function, mortality, extra-pulmonary diseases, COPD

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Introduction

Spirometric lung function is usually used to evaluate respiratory health and diagnose pulmonary disease, such as chronic obstructive pulmonary disease (COPD), asthma and small airway disease.[1,2] Forced expiratory volume in 1 second percent of predicted (FEV_1% predicted), forced vital capacity percent of predicted (FVC% predicted), and FEV_1/FVC ratio are most commonly used indices of lung function, which can be used to define COPD and evaluate the severity of airflow limitation

and lung injury.[3] In addition to the impact on respiratory health, there is increasing evidence that COPD is associated with morbidity and mortality of some extra-pulmonary diseases.[4–7] However, limited research has focused on the influence and its extent of lung function on these diseases and morbidity in the population with normal lung function compared with COPD patients.

COPD often coexists with one or more comorbidities, which can contribute to poor health quality, healthcare costs and morbidity of patients.[3,8,9] The comorbidities reported in previous studies mainly included cardiovascular disease, hypertension, diabetes mellitus (DM), lung cancer, osteoporosis, anxiety and depression, which may be caused independently by COPD or share similar risk factors with COPD.[3,10,11] Lung function impairment is the most important characteristic of COPD, which indicates that the decrease of lung function indices may mediate the impact of COPD on comorbidities and morbidity.[12,13]

FEV_1/FVC is usually used to define COPD, while FEV_1% predicted and FVC% predicted have higher correlations with severity of lung injury.[14,15] Therefore, the main purpose of this study was to determine whether the decrease of FEV_1% predicted and FVC% predicted are associated with the prevalence of 14 extra-pulmonary diseases and morbidity in both the COPD and non-COPD populations after adjusting for potential confounders. We also aimed to evaluate the extent to which the decrease of lung function impacts these diseases and morbidity.

Patients and Methods

Data Source

Data from 3 cycles of the National Health and Nutrition Examination Survey (NHANES) spanning 2007–2012 were used in this study, which were released by the Centers for Disease Control and Prevention (CDC). Demographic data, spirometry test, disease information, dietary data, and laboratory and questionnaire data related with disease definition were extracted and combined from different NHANES files. Mortality status and follow-up time for all subjects were extracted from the National Death Index by 31 December 2015. Among the 30,442 subjects in 3 cycles, we included 13,237 subjects (6,679 men and 6,558 un-pregnant women) for further analysis, who were aged ≥ 20 and underwent spirometry test. Further details about NHANES were introduced in the Supplementary Method. All the data in this study were freely available on the NHANES homepage (http://www.cdc.gov/nchs/nhanes.htm), which was approved by the National Center for Health Statistics Institutional Review Board of the CDC. Ethical approval was not required for this study.

Spirometry Test and COPD

Spirometry test was offered to subjects during NHANES 2007–2012 who meet certain inclusion criteria. Due to the lack of post-bronchodilator spirometry test for most subjects, COPD was defined as pre-bronchodilator FEV_1/FVC < 0.7, which was different from the Global initiative for the management of chronic Obstructive Lung Disease definition.[3] Predicted FEV_1 and FVC were calculated according to the equations of Hankinson et al considering race, gender, age and height.[16] FEV_1% predicted was divided into 5 groups in the COPD population: FEV_1 < 60% predicted, FEV_1 60% ~ 70% predicted, FEV_1 70% ~ 80% predicted, FEV_1 80% ~ 90% predicted, and FEV_1 ≥ 90% predicted, and 4 groups in the non-COPD population: FEV_1 < 80% predicted, FEV_1 80% ~ 90% predicted, FEV_1 90% ~ 100% predicted, and FEV_1 ≥ 100% predicted. FVC % predicted was divided into 4 groups in both the COPD and non-COPD populations: FVC < 80% predicted, FVC 80% ~ 90% predicted, FVC 90% ~ 100% predicted, and FVC ≥ 100% predicted.

Definition of Diseases

In this study, we analyzed the impact of lung function on 14 extra-pulmonary diseases. Three lung diseases (asthma, chronic bronchitis and emphysema) were analyzed as confounding factors. The definition of these diseases were as follows:

Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg, a diastolic blood pressure (DBP) ≥ 90 mmHg, a self-reported physician diagnosis of hypertension, or a use of anti-hypertensive medications. SBP and DBP were the average of 1 to 3 blood pressure measurements.[17]

DM was defined as a fasting plasma glucose ≥ 126 mg/dL, a glycated haemoglobin ≥ 6.5%, 2-hour glucose of Oral Glucose Tolerance Test ≥ 200 mg/dL, a self-reported physician diagnosis of DM, a use of glucose-lowering medications, or a use of insulin injections.[18]

Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2, overweight was defined as 25 kg/m^2 ≤ BMI < 30 kg/m^2, and underweight was defined as BMI < 18.5 kg/m^2, according to the CDC guidelines.[19]

Table 1 Baseline Characteristics of Subjects With and Without COPD

Characteristics	COPD (N=1800)	Non-COPD (N=11,437)	t/χ^2	*P*
Age	58.47 ±14.04	45.07±15.79	−36.98	<0.001
Gender				
Male	1147 (63.72)	5532 (48.37)	146.65	<0.001
Female	653 (36.28)	5905 (51.63)		
Race				
Mexican American	136 (7.56)	1946 (17.01)	288.21	<0.001
Other Hispanic	123 (6.83)	1299 (11.36)		
Non-Hispanic White	1080 (60.00)	4594 (40.17)		
Non-Hispanic Black	360 (20.00)	2534 (22.16)		
Other Race	101 (5.61)	1064 (9.30)		
Height*	170.29 ±9.64	167.6±10.10	−10.91	<0.001
Weight*	80.77 ±19.55	82.39±21.47	3.21	0.001
BMI*	27.77 ±6.02	29.25±6.87	9.51	<0.001
Protein*	81.91 ±44.29	82.71±42.06	0.70	0.483
Carbohydrate*	258.23 ±132.64	263.46 ±128.84	1.56	0.119
Total fat*	81±48.35	80±46.66	−0.80	0.424
Alcohol use*	12.57 ±29.84	10.88±30.25	−2.15	0.032
Smoking status*				
Never-smoker	528 (29.35)	6688 (58.51)	533.54	<0.001
Ex-smoker	624 (34.69)	2365 (20.69)		
Current-smoker	647 (35.96)	2377 (20.80)		
Income level*				
Low income	601 (35.04)	3843 (35.68)	0.89	0.6412
Middle income	233 (13.59)	1522 (14.13)		
High income	881 (51.37)	5406 (50.19)		
Education*				
< High school	522 (29.02)	2845 (24.89)	36.49	<0.001
High school or equivalent	465 (25.85)	2550 (22.31)		
> High school	812 (45.14)	6033 (52.79)		
Mortality*	180 (10.01)	382 (3.35)	169.51	<0.001
FEV_1	2.43±0.83	3.14±0.88	33.15	<0.001
FVC	3.83±1.18	3.90±1.08	2.15	0.031
FEV_1/FVC	0.63±0.07	0.81±0.06	99.81	<0.001
FEV_1% predicted*	0.79±0.18	0.98±0.14	40.60	<0.001
FVC% predicted*	0.96±0.17	0.97±0.14	2.33	0.020
EOS%*	3.16±2.21	2.83±2.11	−5.79	<0.001
NEU%*	59.41 ±9.26	57.52±9.37	−7.83	<0.001

Note: *There were some missing data in these baseline characteristics.

Metabolic syndrome (MS) was defined as a presence of 3 or more of the following 5 criteria: (1) abdominal obesity: waist circumference ≥ 102 cm for non-Hispanic white men, ≥ 88 cm for non-Hispanic white women, ≥ 94 cm for men of other races, and ≥ 80 cm for women of other races; (2) triglyceridemia ≥ 150 mg/dL; (3) high-density lipoprotein cholesterol <40 mg/dL for men and < 50 mg/dL for women; (4) SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, or hypertension; and (5) fasting plasma glucose ≥ 100 mg/dL or DM.[20]

Dyslipidemia was defined as a presence of 1 or more of the following 4 criteria: (1) total cholesterol ≥ 240 mg/dL; (2) triglyceridemia ≥ 150 mg/dL; (3) low-density lipoprotein cholesterol ≥ 130 mg/dL; and (4) high-density lipoprotein cholesterol <40 mg/dL for men and < 50 mg/dL for women.[21]

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate < 60 mL/min/1.73m^2, a urine albumin-creatinine ratio ≥ 30 mg/g, or a self-reported physician diagnosis of CKD. The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation considering race, gender and creatinine.[22,23]

Anemia was defined as a hemoglobin < 13 g/dL in men, an Hb < 12 g/dL in women, or a self-reported physician diagnosis of anemia.[11]

Osteoporosis was defined as T-score of lumbar region, total femur, or femoral neck ≤ −2.5, Osteopenia was defined as −2.5 < T-score of lumbar region, total femur,

or femoral neck ≤ −1. T-score was calculated according to the equations of Looker et al considering bone mineral density and gender.[24]

Depression was defined according to the patient health questionnaire, which was a brief tool to assess the presence and severity of depressive symptoms (Supplementary Method). The severity of depression included none (≤ 4), mild (5 ~ 9), moderate (10 ~ 14), moderately-severe (15 ~ 19) and severe (≥ 20).[25]

Arthritis, cancer (Supplementary Method), congestive heart failure (CHF), coronary disease, stroke, asthma, chronic bronchitis and emphysema were diagnosis according to self-reported physician diagnosis.

Statistical Analysis

Clinical and demographic characteristics of subject with and without COPD were reported and compared using *t*-test for continuous variables and Chi-square test for categorical variable. Prevalence of 14 diseases in the COPD and non-COPD populations were compared using Chi-square test. The associations between decrease of lung function indices and diseases were assessed using logistic regression model in COPD and non-COPD groups, respectively, with age, gender, race, BMI, education level, income level, smoking status, alcohol use, macronutrient intake (protein, carbohydrate, total fat), eosinophils percent (EOS%), neutrophils percent (NEU%), hypertension, DM and dyslipidemia as covariates. Calcium intake was also included as a covariate in the model for osteoporosis. FEV_1% predicted and FVC% predicted were analyzed as categorical variables in the logistic regression models, and the largest group was selected as reference group when the indices were analyzed as dummy variables. Cox proportional hazards model was used to evaluate the association between the reduced lung

Table 2 Prevalence of 14 Diseases in Subjects With and Without COPD

Diseases	Entire Cohort	COPD	Non-COPD	χ^2	*P*
Hypertension	5012 (37.86)	952 (52.89)	4060 (35.50)	199.91	<0.001
DM	2092 (15.80)	386 (21.44)	1706 (14.92)	49.81	<0.001
Dyslipidemia*	8255 (63.03)	1197 (67.02)	7058 (62.40)	14.11	<0.001
MS	3318 (25.07)	518 (28.78)	2800 (24.48)	15.28	<0.001
CHF	250 (1.89)	76 (4.22)	174 (1.52)	61.22	<0.001
Coronary disease	654 (4.94)	198 (11.00)	456 (3.99)	162.86	<0.001
Stroke	302 (2.28)	75 (4.17)	227 (1.98)	33.21	<0.001
CKD	1910 (14.43)	407 (22.61)	1503 (13.14)	112.95	<0.001
Anemia	1324 (10.00)	180 (10.00)	1144 (10.00)	0.00	1.000
Arthritis*	3140 (23.72)	671 (37.28)	2469 (21.59)	211.53	<0.001
Cancer	998 (7.54)	275 (15.28)	723 (6.32)	178.96	<0.001
Obesity*					
Underweight	183 (1.39)	42 (2.35)	141 (1.24)	78.42	<0.001
Normal	3664 (27.82)	594 (33.24)	3070 (26.97)		
Overweight	4417 (33.53)	637 (35.65)	3780 (33.20)		
Obesity	4908 (37.26)	514 (28.76)	4394 (38.59)		
Osteoporosis					
Normal	8093 (61.14)	899 (49.94)	7194 (62.90)	167.19	<0.001
Osteopenia	3403 (25.71)	508 (28.22)	2895 (25.31)		
Osteoporosis	1741 (13.15)	393 (21.83)	1348 (11.79)		
Depression*					
None	9341 (76.52)	1267 (76.23)	8074 (76.56)	7.53	0.110
Mild	1815 (14.87)	263 (15.82)	1552 (14.72)		
Moderate	647 (5.30)	88 (5.29)	559 (5.30)		
Moderately-Severe	294 (2.41)	26 (1.56)	268 (2.54)		
Severe	111 (0.91)	18 (1.08)	93 (0.88)		

Note: *There were some missing data in these diseases.

function and all-cause mortality after adjusting for the previous covariates asthma, emphysema, chronic bronchitis, and 14 extra-pulmonary diseases. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, North Carolina). *P* values < 0.05 were considered statistically significant.

Results

Characteristics of the Study Population

The demographic characteristics and lung function indices of COPD and non-COPD groups were presented in Table 1. Compared with the non-COPD population, COPD patients were more likely to be elder, men, non-Hispanic white and smoker, and had lower level of BMI, education, FEV_1, FVC, FEV_1/FVC, FEV_1% predicted, FVC% predicted, EOS% and NEU% (*P* <0.05). Income level was not significantly different in 2 groups.

Prevalence of Diseases in the COPD and Non-COPD Population

Compared with the non-COPD population, COPD patients have a higher prevalence of hypertension, DM, dyslipidemia, MS, CHF, coronary disease, stroke, CKD, arthritis, cancer, underweight and osteoporosis. Conversely, obesity was more common in the non-COPD population. There was no significant difference in the prevalence of anemia and depression between the 2 groups (Table 2).

Association Between Decrease of Lung Function and Diseases

In COPD patients, the decrease of FEV_1% predicted and FVC% predicted was significantly associated with higher odds of having hypertension, DM, obesity, MS, CHF, coronary disease and depression (odds ratio [OR] > 1, *P*<0.05) after adjusting for a series of covariates (Figure 1). In the non-COPD population, the decrease of FEV_1% predicted and FVC% predicted were also related with higher odds of having 11 diseases after adjusting for a series of covariates, including hypertension, DM, obesity, dyslipidemia, MS, CHF, coronary disease, CKD, arthritis, osteoporosis and depression (Figure 2). The subgroup analysis for the non-COPD population showed that hypertension, obesity, CHF, coronary disease and depression were related with lung function in subjects aged ≥ 40, arthritis and osteoporosis were related with lung function

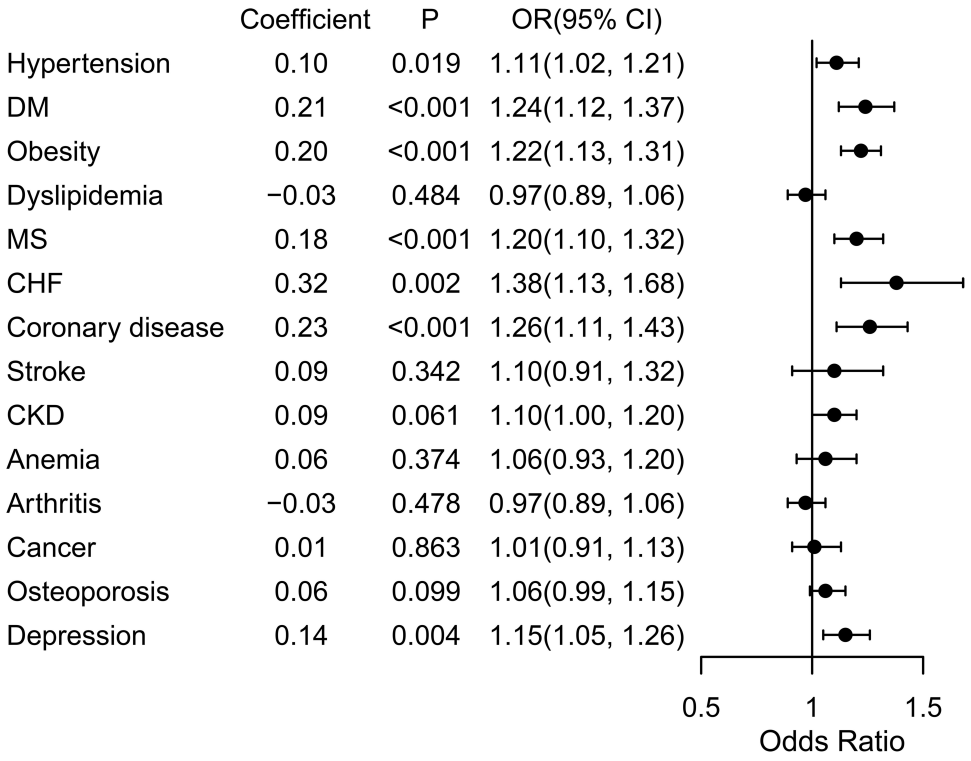

Figure 1 Associations between diseases and lung function in COPD patients after adjusting for multiple factors.
Notes: The following variables were removed from the logistic regression models to avoid collinearity because they are included in the definition of the corresponding diseases: MS: hypertension, DM, dyslipidemia; dyslipidemia: gender; obesity: BMI; CKD: gender, race; anemia: gender.

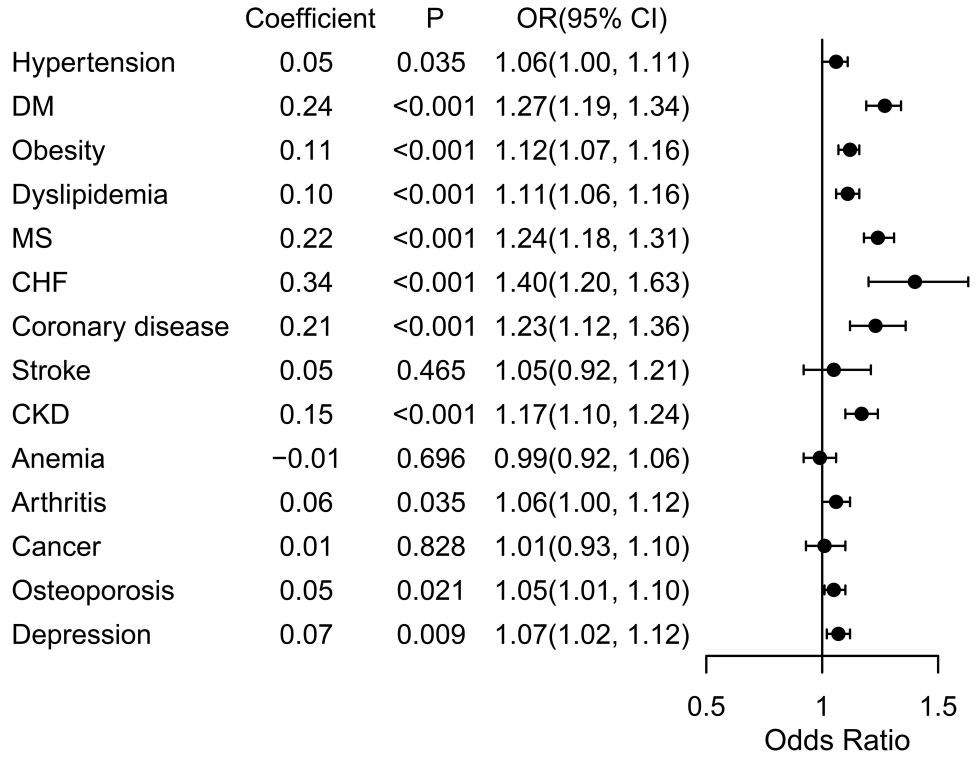

Figure 2 Associations between diseases and lung function in the non-COPD population after adjusting for multiple factors.
Notes: The following variables were removed from the logistic regression models to avoid collinearity because they are included in the definition of the corresponding diseases: MS: hypertension, DM, dyslipidemia; dyslipidemia: gender; obesity: BMI; CKD: gender, race; anemia: gender.

in subjects aged < 40, and DM, dyslipidemia, MS and CKD were related with lung function in both populations (Supplementary Figure 1).

By comparing subject groups of lower lung function with the largest quartile, we found that the odds of these diseases were gradually increased in both the COPD and non-COPD populations (Supplementary Figures 2–5).

Association Between Decrease of Lung Function and All-Cause Mortality

Association of the decrease of FEV_1% predicted and FVC % predicted with all-cause mortality were presented in Table 3 and Supplementary Figure 6. As indicated by hazard ratio (HR) and *P* value, subjects with lower FEV_1 % predicted and FVC% predicted had a higher risk of all-

Table 3 The Impact of Lung Function on All-Cause Mortality in the COPD and Non-COPD Population

Lung Function Indices		COPD			Non-COPD		
		b	*P*	HR (95% CI)	b	P	HR (95% CI)
FEV_1% predicted[a]	1	1.62	<0.001	5.07 (2.67, 9.61)	0.38	0.033	1.46 (1.03, 2.08)
	2	1.44	<0.001	4.21 (2.22, 7.99)	0.41	0.011	1.5 (1.1, 2.06)
	3	0.8	0.016	2.23 (1.16, 4.3)	0.18	0.236	1.2 (0.89, 1.61)
	4	1.08	<0.001	2.96 (1.57, 5.56)	Ref	Ref	1
	5	Ref	Ref	1	–	–	–
FVC% predicted[b]	1	0.93	<0.001	2.52 (1.55, 4.09)	0.44	0.014	1.56 (1.1, 2.22)
	2	0.72	0.003	2.06 (1.28, 3.32)	0.44	0.006	1.56 (1.14, 2.13)
	3	0.26	0.332	1.3 (0.77, 2.19)	0.32	0.039	1.37 (1.02, 1.86)
	4	Ref	Ref	1	Ref	Ref	1

Notes: [a]FEV_1% predicted in the COPD population: 1: < 60%, 2: 60% ~ 70%, 3: 70% ~ 80%, 4: 80% ~ 90%, 5: ≥ 90%; FEV_1% predicted in the non-COPD population: 1: < 80%, 2: 80% ~ 90%, 3: 90% ~ 100%, 4: ≥ 100%. [b]FVC% predicted in the COPD and non-COPD populations: 1: < 80%, 2: 80% ~ 90%, 3: 90% ~ 100%, 4: ≥ 100%.

cause mortality after adjusting for the multiple covariates and all diseases.

Discussion

In this analysis, we found that the decrease of FEV_1% predicted and FVC% predicted were independent risk factors for hypertension, DM, obesity, MS, CHF, coronary disease and depression in both the COPD and non-COPD populations. Furthermore, these 2 indices were related with dyslipidemia, CKD, arthritis and osteoporosis in the non-COPD population. In addition, the decrease of FEV_1 % predicted and FVC% predicted were independent risk factors for the increase of all-cause mortality. These risks were gradually increased with the decrease of lung function.

Some previous studies have reported the association of reduced lung function with extra-pulmonary diseases and mortality, mostly by comparing COPD patients with normal subjects.[5–7,26–29] The population in NHANES has also been used in some studies. Navaneethan et al reported patients with CKD had higher odds of COPD using NHANES 2007–2012.[5] The relation between decrease of lung function and MS has been reported using NHANES III (1988–1994) and NHANES 2007–2010.[27,28] Here, we also found the similar increased prevalence of comorbidities and mortality in COPD patients using NHANES 2007–2012. In contrast to the previous studies focused on COPD patients, the key finding of this study was that the decrease of lung function was also independent risk factor for some extra-pulmonary diseases and mortality in the non-COPD population.

The associations in our study may not be a causal relationship between the decrease of lung function and extra-pulmonary diseases. There are several plausible explanations for these associations. The decrease of lung function and diseases may share same risk factors, such as smoking, age, obesity, hypertension, nutritional status and systemic inflammation.[30,31] These factors may lead to the structural changes in both lung tissue and other biological systems, which will lead to reduced lung function, various diseases and increase of mortality.[32] However, the associations of reduced lung function and these diseases still remained statistically significant even after adjusting for these possible confounders. Systemic hypoxia caused by the decrease of lung function may also contribute to cell damage and systemic inflammatory reactions, which will further lead to multiple diseases.[33]

The decrease of lung function tended to have stronger associations with diseases and all-cause mortality among the COPD population than the non-COPD population. COPD can increase the mortality of population caused by other diseases, such as heart disease and cancer in this study. In the non-COPD population, the HR values were smaller than that of the COPD population. The possible reasons may be that COPD patients had poorer global health status, and the impact of reduced lung function on systemic hypoxia and the adverse effects were more severe in these patients.[33–35]

The present study has several limitations. First, the diagnosis of COPD was based on pre-bronchodilator spirometry test due to the lack of post-bronchodilator spirometry test, which may misdiagnose patients with reversible obstructive lung function as COPD patients, and overestimate the prevalence of COPD. Second, some subjects were excluded from the spirometry test, such as patients with recent chest pain, heart attack, stroke, surgery of eye, chest, or abdomen, and history of collapsed lung, aneurysm, or detached retina, which may exclude subjects with reduced lung function and lead to some biases in the results. Third, this was a cross-sectional study, which was unable to establish causal relationships between lung function and diseases and all-cause mortality. Finally, some unmeasured confounding could not be adjusted in the logistic and Cox models.

Conclusion

In conclusion, the decrease of FEV_1% predicted and FVC % predicted were related with higher risk of multiple diseases and all-cause mortality in both the COPD and non-COPD population, mainly including hypertension, DM, obesity, dyslipidemia, MS, CHF, coronary disease, CKD, arthritis, osteoporosis and depression. Most of these relations tended to be weaker in the non-COPD population compared with the COPD population when the results were statistically significant in the COPD population. The risk of stroke, anemia, and cancer was not related with the decrease of lung function.

Abbreviations

COPD, chronic obstructive pulmonary disease; FEV1% predicted, Forced expiratory volume in 1 second percent of predicted; FVC% predicted, forced vital capacity percent of predicted; DM, diabetes mellitus; NHANES, National Health and Nutrition Examination Survey; CDC, Centers for Disease Control and Prevention; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; MS, Metabolic syndrome; CKD, Chronic kidney

disease; CHF, congestive heart failure; EOS%, eosinophils percent; NEU%, neutrophils percent.

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Disclosure

The authors report no conflicts of interest in this work.

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