Relation of Chronic Obstructive Pulmonary Disease to Cardiovascular Disease in the General Population

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Chronic obstructive pulmonary disease (COPD) is a major health problem that contributes to substantial morbidity and mortality globally. This study investigated the relation between COPD and the risk of cardiovascular disease in the general population. We evaluated the cardiovascular effect of COPD using Korean National Health Insurance Service data from 2002 to 2013. We compared selected cardiovascular disease risk factors depending on pulmonary function using the Korean Health and Nutritional Examination Survey (KNHANES, n = 24,429) data. COPD was diagnosed in 11,771 patients (2.4%) in the National Health Insurance Service cohort. During the follow-up period (45.5 ± 14.9 months), subjects with COPD had lower cumulative survival rate for all-cause mortality, cardiovascular mortality, and sudden cardiac death (SCD, all p values <0.001). COPD was associated with an increased risk of all-cause mortality even after adjustment for potential confounding variables (hazard ratio [HR] 1.43, 95% confidence interval [CI] 1.33 to 1.55, p <0.001). However, COPD did not significantly increase the risk of cardiovascular mortality (HR 1.02, 95% CI 0.84 to 1.22, p = 0.876) and SCD (HR 1.07, 95% CI 0.79 to 1.44, p = 0.664) when adjusted for potential confounding variables. Analysis of the KNHANES cohort showed that systolic blood pressure, current smoking status, and Framingham risk score increased progressively with a decrease in pulmonary function (all p <0.001). In conclusion, COPD was associated with all-cause mortality, but not with cardiovascular mortality and SCD, whereas poor pulmonary function was associated with a heightened cardiovascular risk. **(Am J Cardiol 2017;120:1399–1404)**

Cardiovascular disease accounts for a sizeable proportion of morbidity and mortality in the chronic obstructive pulmonary disease (COPD) population.[1] Furthermore, COPD has also been shown to be an independent predictor of sudden cardiac death (SCD) in high-risk patients.[2–4] Although some studies have suggested that COPD may be a risk factor for SCD,[5] robust population-based data are scarce. Therefore, our objective was to assess whether COPD is an independent risk factor for cardiovascular mortality as well as SCD in the general population. Using data from the Korean National Health Insurance Service—National Sample Cohort (NHIS-NSC) and the Korea National Health and Nutrition Examination Survey (KNHANES), we estimated whether COPD increased the risk of all-cause mortality, cardiovascular mortality, and SCD. We also compared major cardiovascular risks related to cardiovascular events in subjects with varied pulmonary function test (PFT) results.

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Methods

Two large nationally representative databases were used. To assess the association of COPD with all-cause mortality, cardiovascular mortality, and SCD, we used data derived from the Korean NHIS-NSC, which consisted of 1,025,340 Koreans as an initial 2002 cohort and followed up the subjects until 2013. The National Health Insurance Service (NHIS) is the single insurer managed by the Korean government, and the majority of the Korean population (97.1%) is mandatory subscribers. All insured patients are required to undergo a periodic (i.e., mostly biennial) general health examination.[6] We enrolled 495,421 patients older than 18 years with health examination data from the NHIS-NSC after 2009 and analyzed the results of the follow-up until December 31, 2013 (Figure 1). To estimate the proportion of Korean adults with COPD who met the diagnostic criteria of the Global Initiative for Asthma guidelines and to analyze PFT results, data collected by the KNHANES from 2007 to 2014 were used. The KNHANES is a cross-sectional survey that has been assessing the health and nutritional status of Koreans. Details of KNHANES have been described previously.[7,8] We included 24,403 participants in the KNHANES older than 18 years (Supplementary Figure S1). Baseline characteristics of all KNHANES participants (those included in our study) are summarized in Supplementary Table S1. We searched for subjects with a diagnosis of COPD based on International Classification of Diseases—Tenth Revision (ICD-10) codes and prescribed medications because PFT results were not included in the NHIS-NSC. Patients with COPD were defined

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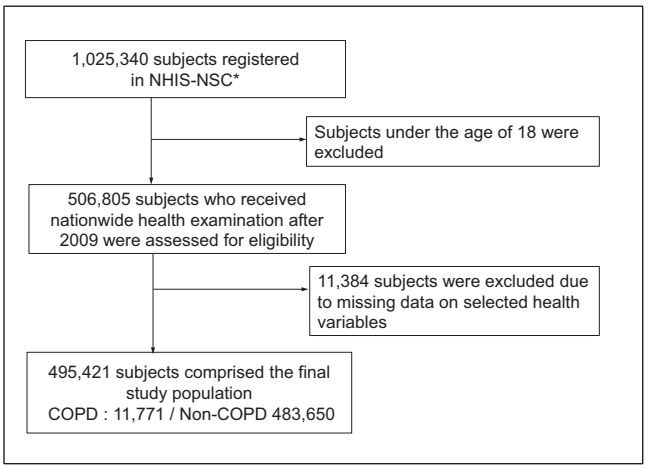

Figure 1. Flowchart of study population from the Korean National Health Insurance Service—National Sample Cohort.

as subjects who met the following 2 criteria: (1) subjects with a diagnosis of ICD-10 codes for COPD or emphysema (J42, J43 [except for J43.0], and J44) and (2) subjects with a prescription of more than 1 of the following COPD drugs at least twice per year: long-acting muscarinic antagonists, long-acting beta-2 agonists, inhaled corticosteroids, short-acting muscarinic antagonists, short-acting beta-2 agonists, or methylxanthine (>1 month).[9] Other co-morbidities (definitions are in Supplementary Table S2), such as hypertension and diabetes, were also identified from the medical claims according to the ICD-10 codes.

The primary clinical outcomes were all-cause mortality, cardiovascular mortality, and SCD. The subject's mortality information, along with the cause of death classified according to the ICD-10 codes, was included in the NHIS-NSC data, obtained from the Korean National Statistical Office. Any discharges from an inpatient clinic or an emergency department with a diagnosis of ICD-10 codes I46 (cardiac arrest) or I49.0 (ventricular fibrillation) were defined as an incident SCD.

Propensity score matching was used to reduce potential selection bias associated with an observational study.[10] The cases were matched (without replacement) with controls 1:1 based on the closest possible value of the propensity score (nearest-neighbor matching).[11]

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as counts and percentages. Student *t* test for continuous variables or chi-square test for categorical variables was used. Multivariable Cox models were applied to determine if there were independent associations between COPD and clinical outcomes. In the KNHANES data, PFT was analyzed as both a continuous and a categorical variable by forced expiratory volume in 1 second (FEV1). The subjects were divided into quartiles based on a percentage of the predicted normal FEV1 for a subject of the same gender, age, and height (% predicted FEV1). A p value of <0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences 23.0 (SPSS 23.0; IBM Corporation, Armonk, New York). The institutional review board of Severance Hospital at Yonsei University College of Medicine in Seoul, Republic of Korea, approved the present study. The institutional review board waived the requirement to obtain informed consent.

Results

Table 1 lists the baseline characteristics of the study population from the NHIS-NSC. The proportions of co-morbidities, including hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease or end-stage renal disease, previous myocardial infarction, previous stroke, malignancy, and smoking history were higher in the COPD group than in the non-COPD group (all p <0.001). After propensity score matching, we identified 11,755 patients with COPD and 11,755 matched controls without COPD. These 2 groups were well balanced

Table 1
Baseline characteristics of the study population

	Overall population before propensity score-matching				Propensity score-matched population			
	COPD (n = 11,771)	Non-COPD (n = 483,650)	p value	Standardized difference	COPD (n = 11,755)	Non-COPD (n = 11,755)	p value	Standardized difference
Age (years)	64.1 ± 12.8	47.4 ± 14.2	<0.001	1.179	64.1 ± 12.8	63.9 ± 13.3	0.293	0.015
Men	5,585 (47.5%)	239,903 (49.6%)	<0.001	-0.048	5,577 (47.4%)	5,588 (47.5%)	0.886	-0.002
Body mass index (kg/m^2)	23.9 ± 3.5	23.7 ± 3.3	<0.001	0.061	23.9 ± 3.5	24.0 ± 3.3	0.016	-0.029
Hypertension	6,717 (57.1%)	102,478 (21.2%)	<0.001	0.881	6,708 (57.1%)	6,816 (58.0%)	0.154	-0.021
Diabetes mellitus	4,314 (36.7%)	60,289 (12.5%)	<0.001	0.773	4,307 (36.7%)	4,409 (37.5%)	0.168	-0.021
Heart failure	1,743 (14.8%)	10,569 (2.2%)	<0.001	1.131	1,732 (14.8%)	1,596 (13.6%)	0.011	0.053
Dyslipidemia	5,383 (45.8%)	91,661 (19.0%)	<0.001	0.707	5,374 (45.7%)	5,508 (46.9%)	0.080	-0.025
CKD	1,950 (16.6%)	27,561 (5.7%)	<0.001	0.656	1,941 (16.5%)	1,877 (16.0%)	0.258	0.022
Previous MI	561 (4.8%)	4,473 (0.9%)	<0.001	0.926	557 (4.7%)	522 (4.4%)	0.275	0.038
Previous stroke	1,710 (14.5%)	17,478 (3.6%)	<0.001	0.833	1,703 (14.5%)	1,672 (14.2%)	0.564	0.012
Malignancy	2,408 (20.5%)	31,344 (6.5%)	<0.001	0.723	2,395 (20.4%)	2,340 (19.9%)	0.371	0.016
Smoking history	7,627 (64.8%)	301,686 (62.4%)	<0.001	0.058	7,628 (64.9%)	7,603 (64.7%)	0.210	0.005
Current smoker	2,046 (17.4%)	118,667 (24.5%)	<0.001	-0.240	2,046 (17.4%)	2,171 (18.5%)	0.210	-0.040

CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, MI = myocardial infarction.
Values are expressed mean ± standard deviation or number (%).