Smoking cessation after diagnosis of COPD is associated with lower all-cause and cause-specific mortality: a nationwide population-based cohort study of South Korean men

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Abstract

Background The most effective way to halt the advancement of COPD is smoking cessation. However, limited data are available on the question of whether quitting smoking within two years after COPD diagnosis reduces the risk of mortality. The goal of our research was to analyze the relationship between quitting smoking after COPD diagnosis and the risks of all-cause and cause-specific mortality, using the Korean National Health Insurance Service (NHIS) database.

Methods This study included 1,740 male COPD patients aged 40 years or more who had been newly diagnosed within the 2003–2014 time period and had smoked prior to their COPD diagnosis. The patients were categorized into two groups according to their smoking status after COPD diagnosis: (i) persistent smokers (ii) quitters (smoking cessation within two years of COPD diagnosis). Multivariate Cox proportional hazard regression was performed to determine the adjusted hazard ratio (HR) and 95% confidence interval (CI) for both all-cause and cause-specific mortality.

Results Among 1,740 patients (mean age, 64.6 years; mean follow-up duration, 7.6 years), 30.5% stopped smoking after COPD diagnosis. Quitters gained a 17% risk reduction in all-cause mortality (aHR, 0.83; 95% CI, 0.69–1.00) and a 44% risk reduction in cardiovascular mortality (aHR, 0.56; 95% CI, 0.33–0.95) compared with persistent smokers.

Conclusion Our study found that patients who quit smoking within two years after COPD diagnosis had lower risks of all-cause and cardiovascular mortality relative to persistent smokers. These results can be used to encourage newly diagnosed COPD patients to stop smoking.

Keywords Smoking cessation, Mortality, COPD, Newly diagnosed COPD, Quitting smoking

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Background

COPD is a respiratory disease caused by inhalation of harmful particles or gases that initiate abnormal inflammatory reactions in the lungs [1]. In 2020, the global prevalence of COPD among people between the ages of 30 and 79 years was 10.3%, among 391.9 million total sufferers [2]. Persistent smoking is the leading cause of COPD, and contributes to rapid decline of lung function [2, 3]. It has been suggested by various studies that quitting smoking is the most effective way to delay the advancement of COPD and improve impaired lung function [4]. Thus, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline instructs COPD patients to quit smoking using both behavioral therapy and pharmacological agents [5]. Individuals tend to follow this advice, in that that the likelihood of quitting smoking increases when diagnosed with a tobacco-related disease [6]. Similarly, after receiving information on COPD, 84.1% of high-risk smoking patients showed an increased willingness to quit smoking [7].

Despite numerous studies demonstrating the beneficial effect of smoking cessation on survival rates in individuals with COPD, accurate assessment of the long-term impact of smoking cessation on mortality has proved challenging, due to studies' limited sample sizes and short follow-up periods [8–10]. Nonetheless, it has been convincingly shown that smoking cessation has significant long-term benefits in terms of reducing mortality in young patients with asymptomatic COPD [11]. However, since most COPD patients do not seek medical advice until their condition has progressed significantly [12], it is important to show that smoking cessation at COPD diagnosis leads to reduced risk of mortality. In the present study, we evaluated the implementation of smoking cessation by comparing patients' smoking status before and after COPD diagnosis and analyzed the mortality risk reduction in those who had quit after COPD diagnosis. We aimed to examine the association of smoking cessation within two years of diagnosis with mortality compared to persistent smoking in newly diagnosed COPD male patients using the National Health Insurance Service (NHIS) database.

Methods

Data source

We obtained data from the Korean National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) database covering the period from January 2002 to December 2019. Since 1989, the NHIS has provided 97% of the Korean population with health coverage. Under the National Health Screening Program, it is recommended that all citizens 40 years old or older have a medical examination every two years. At that time, urine and blood tests, physical measurements, and a questionnaire about health behaviors and sociodemographic information are collected from participants and combined with hospital usage, death register information, and medication prescription data to create the NHIS-HEALS dataset using a random sampling method [13].

Study population

The study participants were male patients aged ≥ 40 years who had been newly diagnosed with COPD between January 2003 and December 2014. These newly diagnosed COPD patients were defined using the ICD-10 codes for COPD (J42.x–J44.x (except J430)), and all had been prescribed one or more of the following medications at least twice per year: LAMA (long acting muscarinic antagonist), LABA (long acting beta-2 agonist), ICS (inhaled corticosteroid), ICS plus LABA, SAMA (short acting muscarinic antagonist), SABA (short acting beta-2 agonist), methylxanthine, systemic corticosteroid or systemic beta-2 agonist [14]. As 89% of female COPD patients were never smokers [15], we excluded them from study participants.

Smoking status

Patients were divided into persistent smokers and quitters according to the pre-to-post-COPD-diagnosis continuation or change of smoking status, respectively. Patients' smoking status was assessed using self-reported questionnaires completed during health examinations before and after COPD diagnosis, respectively. In each questionnaire, patients had to select one response among "never-smoker," "former-smoker," and "current smoker." This study included only current smokers in the pre-diagnosis category so as to demonstrate the benefits of quitting smoking after COPD diagnosis. Among the pre-diagnosis current smokers, those who sustained their smoking habit after COPD diagnosis were classified as persistent smokers, and those reporting that they were former smokers after COPD diagnosis were classified as quitters.

Determination of outcomes

The study outcomes were all-cause and cause-specific mortality among patients who had quit smoking after COPD diagnosis compared with persistent smokers. Participants were selected based on the criterion of surviving a minimum of two years after their COPD diagnosis. The index date was two years after the COPD diagnosis. The cause of death was categorized using ICD-10 codes as cancer (C00-C97), cardiovascular disease (I00-I99) or respiratory disease (J00-J99), and more specifically, as lung cancer (C34), ischemic heart disease (I20-I25),

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stroke (I60-I69) or COPD (J42-J44). The follow-up period for all of the participants started at the index date and ended on the date of the participant's death or December 31st, 2019, whichever came first (Fig. 1).

Covariates

We adjusted for confounding by including the following factors in our analysis: age, household income, systolic blood pressure, total cholesterol, fasting serum glucose, alcohol consumption, physical exercise, body mass index (BMI), Charlson comorbidity index, and severity of COPD. Each variable except Charlson comorbidity index had been obtained from the post-COPD-diagnosis health examination (i.e., the second health examination). Household income had been recorded as deciles on the basis of the NHIS premium, and for the purposes of the present study, was divided into quartile levels. The 'severe COPD' group consisted of patients who had visited a tertiary hospital and been prescribed combinations of ICS+LABA+LAMA, ICS+LABA+systemic corticosteroid, or LAMA+systemic corticosteroid on more than one occasion. The remaining study subjects were classified as the "not severe" group [16]. The Charlson comorbidity index was calculated according to the ICD diagnostic codes recorded between 1 January, 2002 and the index date using the same algorithms as those reported in a previous study [17]

Statistical analysis

Baseline characteristics were presented as means with standard deviations for continuous variables and as numbers with percentages for categorical variables. We performed multivariate Cox proportional hazard regression to calculate the adjusted hazard ratio (HR) and 95% confidence interval (CI) for both all-cause mortality and cause-specific mortality based on smoking status after COPD diagnosis. Persistent smokers were the reference group, and so it was possible to evaluate the HR of quitters relative to persistent smokers. In this study, data were compiled and the statistical analysis was performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). The level of significance was a p-value below 0.05, which was determined using a two-sided approach.

In a supplementary analysis, population attributable fraction (PAF) and numbers needed to treat (NNT) were calculated using the adjusted HR by the method suggested in previous studies [18, 19].
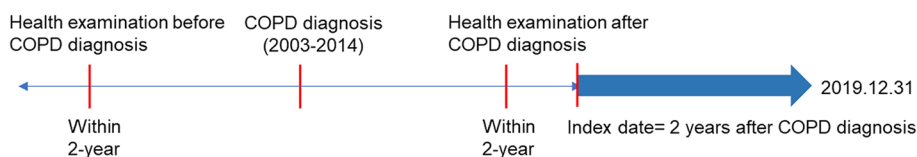
A subgroup analysis was performed for all-cause mortality risk according to smoking status as stratified by age group (<60 years, ≥60 years), alcohol consumption (No, Yes), Charlson comorbidity index (CCI score<3, CCI score≥3), severity of COPD (not severe, severe) and presence of hypertension, cancer or cardiovascular disease (yes, no for each). Presence of comorbidities was identified by analysis of information on inpatient and outpatient visits and prescription records for the period between 1 January, 2002 and the index date. A p score for interaction<0.1 was regarded as a significant interaction.
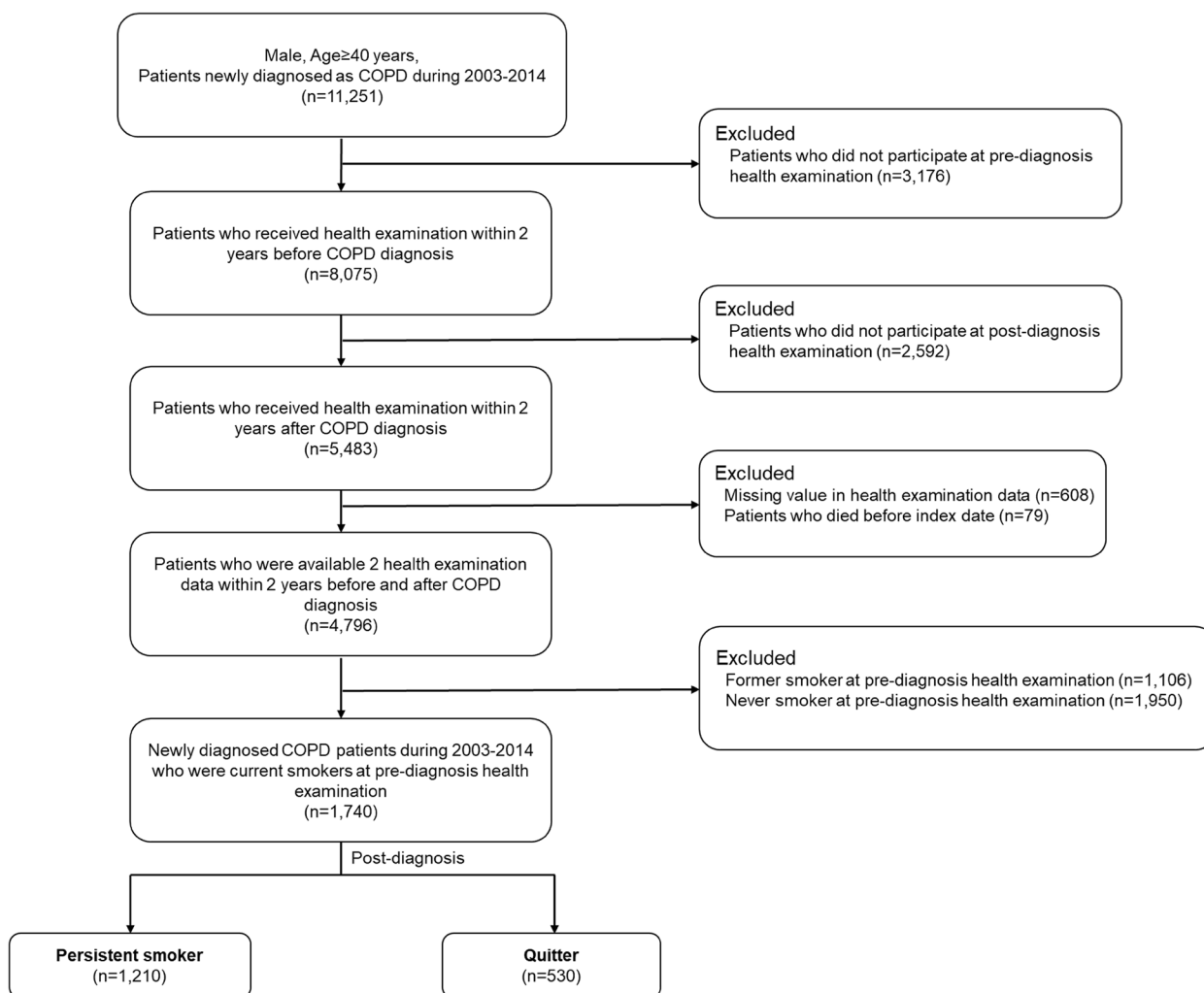
Results

Among 11,251 male patients aged 40 years or more who had been newly diagnosed with COPD between 2003 and 2014, 3,176 and 2,592 who did not undergo pre-diagnosis or post-diagnosis health examination, respectively, were excluded. Then, patients who had died (n=79) before the index date or for whom there were missing covariates (n=608) also were excluded. Finally, patients who had self-reported as former smokers (n=1,106) or never smokers (n=1,950) at the pre-diagnosis health examination were excluded as well. In total, 1,740 male patients who smoked at the time of their pre-diagnosis health examination and were newly diagnosed as COPD between 2003 and 2014 were included in this study (Fig. 2). The mean time span (standard deviation) between the first health examination and COPD diagnosis, between COPD diagnosis and the second health examination, and between the first and second health examination were 0.8(0.5), 0.9(0.6), and 1.8(0.6) years, respectively.

Among these 1,740 patients, 1,210 (69.5%) continued smoking after diagnosis of COPD, while 530 (30.5%) quit smoking. The baseline characteristics of the participants are presented in Table 1. Compared with persistent smokers, quitters were more likely to be older, drink alcohol less frequently, have higher systolic blood pressure, severe COPD, higher Charlson comorbidity index, and higher prevalence of cancer.

During a mean follow-up duration of 7.6 years (standard deviation: 3.8 years), 564 deaths occurred. Table 2 shows that those who quit smoking after COPD diagnosis

Fig. 1 Study design

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Fig. 2 Flow diagram of selection of study subjects

had a lower risk of all-cause (aHR, 0.83; 95% CI, 0.69–1.00) and cardiovascular (aHR, 0.56; 95% CI, 0.33–0.95) mortality relative to persistent smokers.

Table 3 presents the results of the stratified analysis examining the relationship between smoking cessation and all-cause mortality among the subgroups, based on age, alcohol consumption, Charlson comorbidity index, severity of COPD, presence of hypertension, cancer, and cardiovascular disease. Although most of the results were not statistically significant, the overall findings were in line with the main results. Patients without cardiovascular disease who quit smoking after their COPD diagnosis had a lower risk of all-cause mortality (aHR, 0.80; 95% CI, 0.66–0.98). There was no significant interaction between the effect of smoking cessation and the risk of all-cause mortality for any of the above-listed variables.

The supplementary analysis revealed that persistent smokers had a higher risk of all-cause mortality (aHR,

95% CI;1.20, 1.00–1.44) compared with quitters, with a population-attributable fraction of 11.4% and a "number needed to treat at ten-year follow up" of 21.0.

Discussion

In this retrospective cohort study using a nationwide database, we showed that subjects who had quit relatively soon (i.e., within two years) after COPD diagnosis had significantly lower all-cause and cardiovascular mortality risks relative to persistent smokers. The relative risk reduction for quitting smoking for all-cause and cardiovascular mortality was approximately 17 and 44%, respectively. The risk-reducing impact of quitting smoking did not vary significantly based on age, alcohol consumption, Charlson comorbidity index, severity of COPD, presence of hypertension, cancer or cardiovascular disease.

COPD diagnosis is significant, as it can serve as a wake-up call about the negative impacts of smoking on

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Table 1 Baseline characteristics of study population

	Total	Persistent smoker	Quitter	*p*-value
Number of participants	1,740	1,210 (69.5%)	530 (30.5%)	
Age, year, mean (SD)	64.6 (9.0)	63.8 (8.9)	66.7 (8.8)	**< 0.0001**
< 65 years, N (%)	883 (50.8%)	663 (54.8%)	220 (41.5%)	**< 0.0001**
≥ 65 years, N (%)	857 (49.2%)	547 (45.2%)	310 (58.5%)	
Household income, quartile, N (%)				0.5891
1st (highest)	458 (26.3%)	324 (26.8%)	134 (25.3%)	
2nd	542 (31.2%)	371 (30.7%)	171 (32.3%)	
3rd	431 (24.8%)	307 (25.4%)	124 (23.4%)	
4th (lowest)	309 (17.7%)	208 (17.1%)	101 (19.0%)	
Alcohol consumption, times per week, N (%)				**< 0.0001**
0	750 (43.1%)	455 (37.6%)	295 (55.7%)	
0–1	326 (18.8%)	231 (19.1%)	95 (17.9%)	
1–2	243 (14.0%)	193 (16.0%)	50 (9.4%)	
3–4	223 (12.8%)	176 (14.6%)	47 (8.9%)	
≥ 5	198 (11.3%)	155 (12.7%)	43 (8.1%)	
Physical exercise, times per week, N (%)				0.3817
0	972 (55.9%)	665 (55.0%)	307 (57.9%)	
1–2	448 (25.8%)	313 (25.9%)	135 (25.5%)	
≥ 3	320 (18.3%)	232 (19.1%)	88 (16.6%)	
Body mass index (BMI), kg/m², mean (SD)	22.9 (3.3)	22.9 (3.2)	23.0 (3.4)	0.5408
Systolic blood pressure, mmHG, mean (SD)	126.4 (16.0)	125.8 (15.9)	127.7 (16.2)	**0.0285**
Total cholesterol, mg/dL, mean (SD)	191.7 (38.9)	192.3 (38.6)	190.5 (39.4)	0.3643
Fasting serum glucose, mg/dL, mean (SD)	101.9 (26.8)	102.5 (28.2)	100.5 (23.2)	0.1295
Charlson comorbidity index, mean (SD)	3.9 (2.5)	3.8 (2.4)	4.2 (2.6)	**0.0040**
COPD severity				**0.0003**
Not severe	1,410 (81.0%)	1,008 (83.3%)	410 (77.4%)	
Severe	330 (19.0%)	202 (16.7%)	120 (22.6%)	
Hypertension				0.8281
No	1,355 (77.9%)	944 (78.0%)	402 (75.9%)	
Yes	385 (22.1%)	266 (22.0%)	128 (24.1%)	
Cardiovascular disease				0.2563
No	1,577 (90.6%)	1,103 (91.2%)	474 (89.4%)	
Yes	163 (9.4%)	107 (8.8%)	56 (10.6%)	
Cancer				**0.0275**
No	1,615 (92.8%)	1,134 (93.7%)	481 (90.8%)	
Yes	125 (7.2%)	76 (6.3%)	49 (9.2%)	

The chi-squared test was used to calculate the *p* values for the categorical variables, and analysis of variance (ANOVA) was used for continuous variables to compare baseline characteristics according to smoking status

respiratory health [7]. Early implementation of smoking cessation is highly important, as it can help to slow the progression of the disease [20] and reduce the risk of complications such as cardiovascular disease [21]. Our data showed that a significant number of patients who had recently been diagnosed with COPD continued to smoke afterwards (69.5%). In light of the fact that 11.4% of the COPD deaths in our study were attributed to persistent smoking, improving the cessation rate of COPD sufferers may contribute to prevention of future deaths.

Our study also indicated that successful quitting by 21 persistent smokers may result in the prevention of one case of death within 10 years. The results of our study could be used to support the current recommendation of smoking cessation and to remind smokers of the benefits of quitting smoking as near to the time of diagnosis as possible.

Two previous studies have investigated the effect of smoking status at a specific point in time on the outcome of COPD and found that ex-smokers had a higher survival

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Table 2 Association between smoking status and risks of all-cause, cause-specific mortality among newly diagnosed COPD patients

Group	Events	Person-years	Incidence Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*p*-value
All-cause mortality						**0.049**
Persistent smoker	379	9387	404	1 (Reference)	1 (Reference)	
Quitter	185	3975	465	1.16 (0.97–1.38)	**0.83 (0.69–1.00)**	
Cancer mortality						
Persistent smoker	148	9387	158	1 (Reference)	1 (Reference)	0.495
Quitter	77	3975	194	1.23 (0.94–1.62)	0.91 (0.68–1.21)	
Lung cancer mortality						
Persistent smoker	88	9387	94	1 (Reference)	1 (Reference)	0.998
Quitter	49	3975	123	1.32 (0.93–1.87)	1.00 (0.69–1.45)	
Cardiovascular mortality						
Persistent smoker	60	9387	64	1 (Reference)	1 (Reference)	**0.030**
Quitter	20	3975	50	0.79 (0.48–1.31)	**0.56 (0.33–0.95)**	
Ischemic heart disease mortality						
Persistent smoker	15	9387	16	1 (Reference)	1 (Reference)	0.068
Quitter	4	3975	10	0.63 (0.21–1.89)	0.34 (0.11–1.07)	
Stroke mortality						
Persistent smoker	24	9387	26	1 (Reference)	1 (Reference)	0.586
Quitter	10	3975	15	0.99 (0.47–2.07)	0.82 (0.38–1.76)	
Respiratory mortality						
Persistent smoker	83	9387	88	1 (Reference)	1 (Reference)	0.449
Quitter	44	3975	110	1.26 (0.88–1.82)	0.86 (0.59–1.27)	
COPD mortality						
Persistent smoker	51	9387	54	1 (Reference)	1 (Reference)	0.060
Quitter	18	3975	45	0.84 (0.49–1.44)	0.58 (0.33–1.02)	

Abbreviation: *HR* hazard ratio

The incidence rate is per 10,000 person-years. The adjusted HR was calculated by Cox proportional hazards regression analysis after adjustment for age, household income, alcohol consumption, physical exercise, BMI, systolic blood pressure, total cholesterol, fasting serum glucose, Charlson comorbidity index, and COPD severity

rate than persistent smokers [8, 22]. However, these studies could not determine whether smoking cessation after COPD diagnosis affects mortality. Three other studies have compared smoking status at two points in time, but included only an analysis of the post-COPD diagnosis period [9–11]. One of these, a clinical trial, convincingly showed that quitters had lower all-cause mortality compared with persistent smokers, but it had considered only young, asymptomatic COPD patients[11]. The other two studies showed similar results, but had included only a small number of patients with a short follow-up duration [9, 10]. In contrast to the previous studies, our study included newly diagnosed male COPD patients regardless of severity and investigated how smoking cessation affects mortality from various diseases, all of which are common causes of death in COPD patients.

The benefits of quitting smoking after COPD diagnosis appear to be similar to those for the general population in terms of lowering all-cause and cardiovascular mortality. Previous study on Asian populations have found that all-cause and cardiovascular mortality decreased in a dose–response manner with time since quitting [23]. Quitting smoking may not completely reverse impaired lung function in COPD patients [5], but it can still prevent, or at least delay, future deaths. Notwithstanding, the risk of cancer mortality was not significantly reduced in quitters relative to persistent smokers in the present study. A previous study involving mild-to-moderate COPD patients without symptoms found, consistently with the current results, that the relationship between quitting smoking and cancer mortality was uncertain within the first decade after smoking cessation [11]. To accurately determine the link between quitting smoking and cancer mortality in newly diagnosed COPD patients, a longer follow up will be necessary.

Multiple mechanisms may contribute to the increased mortality in COPD patients due to smoking. Smoking and inhalation exposure can increase the production of certain growth factors and lead to remodeling in the airway epithelium [24]. Also, smoking can deplete the levels of intraluminal secretory IgA, leading to macrophage accumulation and resultant peripheral lung inflammation

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Table 3 Stratified analysis of association between smoking status and all-cause mortality according to age, alcohol consumption, CCI, COPD severity, hypertension, cancer, and cardiovascular disease

Subgroup	Persistent smoker			Quitter			p-for interaction
Age group[a]	Number	Events	Adjusted HR (95% CI)	Number	Events	Adjusted HR (95% CI)	
Age < 65 years	663	105	1 (Reference)	220	34	0.89 (0.60–1.33)	0.792
Age ≥ 65 years	547	274	1 (Reference)	310	151	0.91 (0.74–1.12)	
Alcohol consumption[b]							
No	455	295	1 (Reference)	170	124	0.83 (0.65–1.06)	0.652
Yes	755	235	1 (Reference)	209	61	0.80 (0.59–1.07)	
CCI[c]							
CCI score < 3	442	133	1 (Reference)	170	49	0.78 (0.56–1.10)	0.557
CCI score ≥ 3	768	246	1 (Reference)	360	136	0.88 (0.71–1.10)	
COPD severity[d]							
Not severe COPD	1,008	316	1 (Reference)	402	63	0.86 (0.70–1.06)	0.42
Severe COPD	202	144	1 (Reference)	128	41	0.78 (0.50–1.21)	
Hypertension[e]							
No	944	234	1 (Reference)	411	116	0.85(0.67–1.08)	0.799
Yes	266	145	1 (Reference)	119	69	0.92(0.67–1.25)	
Cancer[e]							
No	1,134	340	1 (Reference)	481	163	0.84(0.69–1.02)	0.777
Yes	76	39	1 (Reference)	49	22	0.76(0.42–1.38)	
Cardiovascular disease[e]							
No	1,103	339	1 (Reference)	474	158	0.80 (0.66–0.98)	0.567
Yes	107	40	1 (Reference)	56	27	1.24 (0.69–2.22)	

Abbreviations: *HR* hazard ratio, *CI* confidence interval, *CCI* Charlson comorbidity index

[a] Values are represented as adjusted HR (95% CI) after adjusting for confounding factors (household income, alcohol consumption, physical exercise, BMI, systolic blood pressure, total cholesterol, fasting serum glucose, CCI, and COPD severity) other than age

[b] All confounding factors except for alcohol consumption using multivariate Cox proportional regression model

[c] All confounding factors except for CCI using multivariate Cox proportional regression model

[d] All confounding factors except for COPD severity using multivariate Cox proportional regression model

[e] All confounding factors (age, household income, alcohol consumption, physical exercise, BMI, systolic blood pressure, total cholesterol, fasting serum glucose, CCI, and COPD severity) using multivariate Cox proportional regression model

[25, 26]. It is suggested that peripheral lung inflammation induces "spill-over" of cytokines into systemic circulation [27] and worsens comorbid disease [26]. Smoking also causes vasodilatory dysfunction, increased thrombogenicity, and elevated levels of low-density lipoprotein [28–30]. After smoking cessation, coronary artery vasomotor function and airway hyperresponsiveness are improved [31, 32] and bronchial epithelial remodeling is reversed to some extent [33]. Smoking cessation, by alleviation of the acute inflammatory process, also can lead to reduced risk of COPD exacerbation [34] and improved bronchodilator response [35].

Our study has several limitations. First, a self-reported questionnaire was used to determine smoking status, which may not be completely reliable. Future studies should use more accurate methods such as urine cotinine or carboxyhemoglobin tests. Second, due to the limited number of participants who had undergone health examinations after the index date, we did not account for any

further changes in smoking behavior after the second health examination. Since it is common for people who have quit smoking to start smoking again [20], this could have caused underestimation of the beneficial effect of smoking cessation. Third, COPD severity was not based on the extent of restricted airflow. We attempted to compensate for this limitation by defining severe COPD based on the use of medication to treat COPD exacerbation. Fourth, due to missing data, our study did not consider the number of pack-years, which is the total amount of smoking exposure a person has experienced over time. Fifth, the findings of our study are limited to male patients and cannot be generalized to female patients. Finally, the number of cases where both pre- and post-diagnosis health checkups are conducted has decreased by over 50% as a result of many individuals not receiving health checkups twice in succession. ur study also has several strengths. First, it was conducted on a large, nationwide population in Korea. Second, we compared

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two time points before and after COPD diagnosis to determine the benefits of quitting smoking after being diagnosed with COPD. Third, our analysis considered a wide range of confounding factors in terms of sociodemographic variables. Fourth, the study participants were completely followed up from the index date until their date of death or until the end of the cohort period.

Conclusion

Quitting smoking within 2 years after COPD diagnosis was associated with lower risk of all-cause and cardiovascular mortality relative to persistent smokers. The results of our study suggest that quitting smoking after COPD diagnosis can lead to significant health benefits, and as such, support the current recommendation of smoking cessation.

Abbreviations

aHR   Adjusted hazard ratio
CI   Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-023-02533-1.

Additional file1: Supplementary Table 1.

Declarations

Ethics approval and consent to participate
This study, which was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB number: E-2108–136-1246), utilized the NHIS-HEALS database, the data from which were anonymized and kept confidential. Given the study's retrospective nature, informed consent for all study participants has been waived the Institutional Review Board of Seoul National University Hospital. All research procedures were carried out following the applicable guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References
1. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–65.
2. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. Lancet Respir Med. 2022;10(5):447–58.
3. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, Tashkin DP. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161(2 Pt 1):381–90.
4. Godtfredsen NS, Lam TH, Hansel TT, Leon ME, Gray N, Dresler C, Burns DM, Prescott E, Vestbo J. COPD-related morbidity and mortality after smoking cessation: status of the evidence. Eur Respir J. 2008;32(4):844–53.
5. Venkatesan P. GOLD report: 2022 update. Lancet Respir Med. 2022;10(2):e20.
6. Twardella D, Loew M, Rothenbacher D, Stegmaier C, Ziegler H, Brenner H. The diagnosis of a smoking-related disease is a prominent trigger for smoking cessation in a retrospective cohort study. J Clin Epidemiol. 2006;59(1):82–9.
7. Seo JY, Hwang YI, Mun SY, Kim JH, Kim JH, Park SH, Jang SH, Park YB, Shim JJ, Jung KS. Awareness of COPD in a high risk Korean population. Yonsei Med J. 2015;56(2):362–7.
8. Kanner RE, Renzetti AD Jr, Stanish WM, Barkman HW Jr, Klauber MR. Predictors of survival in subjects with chronic airflow limitation. Am J Med. 1983;74(2):249–55.
9. Kupiainen H, Kinnula VL, Lindqvist A, Postma DS, Boezen HM, Laitinen T, Kilpelainen M. Successful smoking cessation in COPD: association with comorbidities and mortality. Pulm Med. 2012;2012:725024.
10. Bai JW, Chen XX, Liu S, Yu L, Xu JF. Smoking cessation affects the natural history of COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:3323–8.
11. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142(4):233–9.
12 Kornmann O, Beeh KM, Beier J, Geis UP, Ksoll M, Buhl R. Newly diagnosed chronic obstructive pulmonary disease. Clinical features and distribution of the novel stages of the Global Initiative for Obstructive Lung Disease. Respiration. 2003;70(1):67–75.

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13. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, Kang HJ, Do CH, Song JS, Lee EJ, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open. 2017;7(9):e016640.

14. Kim J, Kim K, Kim Y, Yoo KH, Lee CK, Yoon HK, Kim YS, Park YB, Lee JH, Oh YM, et al. The association between inhaled long-acting bronchodilators and less in-hospital care in newly-diagnosed COPD patients. Respir Med. 2014;108(1):153–61.

15. Yoo KH, Kim YS, Sheen SS, Park JH, Hwang YI, Kim SH, et al. Prevalence of chronic obstructive pulmonary disease in Korea: the fourth Korean National Health and Nutrition Examination Survey, 2008. Respirology. 2011;16(4):659–65.

16. Kim J, Lee JH, Kim Y, Kim K, Oh YM, Yoo KH, Rhee CK, Yoon HK, Kim YS, Park YB, et al. Association between chronic obstructive pulmonary disease and gastroesophageal reflux disease: a national cross-sectional cohort study. BMC Pulm Med. 2013;13:51.

17. Chang J, Kim JA, Kim K, Choi S, Kim SM, Nam YY, Park S, Goo AJ, Park SM. Association of antipsychotics adherence and cardiovascular disease among newly diagnosed schizophrenia patients: a national cohort among Koreans. Asian J Psychiatr. 2020;52:102161.

18. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. Am J Epidemiol. 1974;99(5):325–32.

19. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999;319(7223):1492–5.

20. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, Kanner RE, O'Hara P, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1 The Lung Health Study. JAMA. 1994;272(19):1497–505.

21. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med. 2002;166(3):333–9.

22. Postma DS, Gimeno F, van der Weele LT, Sluiter HJ. Assessment of ventilatory variables in survival prediction of patients with chronic airflow obstruction: the importance of reversibility. Eur J Respir Dis. 1985;67(5):360–8.

23. Yang JJ, Yu D, Shu XO, Wen W, Rahman S, Abe S, Saito E, Gupta PC, He J, Tsugane S, et al. Reduction in total and major cause-specific mortality from tobacco smoking cessation: a pooled analysis of 16 population-based cohort studies in Asia. Int J Epidemiol. 2022;50(6):2070–81.

24. Zuo WL, Yang J, Gomi K, Chao I, Crystal RG, Shaykhiev R. EGF-Amphiregulin Interplay in Airway Stem/Progenitor Cells Links the Pathogenesis of Smoking-Induced Lesions in the Human Airway Epithelium. Stem Cells. 2017;35(3):824–37.

25. Polosukhin VV, Richmond BW, Du RH, Cates JM, Wu P, Nian H, Massion PP, Ware LB, Lee JW, Kononov AV, et al. Secretory IgA Deficiency in Individual Small Airways Is Associated with Persistent Inflammation and Remodeling. Am J Respir Crit Care Med. 2017;195(8):1010–21.

26. Sun J, Bao J, Shi Y, Zhang B, Yuan L, Li J, Zhang L, Sun M, Zhang L, Sun W. Effect of simvastatin on MMPs and TIMPs in cigarette smoke-induced rat COPD model. Int J Chron Obstruct Pulmon Dis. 2017;12:717–24.

27. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33(5):1165–85.

28. Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, Deanfield JE. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation. 1993;88(5 Pt 1):2149–55.

29. Fusegawa Y, Goto S, Handa S, Kawada T, Ando Y. Platelet spontaneous aggregation in platelet-rich plasma is increased in habitual smokers. Thromb Res. 1999;93(6):271–8.

30. Barua RS, Ambrose JA, Saha DC, Eales-Reynolds LJ. Smoking is associated with altered endothelial-derived fibrinolytic and antithrombotic factors: an in vitro demonstration. Circulation. 2002;106(8):905–8.

31. Morita K, Tsukamoto T, Naya M, Noriyasu K, Inubushi M, Shiga T, Katoh C, Kuge Y, Tsutsui H, Tamaki N. Smoking cessation normalizes coronary endothelial vasomotor response assessed with 15O-water and PET in healthy young smokers. J Nucl Med. 2006;47(12):1914–20.

32. Willemse BW, ten Hacken NH, Rutgers B, Lesman-Leegte IG, Timens W, Postma DS. Smoking cessation improves both direct and indirect airway hyperresponsiveness in COPD. Eur Respir J. 2004;24(3):391–6.

33. Lapperre TS, Sont JK, van Schadewijk A, Gosman MM, Postma DS, Bajema IM, Timens W, Mauad T, Hiemstra PS. Smoking cessation and bronchial epithelial remodelling in COPD: a cross-sectional study. Respir Res. 2007;8(1):85.

34. Au DH, Bryson CL, Chien JW, Sun H, Udris EM, Evans LE, Bradley KA. The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. J Gen Intern Med. 2009;24(4):457–63.

35. Anthonisen NR, Lindgren PG, Tashkin DP, Kanner RE, Scanlon PD, Connett JE. Bronchodilator response in the lung health study over 11 yrs. Eur Respir J. 2005;26(1):45.

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