Association between chronic obstructive pulmonary disease and chronic rhinosinusitis: a longitudinal follow-up study using a national health insurance database

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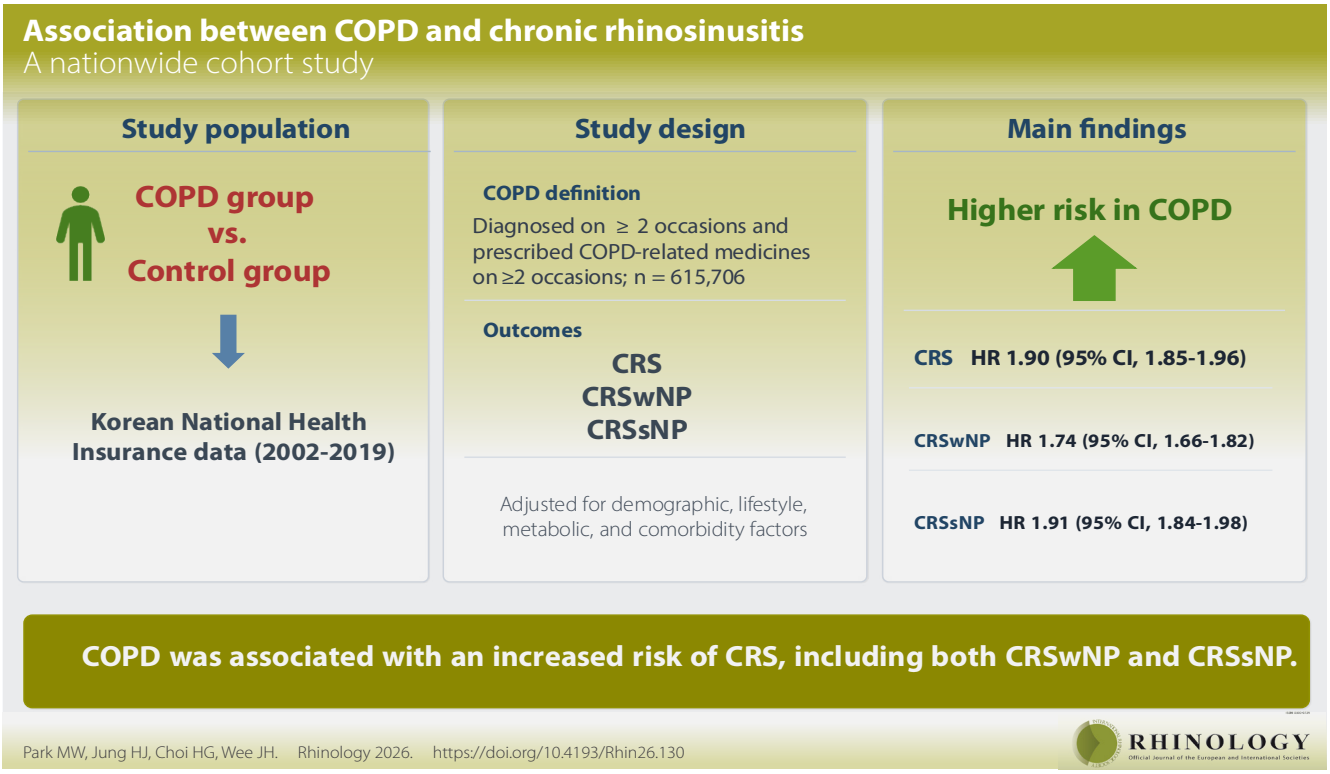


Abstract

Background: This study aimed to examine whether chronic obstructive pulmonary disease (COPD) is associated with the subsequent development of chronic rhinosinusitis (CRS) among Korean adults.

Methodology: Using the 2002–2019 Korean National Health Insurance database, we conducted a retrospective cohort study. Individuals with COPD, definted by relevant ICD-10 codes recorded on at least two occasions together with at least two prescriptions for COPD-related medicines (n=615,706), were matched with control participants (n=2,184,000) by age, sex, income, and region of residence. The incidence of CRS with and without nasal polyps was evaluated in both COPD and control groups. Hazard ratios (HRs) were estimated using stratified Cox proportional hazards models, and prespecified subgroup analyses were conducted.

Results: The incidence rate of CRS was higher in patients with COPD than in control participants. After adjustment, the HR for CRS was significantly higher in the COPD group compared with the control group. Likewise, the HRs for CRS with nasal polyps and CRS without nasal polyps were also significantly higher in the COPD group than in the control group. Statistical significance was observed in all subgroups according to age, sex, income, and region of residence. Kaplan–Meier analyses showed a higher cumulative incidence in participants with COPD.

Conclusions: In this nationwide Korean cohort, COPD was associated with a higher incidence of CRS, both with and without nasal polyps.

Key words: chronic obstructive pulmonary disease, cohort studies, nasal polyps, population surveillance, rhinosinusitis

Introduction

Anatomically, the upper and lower airways are continuous, even though they are often separated conceptually at the level of the vocal cords. The "global respiratory disease" framework proposes that disorders of the nose/sinuses and the bronchi frequently coexist because they can represent different expressions of shared airway inflammation [1-4].

Chronic obstructive pulmonary disease (COPD) is characterised by chronic respiratory symptoms and persistent airflow limitation, most commonly resulting from long-term exposure to noxious particles or gases such as tobacco smoke [5]. COPD is a leading cause of morbidity and mortality worldwide [6] with a particularly high burden in low- and milddle-income countries, and in South Korea its prevalence has increased over time (from 9.2% in 2009 to 16.7% in 2018) [7]. Although classically viewed as a lower-airway condition, accumulating data indicate that upper-airway involvement is common among patients with COPD [8-11]. A previous study reported that patients with asthma and COPD show increased nasal symptoms and more nasal inflammation [12].

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the sinonasal mucosa and paranasal sinuses. It is clinically heterogeneous and is typically categorised into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP), alongside multiple endotypes. From a pathophysiologic perspective, the upper and lower airways are increasingly viewed as a unified respiratory tract sharing common inflammatory mechanisms, epithelial barrier dysfunction, and environmental risk exposures [13]. Several epidemiological studies have shown that CRSwNP is associated with asthma and type 2 inflammation [14,15]. In a prospective population-based study, CRS is associated with increased odds of developing chronic bronchitis over a five-year follow-up period [16]. By contrast, the relationship between COPD–often associated with neutrophilic and mixed T_{H1}/T_{H17} inflammation–and CRS phenotypes (CRSwNP and CRSsNP) is less clearly defined. A Taiwanese population-based study reported an increased risk of CRSsNP among individuals with COPD [17], but it did not evaluate CRSwNP and had a shorter follow-up period. In addition, a small cross-sectional study [18] founded that 22.5% of patients with COPD have CRS; notably, all identified cases were CRSsNP, with no cases of CRSwNP observed. The majority of these patients are undiagnosed and untreated, which have adversely affected their quality of life (QoL). However, the small sample size and cross-sectional design limited the generalizability of the findings.

Given the global burden of both COPD and CRS and the geographic heterogeneity in airway inflammatory phenotypes, clarifying their longitudinal relationship in a nationwide cohort may contribute to the broader international understanding of multimorbid chronic airway disease. Using a nationwide Korean National Health Insurance Database (NHID), we assessed whether COPD is prospectively associated with incident CRS (overall, CRSwNP, and CRSsNP) in adults after matching for key demographic and socioeconomic factors.

Materials and methods

Ethics

The ethics committee of Hallym University (2021-02-004) permitted this study. Written informed consent was waived by the Institutional Review Board. All analyses adhered to the guidelines and regulations of the ethics committee of Hallym University. The detailed description of NHID in South Korea was described previously [19]. The NHID contains sociodemographic characteristics, health care utilization, dates of birth and death, and health screening for whole population of South Korea.

Exposure (chronic obstructive pulmonary disease)

ICD-10 codes were identified from both inpatient and outpatient claims data. COPD was defined using ICD-10 codes for emphysema (J43), and other COPD (J44), excluding MacLeod syndrome (J43.0), recorded on ≥ 2 visits, together with ≥ 2 prescriptions for COPD-related medications, in order to improve diagnostic specificity and reduce misclassification. Medications included long-acting muscarinic antagonists (LAMA), long-acting β2-agonists (LABA), inhaled corticosteroids (ICSs) combined with LABAs, short-acting muscarinic antagonist (SAMA), short acting beta-2 agonists (SABA), methylxanthine, phosphodiesterase-4 (PDE-4) inhibitor, and systemic β-agonists [20].

Outcome (chronic rhinosinusitis)

CRS was identified by a diagnosis of chronic sinusitis (ICD-10: J32). To increase specificity, we required ≥2 treatment visits and evidence of head and neck computed tomography (CT) (claim codes: HA401-HA416, HA441-HA443, HA451-HA453, HA461-HA463, or HA471-HA473). CRSwNP was defined with ICD-10 codes (J33); the remaining CRS cases were categorised as CRSsNP [21].

Participant selection

We obtained a customised NHID dataset covering 2002–2019. Individuals with COPD who visited a clinic or hospital on ≥2 occasions and received ≥2 COPD-related medications prescriptions were identified (n = 663,982). Controls were defined as participants without any ICD-10 codes J41, J42, J43 or J44 during 2002–2019 and randomly selected at approximately a 4:1 ratio, proportionate to the age and sex distribution of the COPD group (n = 2,525,984). Participants who have no records of health screening were excluded (n = 4,541 for COPD, n = 31,042 for Control). Participants who have no records of sociodemographic characteristics were excluded (n = 14,659 for COPD, n = 71,928 for Control). The index date for each COPD participants was the date of COPD treatment; for controls, an index date was as-

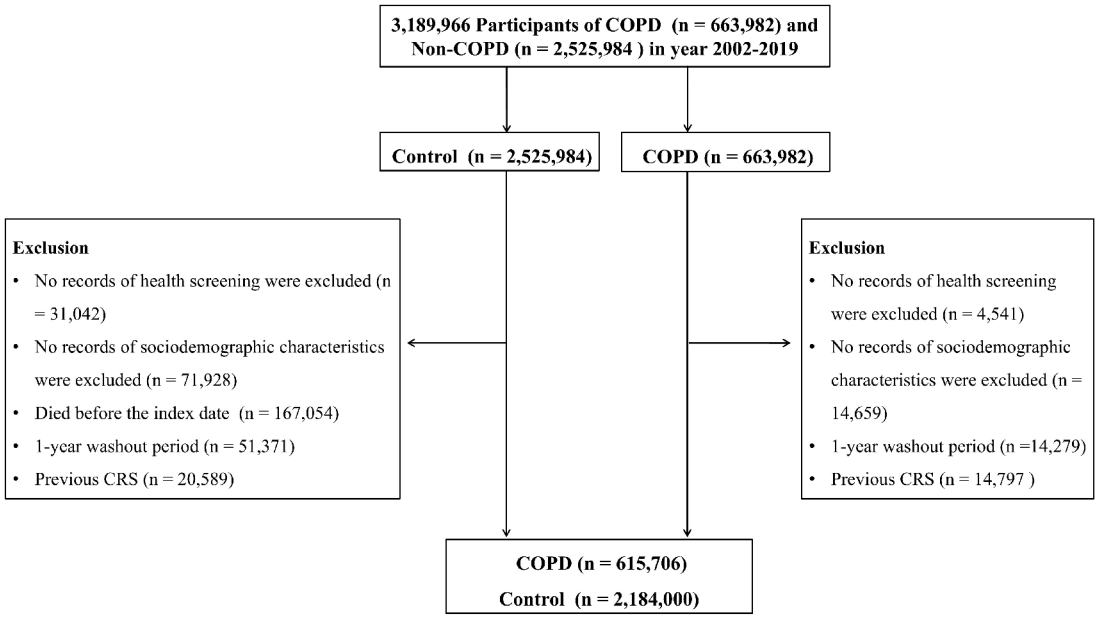


Figure 1. A schematic illustration of the participant selection process that was used in the present study. Of a total of 3,189,966 participants, 615,706 of participants with COPD and 2,184,000 of controls were included. Abbreviations: COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis.

signed to mirror the distribution of index dates within the same age- and sex-stratum. Controls who died before their assigned index date were excluded (n = 167,054). To ensure incident CRS, we applied a washout period by excluding CRS diagnoses in 2002 (n = 14,279 for COPD, n = 51,371 for Control) and removed participants with a history of the outcome before the index date (n = 14,797 for COPD, n = 20,589 for Control). The final analytic sample comprised 615,706 COPD participants and 2,184,000 controls (Figure 1). Thereafter, we analysed the incidence of CRS with and without nasal polyps in the COPD and control groups.

Covariates

Age was grouped in 5-year intervals (<20, 20-24, …, ≥85years). Income was categorised into five quintiles, with level 1 representing the lowest income group and level 5 representing the highest income group. Region of residence was classified according to administrative district as urban and rural, as in prior work [22]. Urban areas were defined as the seven metropolitan cities (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan), and rural areas as the remaining provinces (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju). Tobacco smoking, alcohol consumption, and obesity using BMI (body mass index, kg/m^2) were categorised using the same definitions as our previous study [23]. We also included systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), fasting blood glucose (mg/dL), and total cholesterol (mg/dL) from health screening data. Additional operational details have been reported previously [22,23]. Asthma was defined using ICD-10 codes for asthma (J45), and status asthmaticus (J46) with at least one asthma-related medications (inhaled, oral, or injected) or asthma-related test, based on a validated approach [24], and the Charlson Comorbidity Index (CCI) was calculated excluding respiratory diseases.

Statistical analyses

We used propensity score overlap weighting to balance measured covariates while retaining an effective sample size. The propensity score (PS) was estimated via multivariable logistic regression including all covariates. For overlap weighting, COPD participants received weights proportional to PS, and controls received weights proportional to 1-PS. This approach produces weight between 0 and 1 and is designed to achieve exact covariate balance while improving precision [25-27]. We compared baseline characteristics before and after weighting using standardised differences (SD).

To analyse the overlap weighted hazard ratios (HRs) of COPD for CRS / CRSwNP / CRSsNP, Propensity score overlap weighted cox proportional hazard regression model was used. In these analyses, crude (unadjusted) and overlap weighted model (adjusted for age, sex, income, region of residence, obesity, smoking, alcohol consumption, SBP, DBP, fasting blood glucose, total cholesterol, CCI scores, and asthma) were used.

For the subgroup analyses, we divided the participants by age

(<65 years old ≥65 years old), sex (male and female), income (low [levels 1-3] and high [level 4-5] income), and region of residence (urban and rural). Additional subgroup analyses were performed according to obesity, smoking status, alcohol consumption, blood pressure, fasting blood glucose, total cholesterol, CCI score, and asthma status; these results are presented in the Table S1. Obesity was classified according to BMI as underweight (<18.5 kg/m^2), normal (≥18.5 to <23 kg/m^2), overweight (≥23 to <25 kg/m^2), and obese (≥25 kg/m^2). Smoking status was categorised as non-smoker (<100 cigarettes throughout their entire life), past smoker (more than one-year smoke-free), and current smoker. Alcohol consumption was categorised according to self-reported drinking frequency as <1 time a week and ≥1 time a week. Blood pressure was classified as normal (SBP <140 mmHg and DBP <90 mmHg) and high (≥140 mmHg or DBP ≥90 mmHg). Fasting blood glucose and total cholesterol were each classified as normal (<100 mg/dL and <200 mg/dL, respectively) and high (≥100 mg/dL and ≥200 mg/dL, respectively). CCI scores were categorised as 0, 1, and ≥2. Asthma status was classified as no history of asthma and a history of asthma. As a sensitivity analysis, we computed E-values (and 95% CIs) to evaluate the robustness of the observed associations to potential unmeasured confounding [28]. If the relation between unmeasured confounder and the exposure/outcome was weaker than the E-value, the observed association between CRS and COPD could still be explained as robust to unmeasured confounding (Figure 2B). Time-to-event curves were generated using Kaplan–Meier methods and compared with log-rank tests.

All tests were two-sided, with statistical significance defined as $P < 0.05$. Analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows the general characteristics of the participants. Disparities were observed in the distributions of age, sex, income, region of residence, obesity, smoking status, alcohol consumption, SBP, DBP, fasting glucose level, total cholesterol, CCI scores, and the prevalence of asthma, with all SD values exceeding 0.01. After applying overlap weighting adjustments, all variables showed as an SD of 0.00, indicating no significant differences between COPD and control groups. Within COPD group, 0.93% showed CRS, while in the control group, 0.52% showed CRS (SD = 0.048).

The incidence rates of CRS were 1.43 per 1,000 person-years in the COPD group and 0.60 per 1,000 person-years in the control group (Table 2, Figure 2A). The HR for CRS was significantly higher (1.90, 95% CI = 1.85 – 1.96) in the COPD group compared to control group, after adjusting for age, sex, income, region of residence, obesity, smoking status, alcohol consumption, SBP, DBP, fasting blood glucose, total cholesterol, CCI scores, and asthma

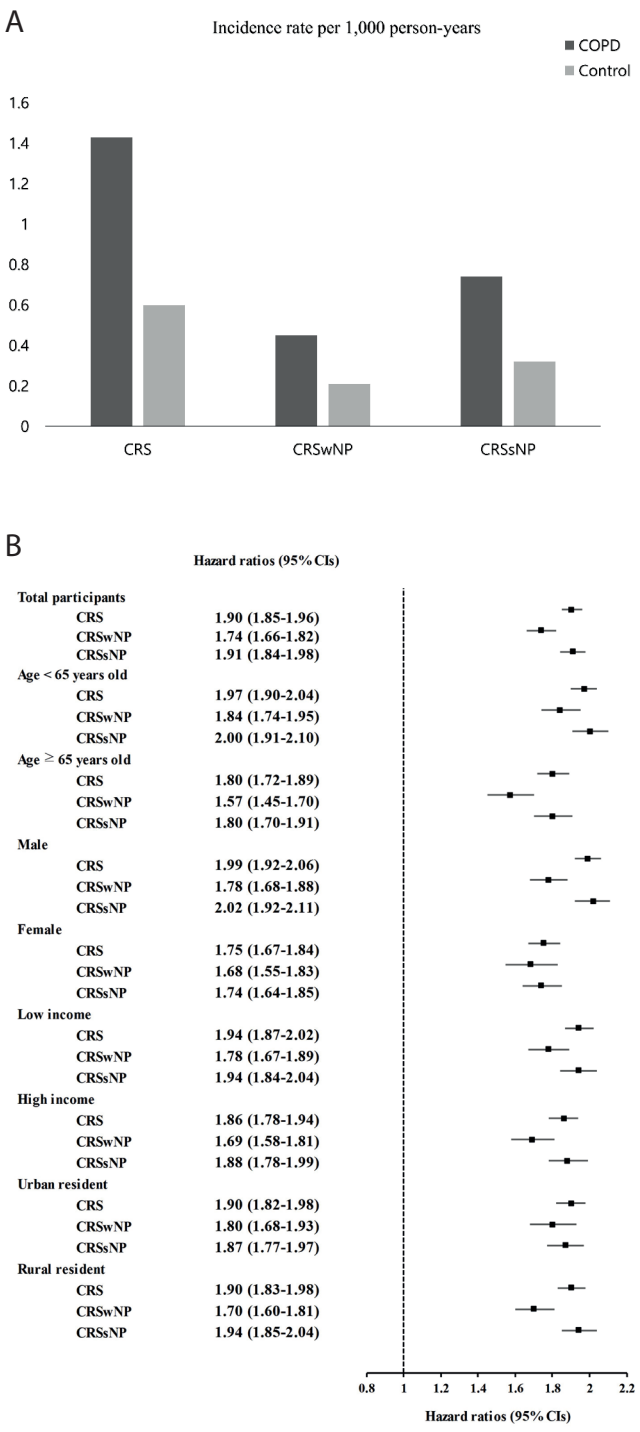


Figure 2. Comparison of CRS, CRSwNP, and CRSsNP between the COPD and control groups. (A) Incidence rates per 1,000 person-years. (B) Overlap propensity score weighted hazard ratios with 95% confidence intervals, including subgroup analyses according to age, sex, income, region of residence. The corresponding E-values for the overall associations were 3.21 (95% CI, 3.10–3.33) for CRS, 2.87 (95% CI, 2.71–3.04) for CRSwNP, and 3.23 (95% CI, 3.08–3.37) for CRSsNP. Abbreviations: COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyps; CI, confidence interval.

Table 1. General characteristics of participants.

Characteristics		Before overlap weighting adjustment			After overlap weighting adjustment		
		COPD	Control	Standardized difference	COPD	Control	Standardized difference
Age group, years				0.230			0.000
	< 20	27 (0.0)	105 (0.0)		16 (0.0)	16 (0.0)	
	20-24	574 (0.1)	2,270 (0.1)		356 (0.1)	356 (0.1)	
	25-29	2,673 (0.4)	10,633 (0.5)		1,605 (0.5)	1,605 (0.5)	
	30-34	5,255 (0.8)	20,832 (0.9)		3,171 (0.9)	3,171 (0.9)	
	35-39	7,532 (1.2)	30,059 (1.4)		4,515 (1.3)	4,515 (1.3)	
	40-44	14,188 (2.3)	56,784 (2.6)		8,385 (2.4)	8,385 (2.4)	
	45-49	25,408 (4.1)	101,796 (4.7)		14,773 (4.3)	14,773 (4.3)	
	50-54	41,934 (6.8)	166,821 (7.6)		24,132 (7.0)	24,132 (7.0)	
	55-59	64,089 (10.4)	253,956 (11.6)		36,781 (10.7)	36,781 (10.7)	
	60-64	87,963 (14.3)	345,000 (15.8)		50,324 (14.6)	50,324 (14.6)	
	65-69	111,026 (18.0)	418,685 (19.2)		63,276 (18.3)	63,276 (18.3)	
	70-74	110,664 (18.0)	376,905 (17.3)		61,442 (17.8)	61,442 (17.8)	
	75-79	82,595 (13.4)	245,392 (11.2)		44,409 (12.9)	44,409 (12.9)	
	80-84	43,227 (7.0)	112,104 (5.1)		22,469 (6.5)	22,469 (6.5)	
	85+	18,551 (3.0)	42,658 (1.9)		9,402 (2.7)	9,403 (2.7)	
Sex				0.054			0.000
	Male	388,656 (63.1)	1,316,350 (60.3)		208,916 (60.5)	208,916 (60.5)	
	Female	227,050 (36.9)	867,650 (39.7)		136,141 (39.4)	136,141 (39.4)	
Income				0.073			
	1 (lowest)	138,028 (22.4)	448,479 (20.5)		74,667 (21.6)	74,667 (21.6)	
	2	112,689 (18.3)	380,947 (17.4)		61,593 (17.8)	61,593 (17.8)	
	3	115,011 (18.7)	398,828 (18.3)		64,017 (18.5)	64,017 (18.5)	
	4	114,637 (18.6)	411,233 (18.8)		64,856 (18.8)	64,856 (18.8)	
	5 (highest)	135,341 (22.0)	544,513 (24.9)		79,924 (23.2)	79,924 (23.2)	
Region of residence				0.209			0.000
	Urban	211,258 (34.3)	971,485 (44.5)		129,468 (37.5)	129,468 (37.5)	
	Rural	404,448 (65.7)	1,212,515 (55.5)		215,589 (62.5)	215,589 (62.5)	
Obesity [a]				0.169			0.000
	Underweight	38,390 (6.2)	70,324 (3.2)		16,623 (4.8)	16,623 (4.8)	
	Normal	232,504 (37.8)	766,446 (35.1)		125,586 (36.4)	125,586 (36.4)	
	Overweight	143,148 (23.2)	573,701 (26.3)		84,106 (24.4)	84,106 (24.4)	
	Obese I	178,147 (28.9)	700,362 (32.1)		105,612 (30.6)	105,612 (30.6)	
	Obese II	23,517 (3.8)	73,167 (3.3)		13,130 (3.8)	13,130 (3.8)	
Smoking status				0.280			0.000
	Non-smoker	335,714 (54.5)	1,394,186 (63.8)		204,265 (59.2)	204,265 (59.2)	
	Past smoker	92,335 (15.0)	387,171 (17.7)		54,921 (15.9)	54,921 (15.9)	
	Current smoker	187,657 (30.5)	402,643 (18.4)		85,870 (24.9)	85,870 (24.9)	
Alcohol consumption				0.065			0.000
	<1 time a week	426,765 (69.3)	1,447,564 (66.3)		237,992 (69.0)	237,992 (69.0)	
	≥1 time a week	188,941 (30.7)	736,436 (33.7)		107,064 (31.0)	107,064 (31.0)	
SBP		128.14 ± 17.21	129.41 ± 17.16	0.074	128.53 ± 12.93	128.53 ± 6.72	0.000
DBP		78.22 ± 10.68	78.61 ± 10.69	0.036	78.28 ± 8.00	78.28 ± 4.22	0.000

Table 1 *continued*.

Characteristics	Before overlap weighting adjustment			After overlap weighting adjustment		
	COPD	Control	Standardized difference	COPD	Control	Standardized difference
Fasting blood glucose	101.52 ± 29.61	105.03 ± 32.06	0.114	102.75 ± 23.95	102.75 ± 11.06	0.000
Total cholesterol	193.34 ± 39.5	195.57 ± 39.3	0.057	194.13 ± 29.70	194.13 ± 15.64	0.000
CCI score	1.48 ± 1.96	1.05 ± 1.72	0.237	1.33 ± 1.37	1.33 ± 0.78	0.000
Asthma	438,462 (71.2)	376,791 (17.2)	1.294	188,165 (54.5)	188,165 (54.5)	0.000
CRS	6,044 (1.0)	9,742 (0.4)	0.063	3,196 (0.9)	1,782 (0.5)	0.048
CRSwNP	2,278 (0.4)	3,833 (0.2)	0.036	1,183 (0.3)	698 (0.2)	0.027
CRSsNP	3,766 (0.6)	5,909 (0.3)	0.051	2,013 (0.6)	1,085 (0.3)	0.040

CCI, Charlson Comorbidity Index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; PS, Propensity score; CRS, Chronic rhinosinusitis; CRSwNP, CRS with nasal polyps; CRSsNP, CRS without nasal polyps. Categorical variables are presented as n (%), and continuous variables as mean ± standard deviation. [a] Obesity (BMI, body mass index, kg/m^2) was categorized as underweight (<18.5), normal (≥18.5 to <23), overweight (≥23 to <25), obese I (≥25 to <30), and obese II (≥30).

(P < 0.001; Table 2, Figure 2B). In addition, the HRs of CRSwNP (1.74, 95% CI = 1.66 – 1.82) and CRSsNP (1.91, 95% CI = 1.84 – 1.98) were also significantly higher in the COPD group than the control group. Statistical significance was seen in all subgroups according to age, sex, income, and region of residence (Table 2, Figure 2B).

Subgroup analyses according to other covariates (obesity, smoking, alcohol consumption, blood pressure, fasting blood glucose, total cholesterol, CCI scores, and asthma) are shown in Supplementary Table S1. The HR for CRS, CRSwNP, and CRSsNP were significantly higher in the COPD group compared with control group in all subgroup analyses.

Figure 3 contains the Kaplan–Meier curves of patients with COPD versus controls for CRS (Figure 3A), CRSwNP (Figure 3B), and CRSsNP (Figure 3C). The incidence probabilities of CRS, CRSwNPs, and CRSsNP in subjects with COPD were significantly higher than those without COPD (each P < 0.001, log-rank test).

Discussion

In this nationwide cohort with 18 years of follow-up (615,706 COPD patients and 2.18 million matched controls), COPD was associated with a higher subsequent risk of incident CRS. Using propensity score overlap weighting to ensure exact balance across measured covariates, the COPD group showed a higher CRS incidence rate (1.43 vs 0.60 per 1,000 person-years) and a consistently elevated hazard of CRS (HR 1.90). Importantly, the association was observed for both CRS phenotypes—CRSwNP (HR 1.74) and CRSsNP (HR 1.91)—and remained consistent across strata of age, sex, income, and region of residence. These findings support a robust epidemiologic link between COPD and CRS within a longitudinal framework.

In the present study, the HR of CRS in COPD was 1.90, which is directionally consistent with but lower than the HR of 3.245 for CRSsNP reported in Taiwan [11]. Although the Taiwanese study did not examine CRSwNP separately, differences in case definitions, environmental exposures, and ethnic genetics may account for the magnitude gap. While prior studies have emphasised the close CRS–asthma relationship, evidence linking COPD to CRS has been comparatively limited and has often been restricted to CRSsNP [10,17,18]. Our findings add to the literature by demonstrating increased risk for both CRSwNP and CRSsNP among individuals with COPD. This pattern suggests that the association between COPD and CRS is not confined to a single inflammatory pathway, and it fills this gap by demonstrating that the risk of CRSwNP is also elevated in COPD. COPD is heterogeneous, and a proportion of patients may exhibit eosinophilic inflammation or asthma–COPD overlap features [29], which could partly explain the signal in CRSwNP. Shared epithelial injury and impaired mucociliary clearance from smoking and other exposures may also promote chronic sinonasal inflammation across phenotypes.

Several mechanisms could plausibly connect COPD and CRS. First, two diseases may share risk factors, including cigarette smoking and biomass exposure, which impair mucociliary clearance in both bronchi and sinonasal epithelium [5,13]. Second, both diseases are systemic and local inflammatory diseases. COPD is characterised by spillover of neutrophil cytokines (IL-6, IL-8) [30] and recent study suggests that the C3-CD163 axis is a common cause of CRS and COPD complications [31]. Third, colonisation with *Haemophilus influenzae* and *Pseudomonas aeruginosa* has been reported in both diseases [32,33], suggesting bidirectional seeding. Lastly, polymorphisms in MMP-9, TGF-β1, and SERPINA1 have been variably linked to airway remodelling in COPD [34] and CRSwNP [35], although evidence remains

Table 2. Crude and overlap propensity score weighted hazard ratios (95% confidence interval) of Chronic Obstructive Pulmonary Disease for CRS / CRSwNP / CRSsNP with subgroup analyses according to age, sex, income, region of residence.

		IR per 1,000 person-year	IRD per 1000 person-years (95% CI)	Hazard ratios for CRS / CRSwNP / CRSsNP			
				Crude	P-value	Overlap weighted model [b]	P-value
Total participants (n = 2,799,706)							
CRS	COPD	1.43	0.83 (0.80 to 0.86)	2.34 (2.27-2.42)	<0.001[a]	1.90 (1.85-1.96)	<0.001[a]
	COPD	0.60		1		1	
		Control					
CRSwNP	COPD	0.45	0.24 (0.22 to 0.25)	2.12 (2.01-2.23)	<0.001[a]	1.74 (1.66-1.82)	<0.001[a]
	COPD	0.21		1		1	
	Control						
CRSsNP	COPD	0.74	0.42 (0.40 to 0.44)	2.28 (2.19-2.37)	<0.001[a]	1.91 (1.84-1.98)	<0.001[a]
	Control	0.32		1		1	
Age <65 years old (n =1,237,899)							
CRS							
	COPD	1.92	1.19 (1.15 to 1.24)	2.61 (2.51-2.72)	<0.001[a]	1.97 (1.90-2.04)	<0.001[a]
	Control	0.73		1		1	
CRSwNP							
	COPD	0.74	0.45 (0.42 to 0.48)	2.53 (2.38-2.70)	<0.001[a]	1.84 (1.74-1.95)	<0.001[a]
	Control	0.29		1		1	
CRSsNP							
	COPD	1.05	0.64 (0.61 to 0.68)	2.55 (2.42-2.69)	<0.001[a]	2.00 (1.91-2.10)	<0.001[a]
	Control	0.41		1		1	
Age ≥65 years old (n =1,561,807)							
CRS							
	COPD	1.00	0.53 (0.49 to 0.57)	2.08 (1.97-2.19)	<0.001[a]	1.80 (1.72-1.89)	<0.001[a]
	Control	0.47		1		1	
CRSwNP							
	COPD	0.24	0.10 (0.08 to 0.11)	1.70 (1.55-1.86)	<0.001[a]	1.57 (1.45-1.70)	<0.001[a]
	Control	0.14		1		1	
CRSsNP							
	COPD	0.52	0.27 (0.25 to 0.29)	2.08 (1.95-2.21)	<0.001[a]	1.80 (1.70-1.91)	<0.001[a]
	Control	0.25		1		1	
Male (n =1,705,006)							
CRS							
	COPD	1.64	0.97 (0.93 to 1.02)	2.41 (2.32-2.51)	<0.001a	1.99 (1.92-2.06)	<0.001a
	Control	0.66		1		1	
CRSwNP							
	COPD	0.51	0.26 (0.24 to 0.28)	2.06 (1.94-2.20)	<0.001a	1.78 (1.68-1.88)	<0.001a
	Control	0.24		1		1	
CRSsNP							
	COPD	0.80	0.47 (0.44 to 0.49)	2.37 (2.25-2.49)	<0.001[a]	2.02 (1.92-2.11)	<0.001[a]
	Control	0.34		1		1	
Female (n =1,094,700)							
CRS							
	COPD	1.12	0.61 (0.57 to 0.65)	2.18 (2.06-2.30)	<0.001[a]	1.75 (1.67-1.84)	<0.001[a]
	Control	0.51		1		1	

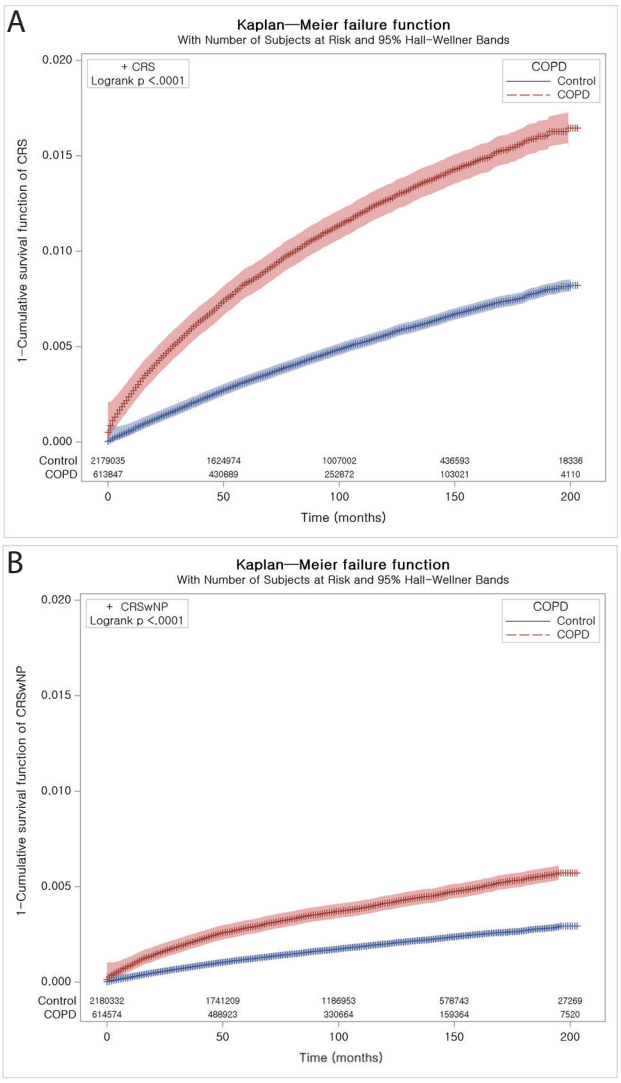
Table 2 *continued*.

		IR per 1,000 person-year	IRD per 1000 person-years (95% CI)	Hazard ratios for CRS / CRSwNP / CRSsNP			
				Crude	P-value	Overlap weighted model [b]	P-value
CRSwNP							
	COPD	0.35	0.19 (0.17 to 0.21)	2.18 (1.98-2.39)	<0.001[a]	1.68 (1.55-1.83)	<0.001[a]
	Control	0.16		1		1	
CRSsNP							
	COPD	0.64	0.33 (0.30 to 0.36)	2.09 (1.95-2.24)	<0.001[a]	1.74 (1.64-1.85)	<0.001[a]
	Control	0.30		1		1	
Low income (n =1,593,982)							
CRS							
	COPD	1.42	0.85 (0.81 to 0.88)	2.44 (2.34-2.55)	<0.001[a]	1.94 (1.87-2.02)	<0.001[a]
	Control	0.57		1		1	
CRSwNP							
	COPD	0.45	0.25 (0.23 to 0.27)	2.22 (2.07-2.37)	<0.001[a]	1.78 (1.67-1.89)	<0.001[a]
	Control	0.20		1		1	
CRSsNP							
	COPD	0.72	0.42 (0.39 to 0.44)	2.37 (2.24-2.50)	<0.001[a]	1.94 (1.84-2.04)	<0.001[a]
	Control	0.30		1		1	
High income (n =1,205,724)							
CRS							
	COPD	1.45	0.81 (0.77 to 0.86)	2.23 (2.12-2.34)	<0.001[a]	1.86 (1.78-1.94)	<0.001[a]
	Control	0.64		1		1	
CRSwNP							
	COPD	0.44	0.22 (0.20 to 0.25)	2.00 (1.85-2.17)	<0.001[a]	1.69 (1.58-1.81)	<0.001[a]
	Control	0.22		1		1	
CRSsNP							
	COPD	0.77	0.42 (0.39 to 0.45)	2.19 (2.05-2.32)	<0.001[a]	1.88 (1.78-1.99)	<0.001[a]
	Control	0.35		1		1	
Urban resident (n =1,182,743)							
CRS							
	COPD	1.60	0.96 (0.91 to 1.01)	2.42 (2.30-2.55)	<0.001[a]	1.90 (1.82-1.98)	<0.001[a]
	Control	0.65		1		1	
CRSwNP							
	COPD	0.52	0.29 (0.27 to 0.32)	2.25 (2.08-2.44)	<0.001[a]	1.80 (1.68-1.93)	<0.001[a]
	Control	0.23		1		1	
CRSsNP							
	COPD	0.85	0.49 (0.45 to 0.52)	2.34 (2.19-2.49)	<0.001[a]	1.87 (1.77-1.97)	<0.001[a]
	Control	0.36		1		1	
Rural resident (n =1,616,963)							
CRS							
	COPD	1.34	0.78 (0.74 to 0.82)	2.36 (2.26-2.46)	<0.001[a]	1.90 (1.83-1.98)	<0.001[a]
	Control	0.56		1		1	
CRSwNP							
	COPD	0.41	0.22 (0.20 to 0.23)	2.10 (1.97-2.25)	<0.001[a]	1.70 (1.60-1.81)	<0.001[a]
	Control	0.20		1		1	

Table 2 *continued*.

		IR per 1,000 person-year	IRD per 1000 person-years (95% CI)	Hazard ratios for CRS / CRSwNP / CRSsNP			
				Crude	P-value	Overlap weighted model [b]	P-value
CRSsNP							
	COPD	0.69	0.39 (0.37 to 0.42)	2.32 (2.20-2.45)	<0.001[a]	1.94 (1.85-2.04)	<0.001[a]
	Control	0.30		1		1	

COPD, Chronic obstructive pulmonary disease; IR, incidence rate; IRD, incidence rate difference; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRS, Chronic rhinosinusitis; CRSwNP, CRS with nasal polyps; CRSsNP, CRS without nasal polyps. [a] Significance at $P < 0.05$. [b] Adjusted for age, sex, income, region of residence, SBP, DBP, fasting blood glucose, total cholesterol, obesity, smoking, alcohol consumption, CCI scores, and asthma.



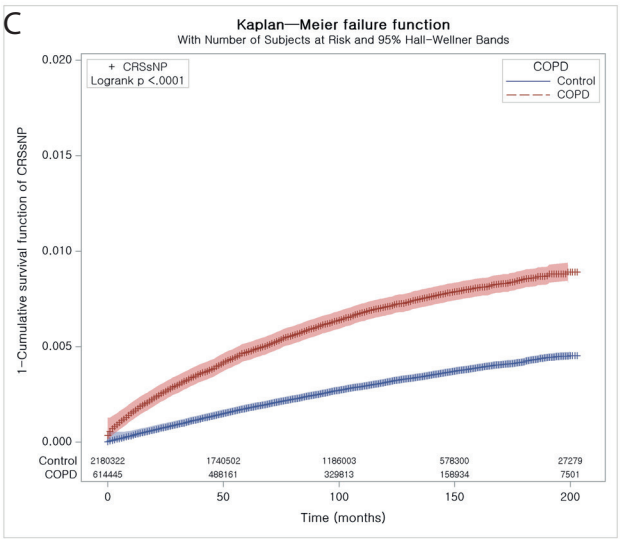


Figure 3. Kaplan–Meier curves of patients with COPD versus controls for CRS (A), CRSwNP (B), and CRSsNP (C). Time (months) indicates the follow-up duration from the index date. Abbreviations: COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyps.

sparse. Additionally, we speculate that intermittent hypoxia and impaired mucosal defences seen in progressive COPD may increase susceptibility to CRS, but mechanistic studies incorporating physiological measures are needed. Taken together, these mechanisms are compatible with a "united airway" concept that may extend beyond the traditional CRS–asthma framework. Several limitations warrant consideration. First, COPD and CRS were identified using claims-based operational definitions, which may introduce misclassification. To improve specificity, we required repeated diagnostic codes and relevant medication prescriptions, and CRS diagnosis was supported by computed tomography; nevertheless, some degree of diagnostic error is possible. Second, detection bias may exist because patients with COPD typically have higher health care utilisation, increasing opportunities for CRS detection and imaging. Third, residual confounding cannot be fully excluded, as claims and screening

data do not completely capture smoking intensity (e.g., pack-years), occupational or environmental exposures, physiological COPD severity, or the effects of COPD pharmacotherapy (e.g., inhaled corticosteroids), which could influence upper-airway inflammation. Finally, the study population consisted of Korean adults, and generalisability to other ethnicities or health care systems should be interpreted with caution.

Notwithstanding these limitations, the present study strengths include a large nationally representative cohort with long follow-up, rigorous operational definitions, and robust confounding control though overlap weighting. Future research incorporating spirometric severity, endoscopic confirmation of polyp status, and biomarker-based endotyping will help clarify phenotype-specific pathways. In addition, prospective clinical studies should evaluate whether optimised CRS treatment modifies COPD outcomes such as exacerbations and health-related QoL.

These findings argue for routine screening of sinonasal symptoms in COPD clinics and vice versa. From a clinical standpoint, incorporating a brief sinonasal symptom screen (e.g., persistent nasal obstruction, discharge, facial pressure, hyposmia) into COPD visits may help identify patients who could benefit from targeted CRS evaluation and treatment. Conversely, in CRS patients with chronic cough or exertional dyspnea—especially smokers—clinicians may consider assessment for COPD and overlap phenotypes. A previous study showed that a high burden of sinonasal symptoms is positively associated with the clinical markers of symptom severity and mortality risk and is inversely associated with physical activity and health-related QoL in COPD [36]. Early identification and management of CRS may reduce exacerbation frequency, improve sleep, and enhance overall health status in COPD, as suggested by smaller interventional studies [37].

Conclusion

COPD was associated with an increased risk of incident CRS, including both CRSwNP and CRSsNP, in a large nationwide cohort. These findings support the concept of interrelated upper and lower airway disease and highlight the importance of integrated assessment and management across the respiratory tract.

Author contributions

Concept and design: HGC, JHW. Acquisition, analysis, or interpretation of data: HJJ, HGC. Drafting of the manuscript: MWP, HJJ. Critical revision of the manuscript for important intellectual content: HGC, JHW. Statistical analysis: HGC. Administrative, technical, or material support: MWP, HJJ. Supervision: JHW. All authors: review and approval of the final manuscript.

Conflict of interest

All authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Table S1. Subgroup analyses of crude and overlap propensity score weighted hazard ratios of COPD for CRS / CRSwNP / CRSsNP according to obesity, smoking, alcohol consumption, blood pressure, fasting blood glucose, total cholesterol, CCI scores, and asthma.

		IR per 1000 person-year	IRD per 1000 person-years (95% confidence interval)	Hazard ratios for CRS / CRSwNP / CRSsNP			
				Crude	P-value	Overlap weighted model [b]	P-value
Underweight [c] (n =108,714)							
CRS							
	COPD	1.08	0.68 (0.56 to 0.80)	2.64 (2.18-3.19)	<0.001[a]	2.12 (1.75-2.58)	<0.001[a]
	Control	0.40		1		1	
CRSwNP							
	COPD	0.29	0.17 (0.11 to 0.22)	2.38 (1.76-3.21)	<0.001[a]	1.97 (1.45-2.68)	<0.001[a]
	Control	0.12		1		1	
CRSsNP							
	COPD	0.43	0.26 (0.19 to 0.32)	2.42 (1.90-3.09)	<0.001[a]	1.94 (1.51-2.50)	<0.001[a]
	Control	0.18		1		1	
Normal weight [c] (n =998,950)							
CRS							
	COPD	1.35	0.79 (0.74 to 0.84)	2.36 (2.24-2.50)	<0.001[a]	1.87 (1.78-1.97)	<0.001[a]
	Control	0.56		1		1	
CRSwNP							
	COPD	0.42	0.24 (0.21 to 0.26)	2.24 (2.06-2.45)	<0.001[a]	1.76 (1.63-1.91)	<0.001[a]
	Control	0.19		1		1	
CRSsNP							
	COPD	0.66	0.36 (0.33 to 0.39)	2.20 (2.05-2.37)	<0.001[a]	1.82 (1.71-1.94)	<0.001[a]
	Control	0.30		1		1	
Overweight [c] (n =716,849)							
CRS							
	COPD	1.55	0.93 (0.87 to 0.99)	2.46 (2.31-2.62)	<0.001[a]	1.98 (1.88-2.10)	<0.001[a]
	Control	0.62		1		1	
CRSwNP							
	COPD	0.50	0.28 (0.25 to 0.32)	2.30 (2.08-2.54)	<0.001[a]	1.78 (1.63-1.94)	<0.001[a]
	Control	0.22		1		1	
CRSsNP							
	COPD	0.82	0.48 (0.44 to 0.52)	2.39 (2.21-2.59)	<0.001[a]	2.03 (1.89-2.18)	<0.001[a]
	Control	0.34		1		1	
Obese [c] (n =975,193)							
CRS							
	COPD	1.50	0.85 (0.80 to 0.91)	2.30 (2.18-2.42)	<0.001[a]	1.86 (1.78-1.95)	<0.001[a]
	Control	0.64		1		1	
CRSwNP							
	COPD	0.47	0.23 (0.20 to 0.26)	1.98 (1.81-2.16)	<0.001[a]	1.69 (1.56-1.82)	<0.001[a]
	Control	0.24		1		1	
CRSsNP							
	COPD	0.85	0.50 (0.46 to 0.53)	2.39 (2.23-2.56)	<0.001[a]	1.91 (1.80-2.03)	<0.001[a]
	Control	0.35		1		1	

		IR per 1000 person-year	IRD per 1000 person-years (95% confidence interval)	Hazard ratios for CRS / CRSwNP / CRSsNP			
				Crude	P-value	Overlap weighted model [b]	P-value
Non-smoker (n =1,729,900)							
CRS							
	COPD	1.31	0.74 (0.70 to 0.78)	2.27 (2.17-2.36)	<0.001[a]	1.78 (1.71-1.84)	<0.001[a]
	Control	0.57		1		1	
CRSwNP							
	COPD	0.40	0.21 (0.19 to 0.23)	2.12 (1.98-2.28)	<0.001[a]	1.67 (1.57-1.77)	<0.001[a]
	Control	0.19		1		1	
CRSsNP							
	COPD	0.71	0.39 (0.36 to 0.41)	2.19 (2.08-2.31)	<0.001[a]	1.75 (1.68-1.84)	<0.001[a]
	Control	0.32		1		1	
Past and current smoker (n =1,069,806)							
CRS							
	COPD	1.59	0.94 (0.89 to 0.99)	2.39 (2.27-2.51)	<0.001[a]	2.10 (2.00-2.20)	<0.001[a]
	Control	0.65		1		1	
CRSwNP							
	COPD	0.51	0.26 (0.23 to 0.29)	2.01 (1.86-2.17)	<0.001[a]	1.84 (1.71-1.97)	<0.001[a]
	Control	0.25		1		1	
CRSsNP							
	COPD	0.78	0.46 (0.42 to 0.49)	2.41 (2.25-2.57)	<0.001[a]	2.19 (2.06-2.33)	<0.001[a]
	Control	0.33		1		1	
Alcohol consumption <1 time a week (n =1,874,329)							
CRS							
	COPD	1.34	0.76 (0.73 to 0.80)	2.28 (2.19-2.37)	<0.001[a]	1.83 (1.77-1.90)	<0.001[a]
	Control	0.58		1		1	
CRSwNP							
	COPD	0.40	0.21 (0.19 to 0.22)	2.07 (1.94-2.21)	<0.001[a]	1.65 (1.55-1.74)	<0.001[a]
	Control	0.19		1		1	
CRSsNP							
	COPD	0.72	0.40 (0.37 to 0.42)	2.22 (2.11-2.33)	<0.001[a]	1.85 (1.77-1.94)	<0.001[a]
	Control	0.32		1		1	
Alcohol consumption ≥1 time a week (n =925,377)							
CRS							
	COPD	1.65	1.01 (0.95 to 1.07)	2.51 (2.38-2.66)	<0.001[a]	2.04 (1.94-2.15)	<0.001[a]
	Control	0.64		1		1	
CRSwNP							
	COPD	0.58	0.32 (0.29 to 0.36)	2.27 (2.09-2.48)	<0.001[a]	1.92 (1.77-2.07)	<0.001[a]
	Control	0.25		1		1	
CRSsNP							
	COPD	0.80	0.47 (0.44 to 0.51)	2.42 (2.25-2.61)	<0.001[a]	2.03 (1.91-2.17)	<0.001[a]
	Control	0.33		1		1	

		IR per 1000 person-year	IRD per 1000 person-years (95% confidence interval)	Hazard ratios for CRS / CRSwNP / CRSsNP			
				Crude	P-value	Overlap weighted model [b]	P-value
SBP <140 mmHg and DBP <90 mmHg (n =1,994,168)							
CRS							
	COPD	1.49	0.86 (0.83 to 0.90)	2.34 (2.25-2.43)	<0.001[a]	1.92 (1.85-1.98)	<0.001[a]
	Control	0.62		1		1	
CRSwNP							
	COPD	0.47	0.25 (0.23 to 0.27)	2.13 (2.00-2.27)	<0.001[a]	1.78 (1.69-1.89)	<0.001[a]
	Control	0.22		1		1	
CRSsNP							
	COPD	0.80	0.45 (0.42 to 0.47)	2.27 (2.17-2.38)	<0.001[a]	1.91 (1.83-1.99)	<0.001[a]
	Control	0.35		1		1	
SBP ≥140 mmHg or DBP ≥90 mmHg (n =805,538)							
CRS							
	COPD	1.29	0.75 (0.70 to 0.80)	2.34 (2.20-2.48)	<0.001[a]	1.86 (1.76-1.96)	<0.001[a]
	Control	0.54		1		1	
CRSwNP							
	COPD	0.41	0.21 (0.19 to 0.24)	2.09 (1.90-2.30)	<0.001[a]	1.63 (1.50-1.77)	<0.001[a]
	Control	0.19		1		1	
CRSsNP							
	COPD	0.62	0.35 (0.31 to 0.38)	2.27 (2.10-2.46)	<0.001[a]	1.91 (1.77-2.05)	<0.001[a]
	Control	0.27		1		1	
Fasting blood glucose <100 mg/dL (n =1,575,670)							
CRS							
	COPD	1.44	0.83 (0.79 to 0.87)	2.33 (2.23-2.42)	<0.001[a]	1.90 (1.83-1.98)	<0.001[a]
	Control	0.61		1		1	
CRSwNP							
	COPD	0.47	0.26 (0.24 to 0.28)	2.19 (2.05-2.34)	<0.001[a]	1.81 (1.70-1.92)	<0.001[a]
	Control	0.22		1		1	
CRSsNP							
	COPD	0.74	0.41 (0.38 to 0.43)	2.21 (2.10-2.33)	<0.001[a]	1.88 (1.79-1.97)	<0.001[a]
	Control	0.33		1		1	
Fasting blood glucose ≥100 mg/dL (n =1,224,036)							
CRS							
	COPD	1.41	0.83 (0.78 to 0.87)	2.35 (2.23-2.47)	<0.001[a]	1.89 (1.81-1.98)	<0.001[a]
	Control	0.59		1		1	
CRSwNP							
	COPD	0.41	0.20 (0.18 to 0.23)	1.98 (1.82-2.16)	<0.001[a]	1.63 (1.51-1.75)	<0.001[a]
	Control	0.20		1		1	
CRSsNP							
	COPD	0.75	0.43 (0.40 to 0.46)	2.36 (2.21-2.52)	<0.001[a]	1.96 (1.85-2.07)	<0.001[a]
	Control	0.31		1		1	
Total cholesterol <200 mg/dL (n =1,597,640)							
CRS							
	COPD	1.46	0.84 (0.80 to 0.88)	2.30 (2.20-2.40)	<0.001[a]	1.88 (1.81-1.95)	<0.001[a]
	Control	0.62		1		1	
CRSwNP							

		IR per 1000 person-year	IRD per 1000 person-years (95% confidence interval)	Hazard ratios for CRS / CRSwNP / CRSsNP			
				Crude	P-value	Overlap weighted model [b]	P-value
	COPD	0.44	0.23 (0.21 to 0.25)	2.06 (1.92-2.20)	<0.001[a]	1.72 (1.62-1.84)	<0.001[a]
	Control	0.21		1		1	
CRSsNP							
	COPD	0.75	0.42 (0.39 to 0.44)	2.23 (2.11-2.35)	<0.001[a]	1.87 (1.78-1.96)	<0.001[a]
	Control	0.34		1		1	
Total cholesterol ≥200 mg/dL (n =1,202,066)							
CRS							
	COPD	1.39	0.82 (0.77 to 0.86)	2.40 (2.28-2.52)	<0.001[a]	1.94 (1.85-2.02)	<0.001[a]
	Control	0.57		1		1	
CRSwNP							
	COPD	0.46	0.25 (0.23 to 0.28)	2.21 (2.04-2.39)	<0.001[a]	1.77 (1.65-1.89)	<0.001[a]
	Control	0.21		1		1	
CRSsNP							
	COPD	0.72	0.41 (0.38 to 0.44)	2.34 (2.19-2.49)	<0.001[a]	1.97 (1.86-2.09)	<0.001[a]
	Control	0.31		1		1	
CCI scores = 0 (n =1,559,879)							
CRS							
	COPD	1.44	0.88 (0.84 to 0.92)	2.52 (2.41-2.64)	<0.001[a]	1.97 (1.89-2.05)	<0.001[a]
	Control	0.56		1		1	
CRSwNP							
	COPD	0.55	0.33 (0.30 to 0.35)	2.49 (2.32-2.67)	<0.001[a]	1.88 (1.77-1.99)	<0.001[a]
	Control	0.22		1		1	
CRSsNP							
	COPD	0.77	0.45 (0.42 to 0.48)	2.39 (2.25-2.54)	<0.001[a]	1.95 (1.85-2.05)	<0.001[a]
	Control	0.32		1		1	
CCI scores = 1 (n =444,971)							
CRS							
	COPD	2.74	0.22 (0.18 to 0.26)	2.14 (1.98-2.31)	<0.001[a]	1.74 (1.63-1.87)	<0.001[a]
	Control	2.68		1		1	
CRSwNP							
	COPD	0.44	0.22 (0.18 to 0.26)	2.02 (1.78-2.29)	<0.001[a]	1.63 (1.45-1.83)	<0.001[a]
	Control	0.21		1		1	
CRSsNP							
	COPD	0.76	0.40 (0.35 to 0.45)	2.09 (1.90-2.30)	<0.001[a]	1.73 (1.59-1.89)	<0.001[a]
	Control	0.36		1		1	
CCI scores ≥2 (n =794,856)							
CRS							
	COPD	1.43	0.77 (0.72 to 0.83)	2.14 (2.02-2.26)	<0.001[a]	1.84 (1.74-1.94)	<0.001[a]
	Control	0.65		1		1	
CRSwNP							
	COPD	0.35	0.16 (0.13 to 0.18)	1.80 (1.63-1.98)	<0.001[a]	1.54 (1.40-1.68)	<0.001[a]
	Control	0.19		1		1	
CRSsNP							
	COPD	0.71	0.39 (0.36 to 0.43)	2.21 (2.06-2.37)	<0.001[a]	1.89 (1.76-2.02)	<0.001[a]
	Control	0.32		1		1	

		IR per 1000 person-year	IRD per 1000 person-years (95% confidence interval)	Hazard ratios for CRS / CRSwNP / CRSsNP			
				Crude	P-value	Overlap weighted model [b]	P-value
No history of asthma (n =1,984,453)							
CRS							
	COPD	1.10	0.55 (0.50 to 0.60)	1.91 (1.80-2.04)	<0.001[a]	1.94 (1.87-2.02)	<0.001[a]
	Control	0.55		1		1	
CRSwNP							
	COPD	0.30	0.10 (0.08 to 0.13)	1.48 (1.33-1.64)	<0.001[a]	1.56 (1.46-1.66)	<0.001[a]
	Control	0.20		1		1	
CRSsNP							
	COPD	0.58	0.28 (0.25 to 0.32)	1.92 (1.78-2.08)	<0.001[a]	2.07 (1.97-2.18)	<0.001[a]
	Control	0.30		1		1	
History of asthma (n =815,253)							
CRS							
	COPD	1.54	0.74 (0.68 to 0.79)	1.87 (1.78-1.96)	<0.001[a]	1.88 (1.80-1.98)	<0.001[a]
	Control	0.80		1		1	
CRSwNP							
	COPD	0.50	0.22 (0.19 to 0.25)	1.82 (1.68-1.97)	<0.001[a]	1.85 (1.71-2.00)	<0.001[a]
	Control	0.28		1		1	
CRSsNP							
	COPD	0.80	0.34 (0.30 to 0.37)	1.73 (1.63-1.84)	<0.001[a]	1.83 (1.72-1.95)	<0.001[a]
	Control	0.46		1		1	

COPD, Chronic obstructive pulmonary diseases; IR, incidence rate; IRD, incidence rate difference; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRS, Chronic rhinosinusitis; CRSwNP, CRS with nasal polyps; CRSsNP, CRS without nasal polyps. [a] Significance at $P < 0.05$. [b] Adjusted for age, sex, income, region of residence, SBP, DBP, fasting blood glucose, total cholesterol, obesity, smoking, alcohol consumption, CCI scores, and asthma. [c] Obesity (BMI, body mass index, kg/m^2) was categorized as (<18.5), normal (≥18.5 to <23), overweight (≥23 to <25), and obese (≥25).