Increased risk of chronic otitis media in chronic rhinosinusitis patients: a longitudinal follow-up study using a national health screening cohort*

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Abstract

Background: Chronic rhinosinusitis (CRS) and chronic otitis media (COM) share pathophysiological mechanisms such as bacterial infection, biofilm, and persistence of the obstruction state of ventilation routes. However, only a few studies have investigated the relationship between these two diseases nationwide and in the general population. The purpose of this study was to determine whether the incidence of COM in patients with CRS differed from that of a matched control from the national health screening cohort.

Methods: Data from the Korean Health Insurance Review and Assessment Service-National Patient Samples were collected from 2002 to 2015. Participants who were treated ≥2 times and underwent head and neck computed tomography evaluation were selected. A 1:4 matched CRS group (n=8,057) and a control group (n=32,228) were selected. The control group included partici- pants who were never treated with the ICD-10 code J32 from 2002 to 2015. The CRS group included CRS patients with/without nasal polyps.

Results: The incidence of COM was significantly higher in the CRS group than in the control group. In a subgroup analysis, the incidence of COM in all age groups and in men and women was significantly higher in the CRS group than in the control group. More, CRS increased the risk of COM.

Conclusions: A significant association was observed between CRS and COM. This indicates that CRS patients have a high risk of developing COM.

Key words: chronic rhinosinusitis, chronic otitis media, risk, cohort, epidemiology

Introduction

Chronic rhinosinusitis (CRS) and chronic otitis media (COM) have the highest prevalence among chronic inflammatory diseases developing in the ears and nose. Prevalence rates for CRS using an administrative database and a population-based investi- gation were 1.0-12.1%, depending on the survey method and region[1-3]. The estimated annual incremental direct cost of CRS is more than $12.5 billion per year, and estimated annual indirect

cost is more than $20 billion per year in the USA[4]. The prevalen- ce of COM varies by country and region and tends to be higher in developing countries (5.1-7.4%) as compared to developed countries (<1%)[5-7]. Because COM is accompanied by hearing loss and otorrhea, it can lead to secondary concerns including decreased cognitive function, social deprivation, and increased medical costs[8].
CRS and COM share several pathophysiological mechanisms

such as bacterial infection, compromised ventilation, and biofilm[9-11]. In practice, otolaryngologists often experience these two diseases concurrently or note that antibiotic treatment and surgery affect each other's clinical progress[12,13]. The middle ear, Eustachian tube, and paranasal sinuses are located anatomically close together, most of which are formed of pseudostratified columnar epithelium. Ventilation and drainage from the middle ear and paranasal sinus can be altered by functional and physiological changes in the Eustachian tube or adjacent structures[14,15]. Therefore, mucosal swelling of the Eustachian tube orifice due to CRS leads to a decreased function of ventilation and can develop negative pressure in the middle ear. This increases the burden of the middle ear mucosa and might, therefore, be associated with the occurrence of chronic comorbid conditions such as attic retraction of the tympanic membrane, middle ear effusion, and acquired cholesteatoma[12,16]. CRS has potential anatomical and pathophysiological associations with COM, but there is limited research on the casual relationship between these two diseases in a large-scale population[17]. This cohort study aimed to investigate the association between COM and CRS and the risk of COM in patients with CRS using data from a nationwide population-based sample.

Materials and methods

Study population
The Ethics Committee of Hallym University (2019-01-003) provided approval for 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. A detailed description of The Korean National Health Insurance Service-Health Screening Cohort data has been given elsewhere (18).

Definition of chronic rhinosinusitis
Chronic Rhinosinusitis (CRS) was defined using ICD-10 codes (J32: Chronic sinusitis). Among them, we selected participants who were treated ≥2 times and underwent head and neck CT evaluation (claim codes: HA401-HA416, HA441-HA443, HA451-HA453, HA461-HA463, or HA471-HA473). Among the CRS patients, 4,423 participants were treated with nasal polyps (J33), and the other 4,137 participants were treated without nasal polyps.

Definition of chronic otitis media and mastoidectomy
Chronic otitis media (COM) was defined as participants treated ≥2 times for the following ICD-10 codes: chronic serous otitis media (H65.2), chronic mucoid otitis media (H65.3), other chronic nonsuppurative otitis media (H65.4), unspecified nonsuppurative otitis media (H65.9), chronic tubotympanic suppurative otitis media (H66.1), chronic atticoantral suppurative otitis media (H66.2), other chronic suppurative otitis media (H66.3),

and unspecified suppurative otitis media (H66.4). Mastoidectomy, the operation for otitis media, was defined if participants were treated with the following operation codes: S5670, S5671, S5672, and S5680.

Participant selection
CRS patients were selected from a total of 514,866 participants with 497,931,549 medical claim codes (n = 8,560). Among these, the control group was included if participants were never treated for the ICD-10 code J32, from 2002 to 2015 (n = 506,306). CRS patients were matched with control participants in a 1:4 ratio for age, sex, income, and region of residence. To minimize selection bias, control participants were selected in a random number order. The index date of each CRS patient was set as the time of CRS treatment. The index date of control participants was set as the index date of their matched CRS patients. Therefore, each matched pair of participants had the same index date. CRS patients with previous COM from the index date were excluded (n = 503). Control participants with previous COM from the index date were also excluded. During the matching process, 474,078 control participants were excluded. Finally, 8,057 CRS patients with/without nasal polyps were matched at a ratio of 1:4 with 32,228 control participants (Figure 1).

Covariates
Age groups were divided into 5-year intervals: 40-44, 45-49, 50-54…, and 85+ years old. In total, 10 age groups were specified. Income groups were classified into five (class 1 [lowest income] to 5 [highest income]). The region of residence was grouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural areas (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju).

Tobacco smoking was categorized based on the participant's current smoking status (nonsmoker, past smoker, and current smoker). Alcohol consumption was categorized on the basis of the frequency of alcohol consumption (<1 time a week and ≥1 time a week). Obesity was measured using BMI (body mass index, kg/m^2). Missing BMI variables were replaced by mean BMI from final selected participants. BMI was categorized as <18.5 (underweight), ≥18.5 to < 23 (normal), ≥23 to <25 (overweight), ≥25 to <30 (obese I), and ≥30 (obese II) based on the Asia-Pacific criteria following the Western Pacific Regional Office (WPRO) 2000 [19].

Gastroesophageal reflux (GERD) was defined if participants were treated with the ICD-10 code K21 (Gastro-esophageal reflux disease) ≥ 2 times and were prescribed a proton pump inhibitor (PPI) for ≥ 2 weeks.

Charlson Comorbidity Index (CCI) has been used widely to measure disease burden using 17 comorbidities. A score was given to each participant depending on the severity and number
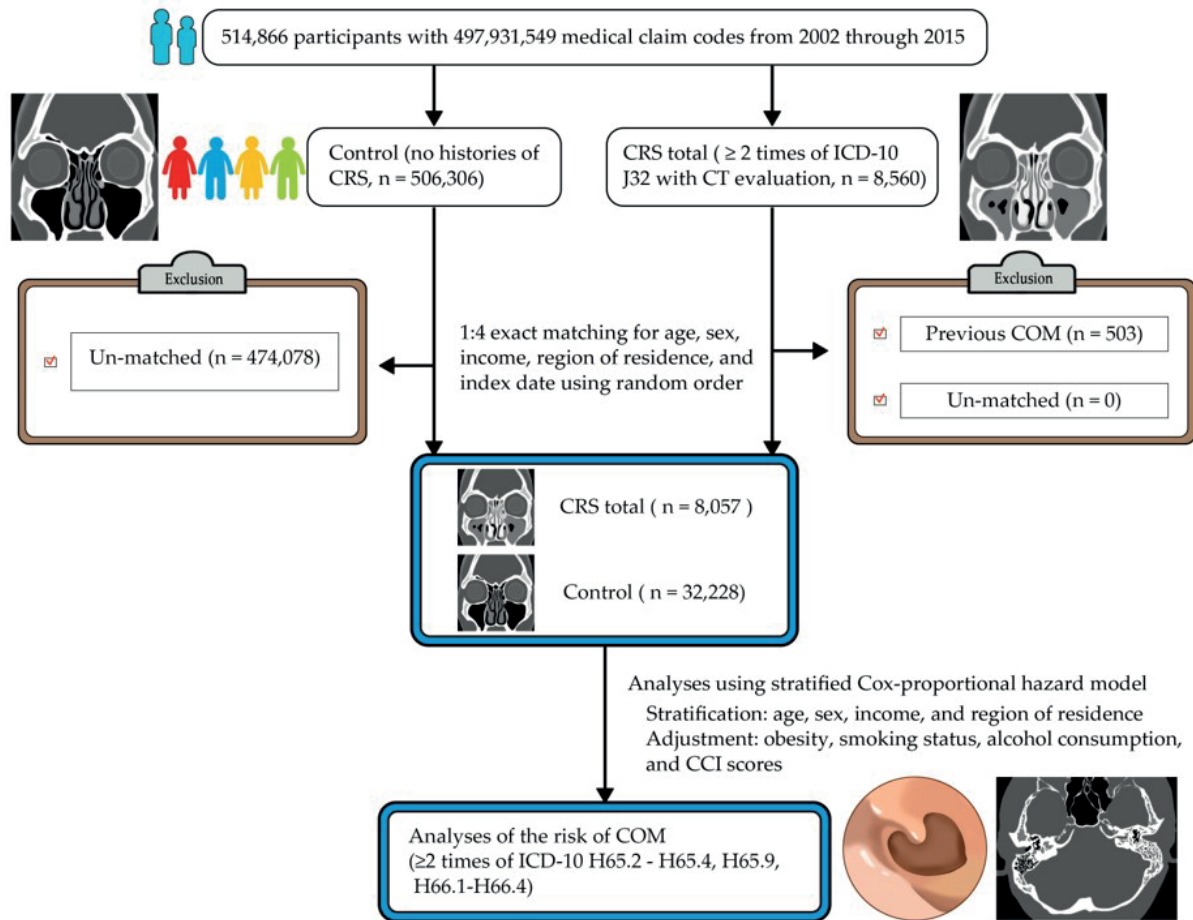
Figure 1. Schematic illustration of the participant selection process used in the present study. Of a total of 514,866 participants, 8,057 chronic rhinosinusitis (CRS) participants were matched with 32,228 control participants for age, sex, income, and region of residence. Chronic otitis media; COM.

of diseases. CCI was measured as a continuous variable (0 [no comorbidities] through 29 [multiple comorbidities]) [20,21]. The scores were calculated without cerebrovascular disease. CCI score was used as a covariate in these analyses.

Statistical analyses

The general characteristics between CRS with/without nasal polyp and control group were compared using the chi-square test. To analyze the hazard ratios (HRs) with 95% confidence intervals (CIs) for COM in CRS patients with/without nasal polyps and compare them with those of control participants, a stratified Cox proportional hazard model was used. In this analysis, the crude and the adjusted models (adjusted for obesity, smoking status, alcohol consumption, and CCI scores) were calculated. The analysis was stratified for matched variables such as age, sex, income, and region of residence.

For the subgroup analyses, we divided participants by age and sex (<60 years old and ≥60 years old; males and females) and analyzed the crude and adjusted models. Additionally, HRs for COM with and without operation were analyzed in CRS patients compared to control participants (S1 Table).

Two-tailed analyses were performed, and significance was defined as P values of less than 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

Results

The mean follow-up time was 97.6 months (standard deviation [SD] = 49.0) in the CRS group and 101.3 months (SD = 47.8) in the control group. The rate of patients with COM was 10.5% (845/8,057) in the CRS group and 4.7% (1,526/506,306) in the control group, showing a significantly higher rate in the CRS group ($p < 0.001$). The distributions of age, sex, income level, and region of residence were comparable between the CRS and control groups. In the CRS group, 52.3% (n = 4,217) of patients had nasal polyps, and 4.5% (n = 38) of patients diagnosed with COM underwent mastoidectomy, which showed a significant difference when compared with the control group. Further, the number of COM patients without surgery was significantly higher in the CRS group than in the control group. The CCIs related to comorbidities were divided into 0, 1, 2, 3 and 4 points or more, and participants with 1, 2, 3, and 4 points or more were mainly from the CRS group. The number of participants with a

Table 1. General characteristics of participants.

Characteristics	Total participants		
	CRS total (n, %)	Control (n, %)	P-value
Age (years old)			1.000
40-44	747 (9.3)	2,988 (9.3)	
45-49	1,498 (18.6)	5,992 (18.6)	
50-54	1,653 (20.5)	6,612 (20.5)	
55-59	1,557 (19.3)	6,228 (19.3)	
60-64	1,180 (14.7)	4,720 (14.7)	
65-69	783 (9.7)	3,132 (9.7)	
70-74	425 (5.3)	1,700 (5.3)	
75-79	164 (2.0)	656 (2.0)	
80-84	43 (0.5)	172 (0.5)	
85+	7 (0.1)	28 (0.1)	
Sex			1.000
Male	4,908 (60.9)	19,632 (60.9)	
Female	3,149 (39.1)	12,596 (39.1)	
Income			1.000
1 (lowest)	960 (11.9)	3,840 (11.9)	
2	927 (11.5)	3,708 (11.5)	
3	1,219 (15.1)	4,876 (15.1)	
4	1,736 (21.6)	6,944 (21.6)	
5 (highest)	3,215 (39.9)	12,860 (39.9)	
Region of residence			1.000
Urban	3,799 (47.2)	15,196 (47.2)	
Rural	4,258 (52.9)	17,032 (52.9)	
Obesity †			<0.001*
Underweight	134 (1.7)	653 (2.0)	
Normal	2,586 (32.1)	11,076 (34.4)	
Overweight	2,396 (29.7)	8,985 (27.9)	
Obese I	2,724 (33.8)	10,669 (33.1)	
Obese II	217 (2.7)	845 (2.6)	
Smoking status			<0.001*
Nonsmoker	5,383 (66.8)	21,089 (65.4)	
Past smoker	1,104 (13.7)	3,946 (12.2)	
Current smoker	1,570 (19.5)	7,193 (22.3)	
Alcohol consumption			0.006*
< 1 time a week	5,469 (67.9)	21,356 (66.3)	
≥ 1 time a week	2,588 (32.1)	10,872 (33.7)	
CCI score			<0.001*
0	5,281 (65.6)	23,104 (71.7)	
1	1,342 (16.7)	4,137 (12.8)	
2	671 (8.3)	2,295 (7.1)	
3	329 (4.1)	1,135 (3.5)	
≥ 4	434 (5.4)	1,557 (4.8)	

Characteristics	Total participants		
	CRS total (n, %)	Control (n, %)	P-value
GERD	3,896 (48.4)	11,176 (34.7)	<0.001*
CRS total	8,057 (100.0)	0 (0.0)	<0.001*
CRS with nasal polyp	4,217 (52.3)	0 (0.0)	<0.001*
CRS without nasal polyp	3,840 (47.7)	0 (0.0)	<0.001*
COM total	845 (10.5)	1,526 (4.7)	<0.001*
COM with operation	38 (0.5)	71 (0.2)	<0.001*
COM without operation	807 (10.0)	1,455 (4.5)	<0.001*

Abbreviations: CCI, Charlson comorbidity index; COM, chronic otitis media; CRS, Chronic Rhinosinusitis. * Chi-square test. Significance at P < 0.05. † Obesity (BMI, body mass index, kg/m^2) was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II).

BMI over 23 (overweight, obese I and II) in the CRS group was significantly higher in the CRS group than in the control group (p < 0.001). Moreover, the number of nonsmokers and past smokers in the CRS group was significantly higher than in the control group, and the current smoker was significantly lower (p < 0.001). However, the number of alcohol consumption was significantly lower in the CRS group than in the control group (p = 0.006). The incidence of GERD was significantly higher in the CRS group (48.4%) than in the control group (34.7%) (p < 0.001) (Table 1).

The adjusted HR was 2.20 (95% CI = 2.02-2.40, p < 0.001), and the incidence of COM in all age groups and in both women and men was significantly higher in the CRS group than in the control group. In addition, adjusted HRs were higher in women than in men at all age groups (Table 2). HR for COM in CRS patients with nasal polyp was 2.42 (95% CI = 2.15-2.71, p < 0.001), which was significantly higher in all age groups and genders, as seen in Table 1. In addition, women had higher HRs than men at all age groups (Table 3). In CRS patients without nasal polyp, HR for COM was 1.98 (95% CI = 1.74-2.25, p < 0.001), which was significantly higher in all age groups and both sexes. Moreover, adjusted HRs for women were higher than those for men at all age groups (Table 4). HR for COM was significantly higher in the CRS group than in the control group regardless of surgery. In addition, patients with no surgery had higher HRs than those who had surgery such as mastoidectomy (Table S1). Figure 2 presents the core results of our study graphically.

Discussion

The HRs for COM were significantly higher in the CRS group than in the control group. CRS has been classified phenotypically

Table 2. Subgroup analyses of crude and adjusted hazard ratios (95% confidence interval, CI) for COM in CRS with/without nasal polyp and control groups according to age and sex.

Characteristics	No. of COM/ No. of participants	Follow-up duration, Person-year	Incidence rate per 1,000 person-years	Hazard ratios for COM (95% CI)			
				Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 40,285)							
CRS total	845/8,057	61,636	13.7	2.29 (2.10-2.49)	<0.001*	2.20 (2.02-2.40)	<0.001*
Control	1,526/32,228	256,447	6.0	1.00		1.00	
Age < 60 years old, men (n = 17,090)							
CRS total	296/3,418	28,580	10.4	2.16 (1.88-2.49)	<0.001*	2.10 (1.82-2.42)	<0.001*
Control	560/13,672	117,354	2.5	1.00		1.00	
Age < 60 years old, women (n = 10,185)							
CRS total	279/2,037	17,070	16.3	2.50 (2.15-2.90)	<0.001*	2.37 (2.04-2.76)	<0.001*
Control	469/8,148	72,867	6.4	1.00		1.00	
Age ≥ 60 years old, men (n = 7,450)							
CRS total	116/1,490	8,951	13.0	1.84 (1.48-2.30)	<0.001*	1.78 (1.42-2.22)	<0.001*
Control	252/5,960	35,806	7.0	1.00		1.00	
Age ≥ 60 years old, women (n = 5,560)							
CRS total	154/1,112	7,035	21.9	2.65 (2.17-3.24)	<0.001*	2.52 (2.06-3.09)	<0.001*
Control	245/4,448	30,420	8.1	1.00		1.00	

Abbreviations: CCI, Charlson comorbidity index; COM, chronic otitis media; CRS, chronic rhinosinusitis; GERD, gastroesophageal reflux disease. * Cox-proportional hazard regression model, Significance at P < 0.05. † Models stratified by age, sex, income, and region of residence. ‡ A model adjusted for obesity, smoking, alcohol consumption, GERD, and CCI scores.

Table 3. Subgroup analyses of crude and adjusted hazard ratios (95% confidence interval, CI) for COM in CRS with nasal polyp and control groups according to age and sex.

Characteristics	No. of COM/ No. of participants	Follow-up duration, Person-year	Incidence rate per 1,000 person-years	Hazard ratios for COM (95% CI)			
				Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 21,085)							
CRS with nasal polyp	477/4,217	34,617	13.8	2.49 (2.22-2.79)	<0.001*	2.42 (2.15-2.71)	<0.001*
Control	792/16,868	144,210	5.5	1.00		1.00	
Age < 60 years old, men (n = 10,280)							
CRS with nasal polyp	187/2,056	18,004	10.4	2.33 (1.95-2.79)	<0.001*	2.26 (1.89-2.71)	<0.001*
Control	328/8,224	73,978	4.4	1.00		1.00	
Age < 60 years old, women (n = 4,805)							
CRS with nasal polyp	144/961	8,495	17.0	2.67 (2.17-3.29)	<0.001*	2.60 (2.1--3.20)	<0.001*
Control	227/3,844	36,469	6.2	1.00		1.00	
Age ≥ 60 years old, men (n = 3,710)							
CRS with nasal polyp	72/742	4,918	14.6	2.20 (1.65-2.94)	<0.001*	2.15 (1.61-2.88)	<0.001*
Control	132/2,968	19,773	6.7	1.00		1.00	
Age ≥ 60 years old, women (n = 2,290)							
CRS with nasal polyp	74/458	3,200	23.1	2.97 (2.20-4.00)	<0.001*	2.84 (2.10-3.83)	<0.001*
Control	105/1,832	13,990	7.5	1.00		1.00	

Abbreviations: CCI, Charlson comorbidity index; COM, chronic otitis media; CRS, chronic rhinosinusitis; GERD, gastroesophageal reflux disease. * Cox-proportional hazard regression model, Significance at P < 0.05. † Models stratified by age, sex, income, and region of residence. ‡ A model adjusted for obesity, smoking, alcohol consumption, GERD, and CCI scores.

Table 4. Subgroup analyses of crude and adjusted hazard ratios (95% confidence interval, CI) for COM in CRS without nasal polyp and control groups according to age and sex.

Characteristics	No. of COM/ No. of participants	Follow-up duration, Person-year	Incidence rate per 1,000 person-years	Hazard ratios for COM (95% CI)			
				Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 19,200)							
CRS without nasal polyp	368/3,840	27,019	13.6	2.07 (1.83-2.35)	<0.001*	1.98 (1.74-2.25)	<0.001*
Control	734/15,360	112,237	6.5	1.00		1.00	
Age < 60 years old, men (n = 6,810)							
CRS without nasal polyp	109/1,362	10,576	10.3	1.93 (1.54-2.42)	<0.001*	1.91 (1.51-2.41)	<0.001*
Control	232/5,448	43,376	5.3	1.00		1.00	
Age < 60 years old, women (n = 5,380)							
CRS without nasal polyp	135/1,076	8,575	15.7	2.34 (1.90-2.89)	<0.001*	2.16 (1.74-2.68)	<0.001*
Control	242/4,304	36,398	6.6	1.00		1.00	
Age ≥ 60 years old, men (n = 3,740)							
CRS without nasal polyp	44/748	4,033	10.9	1.46 (1.03-2.06)	0.032*	1.38 (0.97-1.96)	0.075
Control	120/2,992	16,033	7.5	1.00		1.00	
Age ≥ 60 years old, women (n = 3,270)							
CRS without nasal polyp	80/654	3,835	20.9	2.40 (1.82-3.16)	<0.001*	2.27 (1.71-3.00)	<0.001*
Control	140/2,616	16,430	8.5	1.00		1.00	

Abbreviations: CCI, Charlson comorbidity index; COM, chronic otitis media; CRS, chronic rhinosinusitis; GERD, gastroesophageal reflux disease. * Cox-proportional hazard regression model, Significance at P < 0.05. † Models stratified by age, sex, income, and region of residence. ‡ A model adjusted for obesity, smoking, alcohol consumption, GERD, and CCI scores.

according to the presence of nasal polyps (NP), as the following: CRS with NP (CRS w NP) and CRS without NP (CRS s NP) in EPOS 2012 [22]. The prevalence of CRS was 7.12% in the nation-wide epidemiologic cross-sectional study conducted in Korea, and the prevalence of CRS w NPs was 2.5% (23,24). According to previous studies, CRS w NP accounts for 20 to 35% of patients with CRS [23-25]. In this study, the CRS w NP ratio was considerably higher than in previous studies, which is considered to be a consequence of the analysis being performed on the elderly population (40 years and older). In our study, the CRS group was divided based on the presence or absence of polyps according to EPOS 2012. Adjusted HRs for COM in the CRS with polyps group were higher than those in the CRS without polyps group (2.47, 95% CI = 2.20-2.77 vs. 2.05, 95% CI = 1.80-2.32, respectively), which showed the same results in all sexes and age groups. Although the pathogenesis of CRS has not been clarified, the hypothesis is that the etiology could be related to abnormalities in the epithelial barrier function and mucociliary clearance, bacterial biofilms, tissue remodeling, the host innate and adaptive immune system, and microbiome dysbiosis [26].

CRS and COM are chronic inflammatory conditions, and both diseases have similar pathophysiological associations such as anatomical proximity, biofilm, microbiome dysbiosis, and increased pro-inflammatory mediators. However, few studies have demonstrated the association between the two diseases in a large-scale cohort such as nationwide population. Therefore, herein, we investigated a possible epidemiological association between CRS and COM in a national health screening cohort. Several studies explored a relationship between CRS and COM in Korea through a large-scale population study [27-29]. CRS showed high odds ratios (ORs) (1.87, 95% CI = 1.17-2.98) for COM, and the prevalence of middle ear pathology such as COM and cholesteatoma significantly increased in the nasal polyp group (7.96%) than in the non-polyp group (3.54%) (ORs = 2.008, 95% CI = 1.177-3.425) in the Korea National Health and Nutrition Examination Survey (KNHANES) data [27,29]. However, Chung et al. reported that CRS did not significantly affect the prevalence of COM [28]. In 2009-2012 KNHANES data, adjusted ORs for COM were significantly higher in the CRS group than in the control group. However, in the subgroup analysis, ORs for COM were significantly higher only in the CRS with polyp group, and there was no significant difference in the CRS without polyp group [17]. Although the diagnostic criteria for each disease are the same, the difference between the survey period and enrolled population could have influenced the results. Because the KNHANES is a cross-sectional study, only prevalence and associated factors of diseases can be obtained from data. However, the current study has the advantage of providing estimated incidence and risk
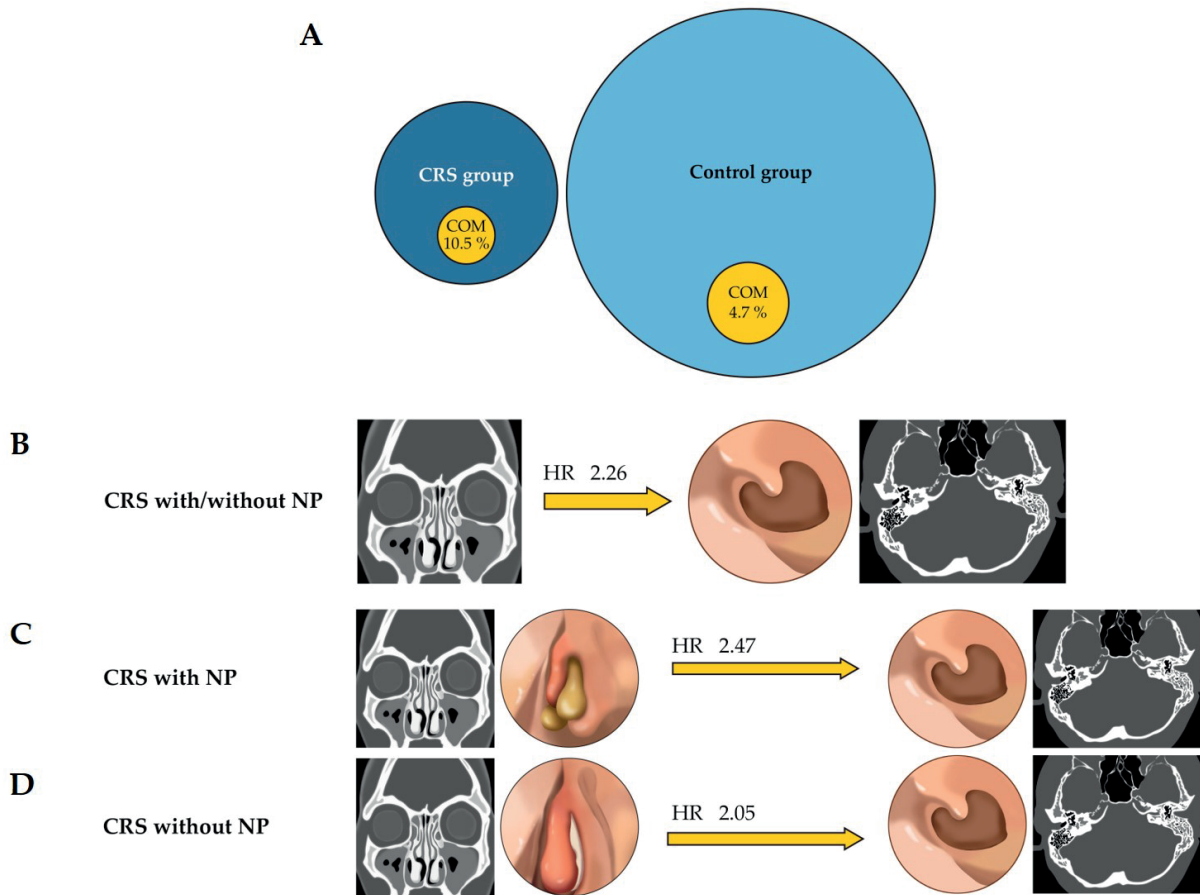
Figure 2. Graphical summary of the findings of this study. The incidence of chronic otitis media (COM) was significantly higher in the chronic rhinosinusitis (CRS) group (A), and the adjusted hazard ratio (HRs) for COM were higher in the CRS group regardless of nasal polyp (B-D).

factors because the enrolled population was followed up during the study period using national health screening data.

One possible piece of evidence supporting the epidemiological association of these two diseases in our results is the mechanical obstruction of the eustachian tube. The persistent inflammatory condition caused by CRS not only thickens of the mucosa of the air cells that constitute the maxillary, ethmoid, and frontal sinus but also affects the mucosa of the anatomically adjacent eustachian tube orifice, causing functional problems in maintaining tubal patency [30,31]. The eustachian tube blockage can be aggravated due to mucopurulent secretion, which might be due to a decrease in muco-ciliary clearance polypoid tissues as well as sino-nasal mucosal swelling. In addition, constant decreased function of the Eustachian tube leads to a change in pressure to negative in the middle ear, causing irreversible damage to the tympanic membrane and the middle ear mucosa. In this regard, Kuo et al. reported that CRS could be associated with acquired middle ear cholesteatoma in Taiwan (HRs = 1.69, 95% CI = 1.23-2.32) and showed highest HRs (2.62; 95% CI = 1.65-4.17) for cholesteatoma in the first 3-year period of CRS onset. In our study, CRS was classified according to the presence or absence

of polyps as well as the control group, and the overall risk for COM was evaluated, which has a higher incidence than that of cholesteatoma. Further, we analyzed objective factors such as the degree of obesity, smoking status, alcohol consumptions, and CCI score. It provided reliable information on lifestyle and underlying diseases as well as the difference in the incidence of COM in each group.

Several lines of evidence support that CRS and COM have common biomolecular mechanisms in terms of chronic inflammatory conditions. First, the concentrations of pro-inflammatory cytokines such as IL-1β, IL-6, and IL-8 are increased in the middle ear and sinus mucosa, leading to the recruitment of immune cells such as macrophages, dendritic cells, neutrophils, NK cells, and T cells [26,32]. IL-6 and TNF-α are known to affect mucosal tissue remodeling by increasing vessel permeability, disrupting cell-to-cell tight junctions, and causing osteolysis of bones [33,34]. Next, a bacterial interference occurs on mucosal surface with CRS and COM, where the commensal microbiome interferes with pathogenic bacteria by competing for resources or nutritional substances [35-37]. Microbiome dysbiosis is apparent when there is active inflammation accompanied by purulent rhinor-

rhea or otorrhea. In COM with pulsatile otorrhea, the proportion of Proteobacteria identified in normal middle ear mucosa was lowered, and bacteria of the phylum *Firmicutes* were dominant [36]. *Staphylococcus* and *Peptoniphilus* genera from *Firmicutes* were identified as dominant [36]. In the inflammatory sinus mucosa of CRS, [S. aureus], *Streptococcus* species, *Corynebacterium* species, *S. epidermidis*, and *P. acnes* were abundant compared to those in healthy mucosa [38,39]. These microbiome can form a three-dimensionally structured biofilm, which produces superantigen that inhibits muco-ciliary clearance in the sinus and ear [40-42]. Our study findings demonstrated that timely antibiotic treatment and surgical intervention of CRS could prevent the progression to COM. The major strengths of our current research were that we demonstrated the epidemiological association of CRS and COM using a large representative nationwide cohort database on a health check-up and matched confounding factors such as age, sex, area of residence, and level of income. In addition, it was possible to increase the reliability of the results because the matching ratio of the CRS and control groups was 1:4. Because the medical checkup data by each life cycle for the national population were analyzed, it was possible to obtain not only the classification of diseases according to the medical claim codes during the follow-up period but also objective information such as individual habits that affect health, such as underlying diseases and BMI of the population. The amount of information from the Health Screening Cohort is less than the amount of objective data from KNHANES, but it can have an advantage of providing additional information about the cohort based on the medical claim codes and prescribed medications. Although our research postulates that CRS increases the incidence of COM, there are also several limitations. First, we could not collect descriptive information related to the disease, such as hearing threshold, ossicular erosion, anatomic variation, and extent of disease from the patient. Such specific information may be a clue to evaluate the severity of the disease, but this is not included in the dataset we used. Second, for CRS, we could perform the analysis only phenotypically according to the

presence of NP. However, we could not collect the data about the different pathophysiological mechanisms and endotypes of CRS. Third, it was not corrected for the difference in the number of medical encounters between the CRS and control groups. CRS has a chronic clinical progress; therefore, the number of visits to the physicians may be higher than that in the control group. This may have influenced the detection timing of COM. Therefore, it is a need to determine factors that affect the incidence of COM in patients with CRS to minimize confounding bias by controlling factors related to the number of medical encounters in a future study.

Conclusion

Current research showed that CRS was significantly associated with an increased incidence of COM during a 14-year follow-up period. The incidence of COM was higher in patients with CRS of all ages and sexes. Therefore, the present study provides a new perspective into the consequences of chronic inflammatory condition in sinunasal cavity on COM. Physicians should consider the potential risk of COM when a patient is diagnosed with CRS and provide treatment early to reduce the burden of COM.

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Authorship contribution

SKK, HGC, SJH - design of study, interpretation of data; SKK, MWP, CM - data analysis; SKK, ISP, BP - drafting of manuscript; BP, SHB, HGC, SJH - involved in revising the manuscript it critically. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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SUPPLEMENTARY DATA

Supplementary Table 1. Crude and adjusted hazard ratios (95% confidence interval, CI) for COM with operation and COM without operation in CRS with/without nasal polyp and control groups.

Characteristics	No. of COM/ No. of partici- pants	Follow-up duration, Person-year	Incidence rate per 1,000 person-years	Hazard ratios for COM (95% CI)			
				Crude†	P-value	Adjusted†‡	P-value
Hazard ratios for COM with operation							
CRS total	38/8,057	67,046	0.6	2.13 (1.43-3.15)	<0.001*	2.07 (1.39-3.09)	<0.001*
Control	71/32,228	265,493	0.3	1.00		1.00	
Hazard ratios for COM without operation							
CRS total	807/8,057	61,943	13.0	2.29 (2.10-2.49)	<0.001*	2.20 (2.02-2.40)	<0.001*
Control	1455/32,228	256,993	5.7	1.00		1.00	

Abbreviations: CCI, Charlson comorbidity index; COM, chronic otitis media; CRS, chronic rhinosinusitis; GERD, gastroesophageal reflux disease. * Cox-proportional hazard regression model, Significance at $P < 0.05$. † Models stratified by age, sex, income, and region of residence. ‡ A model adjusted for obesity, smoking, alcohol consumption, GERD, and CCI scores.