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

Y.J. Jeon[1,2], T.H. Lee[1], Y.H. Joo[2,3], H.J Cho[1,2], S.W. Kim[1,2], B. Park[4], H.G. Choi[4]

[1] Department of Otorhinolaryngology, Gyeongsang National University Hospital, Jinju, Republic of Korea

[2] Institute of Health Sciences, Gyeongsang National University, Jinju, Republic of Korea

[3] Department of Otorhinolaryngology, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea

[4] Department of Otorhinolaryngology-Head and Neck Surgery, Hallym University College of Medicine, Anyang, Republic of Korea

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Abstract

Background: Chronic rhinosinusitis (CRS) is one of the most common chronic inflammatory diseases and is characterized by sinonasal inflammation that lasts longer than 12 weeks. Whether the effect of chronic inflammation caused by CRS on cardiovascular diseases (CVDs) is similar to its effect on other inflammatory disorders has not been thoroughly evaluated. We aimed to demonstrate whether CRS patients have a higher prevalence of CVDs, including stroke and ischemic heart disease (IHD).

Methodology: We compared the prevalence of various comorbidities between CRS and control participants through a case-control cohort study from 2002 to 2015 that included 514,866 participants. CRS (n=6,552) and control (n=26,208) participants who were over 40 years old were selected by matching age, sex, income, and area of residence at a 1:4 ratio.

Results: A stratified Cox proportional hazards model was utilized to assess the hazard ratio (HR) of CRS for stroke and IHD. The HRs for stroke and IHD were significantly increased in CRS patients compared to controls after adjusting for obesity, alcohol consumption, smoking, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, and Charlson Comorbidity Index (CCI) scores. The HR of stroke was significantly higher in the absence of nasal polyps than in the presence of nasal polyps. The HR of IHD was significantly increased in the CRS group regardless of the presence of nasal polyps.

Conclusions: This study showed that CRS participants had a significantly higher prevalence of stroke and IHD.

Key words: chronic rhinosinusitis, cardiovascular disease, stroke, ischemic heart disease

Introduction

Chronic rhinosinusitis (CRS) is currently one of the most prevalent disorders in the field of otorhinolaryngology [(1)]. CRS affects 5%-12% of the industrialized population worldwide [(2,3)]. CRS usually causes persistent discomfort to patients, including nasal congestion or obstruction, nasal discharge, facial pressure or pain, and a reduction in or loss of the ability to smell. CRS is usually accompanied by nasal symptoms as well as non-nasal symptoms such as fatigue, cognitive impairment, sleep disturbances, mood disorders, and decreased work productivity [(4)]. If CRS is not managed in a timely manner or fails to have successful treatment outcomes, CRS can result in serious health problems such as orbital and intracranial infections, cavernous sinus thrombosis and osteomyelitis leading to visual and neurological deficits [(2)]. For these various negative outcomes, CRS can greatly influence the quality of life of patients and the socioeconomic burden [(5)].

Cardiovascular diseases (CVDs), including stroke, heart failure, and coronary heart disease, are well known as major leading causes of death worldwide. The National Health and Nutrition Survey stated that the overall prevalence of CVD was 9.3% (26.1 million in 2018) and increased with age regardless of sex in the US. According to a county-level study in the US population, the stroke mortality rate of adults aged 35 to 64 years increased

from 14.7 per 100,000 in 2010 to 15.4 per 100,000 in 2016 (6). In Europe, CVD accounted for 3.9 million deaths, which was 45% of all deaths, in 2017 [7]. In South Korea, CVD has also become a leading reason for morbidity and mortality; in 2016, 28.4% of all deaths were caused by neoplasms, and 21.5% were attributed to CVD [8]. Among the Organization for Economic Co-operation and Development (OECD) countries, the population is aging the fastest in South Korea, which will significantly increase the CVD burden in the near future [9].

Chronic inflammation plays a crucial role in atherogenesis in the pathogenesis of CVD. Several studies have demonstrated an increased prevalence of CVD in patients with chronic inflammatory disorders such as psoriasis, bullous skin diseases, inflammatory bowel diseases, inflammatory arthritis, and systemic vasculitis [10,11]. These observations of the increased risk of CVD and decreased life expectancy have accelerated considerable research and initiated an ongoing discussion on dedicated guidelines for CVD prevention in these patients. Subsequently, it has become possible to manage chronic inflammation as a potential means of its prevention in recent years. CRS is one of the most prevalent chronic inflammatory disorders, and it is characterized by persistent inflammation of the sinonasal mucosa that lasts more than 12 weeks. Recently, researchers have explored whether CRS is related to the increased prevalence rates of stroke and myocardial infarction in a population-based study [12-15].

The objective of the current study was to reveal whether CRS participants have an increased prevalence of developing subsequent CVDs, such as stroke and ischemic heart disease (IHD), using the database of a national sample cohort of Korean adults. We also analyzed how the prevalence rates of stroke and IHD vary depending on whether nasal polyps were present in CRS participants.

Materials and methods

Ethics

The Hallym University Ethics Committee approved this study (2019-10-023). The Institutional Review Board waived written informed consent. All analyses were performed following the instructions of the Hallym University Ethics Committee.

Study population and participant selection

A detailed description of the Korean National Health Insurance Service-Health Screening Cohort data is provided elsewhere [16]. Chronic rhinosinusitis participants were selected from among 514,866 participants with 615,488,428 medical claim codes from 2002 through 2015 (n=8,560). Individuals were included in the control group if they did not meet the criteria for CRS from 2002 through 2015 (n=506,306). To choose CRS participants who were diagnosed for the first time, CRS participants diagnosed in 2002 were excluded (n=1,366, washout periods). We excluded controls if the participants had been diagnosed with CRS in the absence of either a paranasal sinus (PNS) X-ray or computed tomography (CT) examination, as well as if they had been diagnosed with CRS once (n=123,209).

CRS participants were matched with control participants at a 1:4 ratio for age, sex, income, and area of residence. The controls were assorted and selected in order from top to bottom using a sequence of random numbers to avoid selection bias of deciding the matched participants. The matched controls were expected to be evaluated concurrently by each matched CRS participant (index date). The index date was defined as the date on which the participant was diagnosed with CRS from 2003 to 2015. The duration of longitudinal follow-up was calculated from the index date to the date of occurrence of stroke or IHD. The participants were excluded if they expired prior to the index date. Participants who had a history of stroke or IHD before the index date were excluded from both the CRS and control groups. For example, a 50-year-old male participant with CRS (income=1, urban residence) visited the medical institution on March 7, 2005. He was matched to a 50-year-old male participant without CRS (income=1, urban residence) as a control. The index date for the CRS and control participants was set to March 7, 2005. The underlying comorbid diseases were evaluated before the index date.

Consequently, 642 participants were excluded from the CRS group. During the matching procedure, 356,889 control participants were excluded. Finally, 6,552 CRS participants were matched with 26,208 controls at a 1:4 ratio (Figure 1). Among the CRS participants, 3,199 had CRS with nasal polyps, and 3,353 had CRS without nasal polyps.

Definition of chronic rhinosinusitis

CRS was identified by International Classification of Diseases, tenth revision (ICD-10) codes (J32). The participants who underwent head and neck CT (claim codes HA401-HA416, HA441-HA443, HA451-HA453, HA461-HA463, or HA471-HA473) and were managed with code J32 more than twice were selected. CRS with nasal polyps (CRScNP) was defined by the ICD-10 code J33, and CRS without nasal polyps (CRSsNP) in the other participants was defined as described in previous studies [16,17].

Definition of cardiovascular diseases

Stroke and IHD were selected according to ICD-10 codes (I60-I69 for stroke and I20-I25 for ischemic heart disease). We included only participants who were hospitalized ≥2 days or who died because of each disease, as described previously [18,19].

Covariates

Age groups were divided into 5-year intervals: 40- 44…, and 85+ years old. A total of 10 age groups were specified. Income groups were classified into 5 classes (lowest to highest). The area

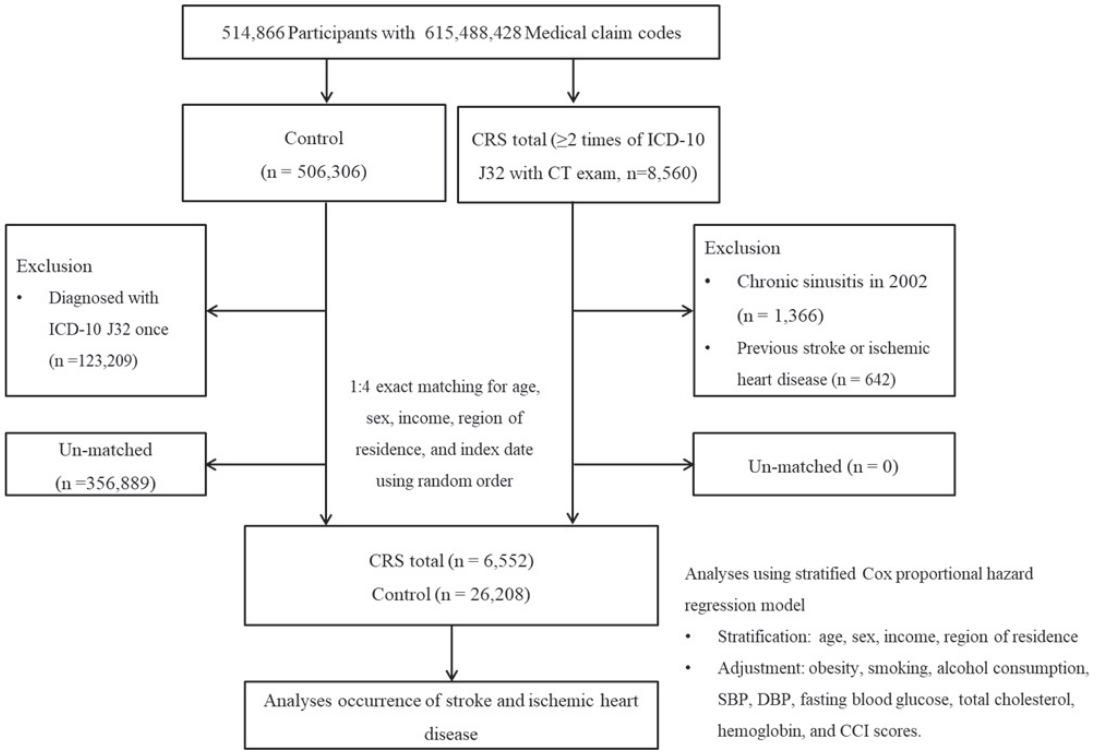

Figure 1. A schematic illustration of the participant selection process that was used in the present study. Of 514,866 participants, 6,552 chronic rhinosinusitis (CRS) participants were matched with 26,208 control participants for age, sex, income, and area of residence. Abbreviations: ICD-10 =International Classification of Diseases, tenth revision; CT=Computed tomography; CCI=Charlson Comorbidity Index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

of residence was grouped into rural and urban areas as described previously [16,20]. Alcohol consumption, tobacco smoking, and obesity were grouped as described previously [16,20,21]. Systolic and diastolic blood pressure (mmHg), fasting blood glucose (mg/dL), total cholesterol (mg/dL), and hemoglobin (g/dL) were measured. The Charlson Comorbidity Index (CCI) was applied to score 17 categories of comorbidities on a scale from 0 through 29 [22,23]. Among them, acute myocardial infarction, congestive heart failure, and cerebrovascular diseases were not included.

Statistical analyses

Statistical analyses were conducted using SAS statistical software Version 9.4 (SAS Institute Inc., Cary, NC, USA). The rate of general characteristics was compared by a chi-square test between the CRS and control groups. Stratified Cox proportional hazards models were utilized to evaluate the hazard ratio (HR) with 95% confidence intervals (CIs) of CRS for cardiovascular disease. Crude and adjusted models (for obesity, alcohol consumption, smoking, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, and CCI scores) were utilized. The analysis was stratified by matching variables such as age, sex, income, and area of residence. Then, we created Kaplan-Meier curves and carried out log-rank tests.

To analyze the subgroups using the stratified Cox proportional hazards model, we divided the participants by age (<55 and ≥55 years old), sex, income (low and high), and area of residence. Additionally, we analyzed subgroups using the unstratified Cox proportional hazards model for obesity, smoking, alcohol consumption, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin (≥12 g/dL for men and ≥10 g/dL for women, <12 g/dL for men and <10 g/dL for women), and CCI scores. Two-tailed analyses were performed, and a P value < 0.05 was defined as significant.

Results

The general characteristics of participants in the CRS and control groups were matched. Age, sex, income, area of residence, alcohol consumption, and hemoglobin levels of the CRS group were similar to those of the control group (P=1.000). However, the prevalence rates of hemorrhagic or ischemic stroke, IHD, obesity, and smoking; systolic and diastolic blood pressure; fasting blood glucose; total cholesterol; and CCI score were significantly increased in the CRS group (P <0.005, Table 1).

The overall CRS group had a significantly higher prevalence of stroke (crude HR, 1.27 [95% CI, 1.16-1.40]) and IHD (crude HR, 1.56 [95% CI, 1.43-1.70]). The mean interval from the index date through stroke onset was 92.86 months in the CRS group and 92.96 months in the control group; for IHD, it was 91.06 months

Table 1. General characteristics of the participants.

Characteristics	Total participants		
	Chronic rhinosinusitis (n, %)	Control (n, %)	P-value
Total number	6,552 (100.0)	26,208 (100.0)	
Age (years old)			1.000
40-44	416 (6.4)	1,664 (6.4)	
45-49	1,188 (18.1)	4,752 (18.1)	
50-54	1,435 (21.9)	5,740 (21.9)	
55-59	1,357 (20.7)	5,428 (20.7)	
60-64	989 (15.1)	3,956 (15.1)	
65-69	647 (9.9)	2,588 (9.9)	
70-74	342 (5.2)	1,368 (5.2)	
75-79	134 (2.1)	536 (2.1)	
80-84	38 (0.6)	152 (0.6)	
85+	6 (0.1)	24 (0.1)	
Sex			1.000
Male	4,000 (61.1)	16,000 (61.1)	
Female	2,552 (39.0)	10,208 (39.0)	
Income			1.000
1 (lowest)	778 (11.9)	3,112 (11.9)	
2	787 (12.0)	3,148 (12.0)	
3	991 (15.1)	3,964 (15.1)	
4	1,408 (21.5)	5,632 (21.5)	
5 (highest)	2,588 (39.5)	10,352 (39.5)	
Region of residence			1.000
Urban	3,096 (47.3)	12,384 (47.3)	
Rural	3,456 (52.8)	13,824 (52.8)	
Obesity †			<0.001*
Underweight	117 (1.8)	579 (2.2)	
Normal	2,145 (32.7)	9,234 (35.2)	
Overweight	1,942 (29.6)	7,332 (28.0)	
Obese I	2,171 (33.1)	8,357 (31.9)	
Obese II	177 (2.7)	706 (2.7)	
Smoking status			<0.001*
Nonsmoker	4,318 (65.9)	17,058 (65.1)	
Past smoker	919 (14.0)	3,104 (11.8)	
Current smoker	1,315 (20.1)	6,046 (23.1)	
Alcohol consumption			0.431
<1 time a week	4,357 (66.5)	17,293 (66.0)	
≥1 time a week	2,195 (33.5)	8,915 (34.0)	
Systolic blood pressure (mmHg)			<0.001*
<120	2,089 (31.9)	7,923 (30.2)	
120-139	3,195 (48.8)	12,487 (47.7)	
≥140	1,268 (19.4)	5,798 (22.1)	
Diastolic blood pressure (mmHg)			<0.001*
<80	2,928 (44.7)	11,288 (43.1)	

Characteristics	Total participants		
	Chronic rhinosinusitis (n, %)	Control (n, %)	P-value
80-89	2,396 (36.6)	9,458 (36.1)	
≥90	1,228 (18.7)	5,462 (20.8)	
Fasting blood glucose (mg/dL)			0.002*
<100	4,321 (66.0)	16,915 (64.5)	
100-125	1,744 (26.6)	6,990 (26.7)	
≥126	487 (7.4)	2,303 (8.8)	
Total cholesterol (mg/dL)			0.005*
<200	3,590 (54.8)	13,798 (52.7)	
200-239	2,143 (32.7)	8,862 (33.8)	
≥240	819 (12.5)	3,548 (13.5)	
Hemoglobin (g/dL)			0.617
≥ 12 for men and ≥ 10 for women	6,466 (98.7)	25,843 (98.6)	
< 12 for men and < 10 for women	86 (1.3)	365 (1.4)	
CCI score ‡			<0.001*
0	4,384 (66.9)	19,221 (73.3)	
1	1,033 (15.8)	3,079 (11.8)	
≥ 2	1,135 (17.3)	3,908 (14.9)	
Stroke	573 (8.6)	1,803 (6.9)	<0.001*
Ischemic heart disease	5,833 (11.0)	1,862 (7.1)	<0.001*

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ppb, parts per billion; SD, standard deviation. [a] Chi-square test or CCI, Charlson comorbidity index; * 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). ‡ CCI scores were calculated without considering cerebrovascular disease, acute myocardial infarction, and congestive heart failure.

in the CRS group and 92.10 months in the control group. After adjusting for obesity, alcohol consumption, smoking, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, and CCI scores (Tables S1 and S2), the prevalence of stroke (adjusted HR, 1.27 [95% CI, 1.15-1.39]) and IHD (adjusted HR, 1.55 [95% CI, 1.43-1.69]) was still increased significantly, as shown in the Kaplan-Meier survival curves in Figure 2.

The total CRS group was divided into two groups based on the presence or absence of nasal polyps (CRSsNP or CRScNP groups). In the CRSsNP group, the prevalence of stroke was significantly increased (crude HR, 1.50 [95% CI, 1.32-1.72] and adjusted HR, 1.51 [95% CI, 1.32-1.72]) compared with the control group. However, the CRScNP group showed crude and adjusted HRs of stroke of 1.09 (95% CI, 0.95-1.24) and 1.09 (95% CI, 0.96-1.25), respectively, which were not significantly different from those of the control group (P=0.225 and P=0.197, respectively) (Table 2).

The prevalence of IHD was significantly increased regardless of the presence of nasal polyps in both the CRSsNP and CRScNP groups (adjusted HR, 1.83 [95% CI, 1.62-2.06] and adjusted HR, 1.34 [95% CI, 1.18-1.51], respectively) (Table 3).

Discussion

In this study, CRS patients had increased prevalence rates of stroke and IHD compared to controls, and this finding was independent of other possible confounding factors, including hypertension, diabetes, high blood cholesterol levels, alcohol consumption, and smoking. To the best of our knowledge, none of the previous studies distinguished among subtypes of CRS, and this study was the first to report an evaluation of the relation between CVD and CRS subtypes during the long-term follow-up period.

The overall prevalence of stroke was significantly increased by 1.27-fold (95% CI, 1.15-1.39) compared to that in the controls. The increasing trend was consistent with the data for stroke from our previous study (13), but the degree of increase in the prevalence was small (adjusted HR=2.43 for hemorrhagic stroke; adjusted HR=1.76 for ischemic stroke). In the current study, 1,021,172 participants from completely different cohorts

Table 2. Crude and adjusted hazard ratios (95% confidence interval) of CRS total/CRScNP/CRSsNP compared with each control group for stroke.

Independent variables	Stroke/participants (n, %)	Follow-up duration (PY)	IR per 10000 (PY)	Hazard ratios (95% CI) for stroke			
				Crude†	P-value	Adjusted†‡	P-value
CRS total and Control group (n = 32,760)							
CRS total	573/6,552 (8.7)	47,507	120.6	1.27 (1.16-1.40)	<0.001*	1.27 (1.15-1.39)	<0.001*
Control	1,803/26,208 (6.9)	190,337	94.7	1		1	
CRSsNP and Control group (n = 15,995)							
CRSsNP	296/3,199 (9.3)	21,314	138.9	1.50 (1.32-1.72)	<0.001*	1.51 (1.32-1.72)	<0.001*
Control	803/12,796 (6.3)	86,450	92.9	1		1	
CRScNP and Control group (n = 16,765)							
CRScNP	277/3,353 (8.3)	26,193	105.8	1.09 (0.95-1.24)	0.225	1.09 (0.96-1.25)	0.197
Control	1,000/13,412 (7.5)	103,887	96.3	1		1	

CRS, Chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRScNP, CRS with nasal polyps; CCI, Charlson Comorbidity Index; IR, Incidence rate; PY, Person-years. * Stratified Cox proportional hazard regression model, significance at P < 0.05. † Models were stratified by age, sex, income, and region of residence. ‡ The model was adjusted for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, and CCI score.

Table 3. Crude and adjusted hazard ratios (95% confidence interval) of CRS total/CRScNP/CRSsNP compared with each control group for ischemic heart disease.

Independent variables	Ischemic heart disease/ participants (n, %)	Follow-up duration (PY)	IR per 10000 (PY)	Hazard ratios (95% CI) for ischemic heart disease			
				Crude†	P-value	Adjusted†‡	P-value
CRS total and Control group (n = 32,760)							
CRS total	719/6,552 (11.0)	46,527	154.5	1.56 (1.43-1.70)	<0.001*	1.55 (1.43-1.69)	<0.001*
Control	1,862/26,208 (7.1)	188,476	98.8	1		1	
CRSsNP and Control group (n = 16,765)							
CRSsNP	384/3,199 (12.0)	20,875	184.0	1.82 (1.61-2.05)	<0.001*	1.83 (1.62-2.06)	<0.001*
Control	863/12,796 (6.7)	85,540	100.9	1		1	
CRScNP and Control group (n = 15,995)							
CRScNP	335/3,353 (10.0)	25,652	130.6	1.35 (1.19-1.53)	<0.001*	1.34 (1.18-1.51)	<0.001*
Control	999/13,412 (7.4)	102,936	97.1	1		1	

CRS, Chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRScNP, CRS with nasal polyps; CCI, Charlson Comorbidity Index. * Stratified Cox proportional hazard regression model, significance at P < 0.05. † Models were stratified by age, sex, income, and region of residence. ‡ The model was adjusted for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, and CCI score.

from the previous study were analyzed. To have more useful implications in the clinical setting, the current study enrolled new participants aged 40 years or older who had undergone an otolaryngology examination, unlike the previous study, which included subjects of all ages from 0 to 100 years old. The previous study limited the diagnosis of stroke to hemorrhagic (I60-I62) and ischemic (I63) stroke, but this study expanded the range of diagnostic ICD-10 codes (I60-I69) to include all primary or secondary cerebrovascular diseases, including unspecified stroke (I64), precerebral or cerebral artery stenosis (I65-I66), other cerebrovascular diseases (I67-I68) and sequelae of cerebrovascular disease (I69). Moreover, the major finding of the present study added that CRS patients had a higher prevalence of IHD, expanding on the previous study.

Specifically, several studies have presented a positive association between CRS and CVD. Consistent with the current results, Wattanachayakul et al. demonstrated that CRS patients had a 1.79-fold (95% CI, 1.34 to 2.40) higher risk of stroke through a systematic review and meta-analysis comprising 447,065 patients, in which three retrospective cohort, case-control, and

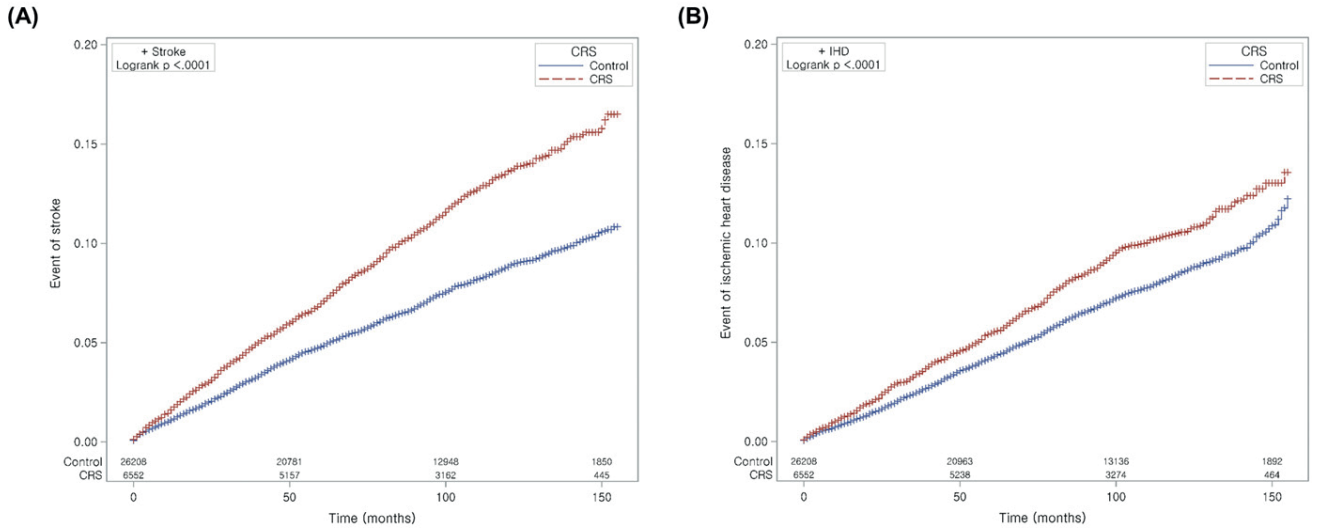

Figure 2. Kaplan-Meier curves are presented for the prevalence of stroke (A) and ischemic heart disease (B) among chronic rhinosinusitis (CRS) and control participants. The log-rank test displays the significant difference between two survival curves. Abbreviations: IHD=, ischemic heart disease.

cross-sectional studies were included [24]. In addition, two previous studies presented outcomes for the relation between CRS and acute myocardial infarction (AMI). Hao et al. reported an HR for developing AMI of 1.78 (95% CI, 1.37 to 2.32) in CRS patients after adjusting for age, sex, area of residence, hypertension, diabetes, hyperlipidemia, and cancer [15]. Wang et al. also investigated the 1.48-fold (95% CI, 1.32 to 1.67) increase in the risk of AMI in CRS patients compared with that in the controls during the 6-year follow-up period [14]. In addition to acute AMI (I21) in previous studies, we expanded heart diseases to include angina pectoris (I20), other myocardial infarctions and other complications (I22-I23), and chronic ischemic heart diseases (I25). Similarly, the present study found a 1.55-fold (95% CI, 1.43 to 1.69) increased prevalence of IHD, consistent with earlier reports.

The detailed pathological mechanisms underlying the relationship between CRS and CVD are unclear. CRS is a predisposing factor for CVD through certain pathophysiological pathways and is possibly related to the chronic inflammatory response of this disease. Numerous studies have revealed that chronic inflammation plays a crucial mediating role in the development of atherosclerosis by disrupting the integrity and function of endothelial cells [15]. First, numerous studies have provided epidemiological evidence of the positive association between high plasma C-reactive protein (CRP) levels and atherosclerosis [25,26], and previous studies reported positive staining for CRP deposition in atherosclerotic lesions [27-29]. Consistent with these findings, elevated CRP levels can predict the risk of a predisposition to atherosclerosis, which suggests myocardial necrosis accompanying lethal coronary thrombosis [30]. CRP is well known as an acute-phase protein stimulating the complement system via classic inflammatory responses and may maintain chronic inflammatory responses by activating complement in the arterial wall [27]. Moreover, Torzewski et al. demonstrated the active role of CRP in inducing chemotactic activity for monocyte migration in human atherogenesis [25]. Second, Huber et al. demonstrated that exogenous administration of IL-6 significantly increased fatty lesion occurrence in atherosclerosis-prone mice [31]. Many studies have emphasized that IL-6 is one of the upstream proinflammatory cytokines that play a critical role in generating the downstream inflammatory reactions responsible for atherosclerosis [32]. Third, reactive oxygen species (ROS) are regarded as hyperactive oxygen species produced during the normal oxidative chemical reactions of cells and participate in oxidative reactions with various vital cellular processes. Dalgi et al. demonstrated a positive correlation with the plasma and tissue levels of ROS, which are peroxidation products, but a negative correlation with antioxidants in patients with nasal polyposis via a prospective randomized controlled study [33]. Consistently, oxidative stress is associated with vascular inflammatory responses induced by angiotensin II, which is a major stimulator of ROS production [34]. These common predisposing conditions are associated with the increased production of ROS [35]. Various potential inflammatory pathways have been shown to be increasingly involved in the process of atherosclerosis and in the pathogenesis of CVD [11,36,37]. Another emerging paradigm is that infection with bacterial and/or viral pathogens in patients with inflammatory diseases may cause atherosclerosis through direct invasion of vascular cells or through the indirect effects of acute-phase proteins or cytokines, such as alpha-1-antitrypsin, C3 complement, ferritin, haptoglobin, plasminogen activator inhibitor 1, IL-6 or IL-1β, induced by infection in the nonvascular site [32,38-40]. Several studies have reported that *C. pneumoniae* may accelerate the development of atherosclerosis [41]. Danesh et al. reviewed epidemiological studies of *C. pneumonia* antibodies and CVD that reported 2-fold

or greater odds ratios [42]. Since the initial study by Fong et al. demonstrated that *C. pneumoniae* can cause atherosclerotic changes in the aorta using a rabbit model, additional experiments have been performed [43,44]. *Chlamydia pneumoniae* is a common respiratory pathogen and is known to be an important causative pathogen of respiratory infection, including sinusitis [45]. These findings suggest that comorbid pathogens of sinusitis may be implicated as a possible cause of atherosclerosis.
Alternatively, drugs used to manage CRS may pose a risk of side effects from corticosteroids or decongestants. Glucocorticoid excess not only stimulates cardiovascular risk factors but also accelerates the development and progression of atheromatous vascular disease [46,47]. Decongestants are α-adrenergic agonists and are usually prescribed to relieve the nasal obstructive symptoms of CRS patients. Decongestants can cause systemic peripheral vasoconstriction leading to high blood pressure and adverse interactions with other drugs, including tricyclic antidepressants, monoamine oxidase inhibitors, some general anesthetics, and other central nervous system stimulants [48]. Some concomitant symptoms or complications of CRS can increase the risk of atherosclerosis. For example, CRS patients experience sleep-disordered breathing, including obstructive sleep apnea, which plays a critical role in developing atherosclerotic conditions [49]. In the case of stroke, infected thrombi or septic emboli originating from a primary infected focus, especially posterior ethmoiditis and sphenoiditis, can lead to stroke because of anatomical characterization in which these sinuses intersect the internal cerebral artery with a 0.1-mm thin bone wall and vessels originating from the internal carotid artery (ICA) system through the anterior and posterior ethmoidal arteries supply the roof of the skull base [50,51].
Previous studies on the association between CRS patients and CVD have generally overlooked diverse subtypes of CRS [12-15]. Simply, CRS can be classified according to whether it is accompanied by nasal polyps. In our subgroup analysis, the CRSsNP group had a slightly (1.09-fold) higher stroke incidence, but the difference did not achieve statistical significance compared to the control group. Many studies have indicated that cerebral and myocardial ischemic diseases have similar pathophysiological mechanisms and share various cardiovascular risk factors [52,53]. However, there were differences between the incidence of ischemic stroke and myocardial infarction; specifically, older subjects with a higher diastolic blood pressure had an increased incidence of ischemic stroke, while male subjects with hyperlipidemia and a smoking history had an increased incidence of myocardial infarction [52]. Additionally, we compared the incidence of stroke between two groups according to the presence or absence of NP after adjusting for the traditional risk factors of age, sex, hypertension, hyperlipidemia, and smoking. Interestingly, the results showed that the higher incidence of stroke in the CRSsNP group did not attain statistical significance. We hypothesized that other unidentified confounding factors associated with the pathological mechanism of nasal polyp formation may have contributed to this difference. Nasal polyp formation is frequently associated with allergic sensitization to aeroallergens, and its prevalence is higher in subjects with asthma than in those without [2,17]. Furthermore, Matheson et al. reported that participants with both an atopic respiratory condition and positive allergy skin testing had a significantly increased HR for fatal stroke mortality (2.11 [95% CI, 1.02–4.37]) [54]. Unfortunately, we did not have information on either asthma or allergic traits, including allergy tests for specific aeroallergens, plasma levels of immunoglobulin E, and eosinophils. If the subgroup analysis was performed again considering confounding factors such as allergic status or asthma history, a different result may have been obtained.
The present study has several strengths. Foremost, the advantage of this cohort study is that it provides enough time for CVD progression after CRS with a longer follow-up period of 14 years compared to previous large population-based studies. We were able to adjust for general characteristics of the CRS group as well as potential confounding variables such as obesity, alcohol consumption, smoking, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, and CCI scores. High blood pressure is a major adjustable risk factor for stroke, and it is estimated that 51% of stroke deaths are due to elevated systolic blood pressure [55]. Therefore, adjusting for blood pressure was a strength of this study. In addition, this study found that CRS and CVD were not based on self-report but on physician diagnosis determined through established clinical guidelines to improve diagnostic accuracy. However, missed diagnoses of physicians could not be avoided.
There are some limitations to our study. The results of this case-control cohort study showed that CRS may be a predisposing factor influencing the incidence of CVD, but more additional confounding factors can be considered depending on the level of evidence in future studies. We were also unable to directly investigate and analyze the pathomechanisms based on the causal relationship between CRS and CVD. Although there were no missing clinical and mortality data from medical institutions, including all hospitals across the country, during the follow-up period, a possible selection bias may exist. This is because participants are more likely to miss a follow-up visit if they emigrate to another country. Additionally, patients with chronic underlying diseases, such as hypertension, a major factor of CVD, are likely to visit medical institutions more frequently than healthy volunteers, which increases the probability of being diagnosed with CRS. For this reason, detection or surveillance bias may have occurred in this study. The degree, duration, and severity of CRS and the history of medications, such as oral or topical intranasal formulations of corticosteroids or decongestants, were not reflected in this study. Erickson et al. demonstrated

that systemic and topical decongestants exhibit comparable activity in the nasal cavity and produce similar cardiovascular effects, characterized by significant elevation in blood pressure [56]. Moreover, we did not fully understand the impact of surgical treatments of CRS on CVD prevalence. Jeremiah et al. revealed that CRSwNP patients showed significant improvement of cognitive dysfunction following endoscopic sinus surgery [4]. Further studies are needed to confirm the existence of an effect of surgical treatment on CVD prevalence. Likewise, we could not eliminate the impact of unmeasured or residual confounding factors because CRS is related to many known risk factors for CVD. Even though the CCI scores include the 17 categories of comorbidities, there may be numerous comorbidities that were not considered covariates in this study. Although this study considered the subgroups of CRS according to accompanying nasal polyps, CRS has been recognized as a heterogeneous disease and is characterized as a constellation of inflammatory conditions [57].

Conclusion

The current study investigated whether CRS may have a significant association with CVD. We observed that CRS patients had a higher prevalence of comorbid stroke and IHD. Therefore, we can suggest that clinicians who manage CRS patients need to intensively monitor the development of stroke and IHD.

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Authorship contribution

YJJ, HGC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YJJ, HGC; Acquisition, analysis, or interpretation of data: THL, HJC, SWK, YHJ; Drafting of the manuscript: BP, HGC; Critical revision of the manuscript for important intellectual content: BP, HGC; Statistical analysis: YJJ, THL, HGC; Obtained funding: YJJ, HGC; Administrative, technical, material support: YJJ, HGC; Supervision: HGC.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Hyo Geun Choi, MD, PhD
Department of Otorhinolaryngology
Head & Neck Surgery
Hallym University Sacred Heart Hospital
Hallym University College of Medicine
22, Gwanpyeong-ro 170-beon-gil
Dongan-gu, Anyang
Gyeonggi-do, 14068
Republic of Korea

Tel: 82-31-380-3849
Fax: 82-31-386-3860
E-mail: pupen@naver.com