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Association between neurodegenerative dementia and chronic rhinosinusitis

A nested case-control study using a national health screening cohort

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Abstract

The aim of this case-control study was to evaluate the association between chronic rhinosinusitis (CRS) and neurodegenerative dementia in a large representative Korean population. The ≥ 50-year-old population was selected from the Korean Health Insurance Review and Assessment Service – National Sample Cohort from 2002 to 2015. A total of 17,634 neurodegenerative dementia patients were matched in a 1:4 ratio with 70,536 control participants for age, sex, income, and region of residence. Neurodegenerative dementia was defined using the ICD-10 codes G30 and F00. CRS was identified based on the ICD-10 code J32. Among the cohort, we selected participants who were treated ≥ 2 times and those who underwent head and neck computed tomography. The odds ratio (OR) for CRS in patients with dementia was analyzed using a conditional logistic regression model. Subgroup analyses were conducted according to age and sex. There was no difference in the prevalence of CRS with/without nasal polyps between the dementia (1.1%) and control (1.2%) groups ($P = .825$). CRS with/without nasal polyps was not significantly associated with dementia (adjusted OR = 0.96, 95% CI = 0.82–1.13, $P = .653$). In the subgroup analyses according to age and sex, the adjusted ORs for CRS with/without nasal polyps were not higher in the dementia group than in the control group. Previous CRS was not associated with neurodegenerative dementia in the Korean population.

Abbreviations: BMI = Body mass index, CI = Confidence interval, CCI = Charlson Comorbidity Index, CRS = chronic rhinosinusitis, OR = odds ratio.

Keywords: Alzheimer disease, case-control studies, dementia, population surveillance, sinusitis

1. Introduction

Dementia is a prevalent neurodegenerative disease that results in a significant public health burden. Worldwide, approximately 50 million people have dementia, and there are nearly 10 million new cases every year.[1] Alzheimer disease is the most common cause of dementia. In Korea, the prevalence of dementia was 9.2% and of Alzheimer disease was 5.7% in elderly patients (aged ≥ 65 years); these values were higher than those from Western and other Asian countries.[2] Several epidemiologic studies have suggested that infectious diseases, such as

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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periodontitis,[3] and noninfectious diseases, including atherosclerosis,[4] type 2 diabetes,[5] and obesity,[6] are risk factors for the development of neurodegenerative dementia. These diseases are related to a chronic inflammatory phenotype.[7]

Chronic rhinosinusitis (CRS) is chronic inflammation of the nose and paranasal sinuses, with significant effects on several comorbidities and quality of life. Previous studies have reported an association between CRS and cognitive dysfunction, although the subjects in these studies were aged more than 18 years; there were not considered elderly. In a U.S. case-control study, total Cognitive Failure Questionnaire scores (subjective cognitive function; 38.3 ± 16.5 vs 30.9 ± 12.5, $P = .009$) and simple reaction time (objective cognitive function test; 162.4 ± 56.2 vs 193.0 ± 44.6, $P = .003$) were significantly worse in the CRS group than in the control group.[8] A cross-sectional study in the U.S. reported a significant positive correlation between cognitive dysfunction and disease-specific quality of life and facial pain scores in patients with CRS.[9]

We hypothesized that CRS would increase the risk of dementia because CRS is a chronic inflammatory disease and chronic inflammation is known to play an important role in the development and progression of dementia. The aim of this case-control study was to compare the previous history of CRS in patients with neurodegenerative dementia and a control group matched for age, sex, income, and region of residence in a large representative population.

2. Materials and methods

2.1. Study population

The ethics committee of Hallym University (2017-I102) 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. A detailed description of the Korean National Health Insurance Service – Health Screening Cohort data is described elsewhere.[10]

2.2. Definition of dementia

Neurodegenerative dementia was defined as a diagnosis of Alzheimer disease (G30) or dementia in Alzheimer disease (F00). For the accuracy of the diagnosis, we selected only participants who were treated ≥ 2 times following the methods in our previous studies.[11,12]

2.3. Definition of chronic rhinosinusitis

CRS was defined using an ICD-10 code (J32). Among those with CRS, we selected the participants who were treated ≥ 2 times and those who underwent head and neck computed tomography evaluations (claim codes: HA401-HA416, HA441-HA443, HA451-HA453, HA461-HA463, or HA471-HA473). A total of 4423 participants were also diagnosed with nasal polyps (J33), and 4,137 participants were not.

2.4. Participant selection

Dementia patients were selected from 514,866 patients with 497,931,549 medical claim codes from 2002 through 2015 (n = 20,087). The control group included participants who were not diagnosed with dementia from 2002 through 2015 (n = 494,779). Dementia patients with a 1-year washout period were excluded (n = 168). Control participants were excluded if they were diagnosed with dementia once (n = 5,440). Dementia patients were matched in a 1:4 ratio with control participants for age, sex, income, and region of residence. To minimize selection bias, the control participants were selected with a random number method. The index date of each dementia patient was considered the time of treatment of dementia. The index date of control participants was considered the index date of their matched dementia patients. Therefore, each matched dementia patient and control participants had the same index date. During the matching procedure, 2,234 dementia patients and 418,599 control participants were excluded. Additionally, participants were excluded if they were < 50 years old (n = 51 for dementia patients, n = 204 for control participants). Finally, 17,634 dementia patients were 1:4 matched with 70,536 control participants (Fig. 1).

2.5. Covariates

Age groups were divided into 5-year intervals, from 50 to 54 . . . to 85+ years old. A total of 8 age groups were specified. Income groups were classified into 5 classes (class 1 [lowest income]–5 [highest income]). The region of residence was classified as urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) or rural (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, or 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 body mass index (BMI, kg/m^2). Missing BMI variables (n = 63) were replaced by the mean BMI ($23.75\,kg/m^2$) of the 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.[13] The Charlson Comorbidity Index (CCI) has been used widely to measure disease burden considering 17 comorbidities. In our study, we excluded dementia from the CCI score. A score was given to each participant depending on the severity and number of diseases. The CCI was measured as a continuous variable (0 [no comorbidities] through 29 [multiple comorbidities]).[14,15] The CCI score was used as a covariate in the analyses.

Regarding dementia and CRS, extrapyramidal and movement disorders (ICD-10 codes: G20 to G26), other degenerative diseases of the nervous system (G31 to G32), and head trauma histories (S00–S09) were additionally noted if participants were treated ≥ 2 times.

2.6. Statistical analysis

The general characteristics of the dementia and control groups were compared using the Chi-squared test. To analyze the odds ratios (ORs) with 95% confidence intervals (CIs), a conditional logistic regression model was used for total CRS, CRS with nasal polyps, and CRS without nasal polyps in the dementia and control groups. In these analyses, the crude model and the model adjusted for obesity, smoking, alcohol consumption, extrapyramidal and movement disorders, other degenerative diseases of the

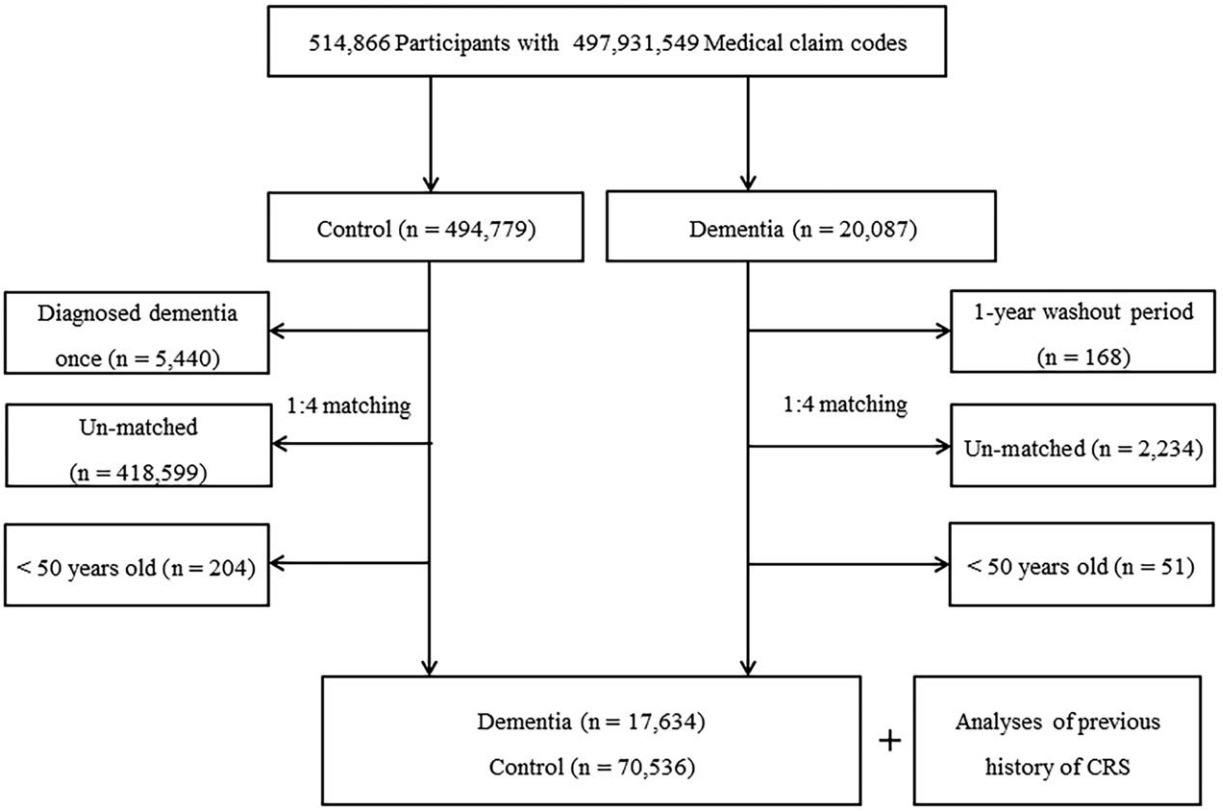

Figure 1. A schematic illustration of the participant selection process that was used in the present study. Of a total of 514,866 participants, 17,634 dementia patients were matched in a 1:4 ratio with 70,536 control participants for age, sex, income, and region of residence.

nervous system, head trauma histories, and CCI scores were calculated. The analysis was stratified by matching variables such as age, sex, income, and region of residence.

For the subgroup analyses, we divided participants by age and sex (< 75 and ≥ 75 years old; men and women) and analyzed the crude and adjusted models in both studies.

Two-tailed analyses were performed, and significance was defined as a *P* value less than .05. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for the statistical analyses.

3. Results

There was no difference in the prevalence of CRS with/without nasal polyps between the dementia (1.1%) and control (1.2%) groups ($P = .825$, Table 1). The general characteristics of the participants, including age, sex, income, region of residence, and smoking status, did not differ due to matching. Obesity ($P < .001$) and frequent alcohol consumption ($P = .026$) were more common in the control group than in the dementia group. The numbers of subjects with a high CCI score, extrapyramidal and movement disorders, other degenerative diseases of the nervous system, and head trauma history were higher in the dementia group than in the control group (all $P < .001$).

CRS with/without nasal polyps was not significantly associated with dementia (adjusted OR [aOR] = 0.96, 95% CI = 0.82–1.13, $P = .653$, Table 2). The aOR for CRS with nasal polyps was 0.91 (95% CI = 0.72–1.15, $P = .433$), and the aOR for CRS without nasal polyps was 1.02 (95% CI = 0.81–1.27, $P = .882$) between the dementia and control groups.

Subgroup analyses according to age and sex were performed (Table 3). The aOR for CRS with/without nasal polyps was not higher in the dementia group than in the control group. The aORs were 1.11 (95% CI = 0.81–1.51) in < 75-year-old men, 1.08 (95% CI = 0.81–1.44) in < 75-year-old women, 0.60 (95% CI = 0.39–0.92) in ≥ 75-year-old men, and 1.00 (95% CI = 0.73–1.37) in ≥ 75-year-old women.

4. Discussion

The present study showed that CRS was not associated with neurodegenerative dementia. We obtained consistent results in the subgroup analyses according to age and sex.

Chronic inflammation has been suggested as a potential mechanism for the association between CRS and dementia. In a meta-analysis, neurodegenerative dementia was accompanied by an inflammatory response, particularly increased peripheral concentrations of IL-6, TNF-α, IL-1β, TGF-β, IL-12, and IL-18.[16] IL-6, TNF-α, and IL-1β are generally considered important proinflammatory cytokines and are increased in the mucosa of patients with CRS.[17] TGF-β controls remodeling and is upregulated in CRS without nasal polyps.[18] However, it is unknown whether increased cytokines in CRS patients actually play a role in the onset or progression of neurodegenerative dementia. Similar to the present study, the prevalence of sinusitis in patients with Alzheimer disease or dementia was not higher than in the general population in Japan (6.3% vs 5.4%).[19] In another study of elderly individuals in Japan, there was also no significant difference in the Mini-Mental State Examination

Table 1

General Characteristics of Participants.

Characteristics	Total participants		
	Dementia (n, %)	Control (n, %)	*P*-value
Age (yr old)			1.000
50–54	188 (1.1)	752 (1.1)	
55–59	443 (2.5)	1772 (2.5)	
60–64	983 (5.6)	3932 (5.6)	
65–69	2269 (12.9)	9076 (12.9)	
70–74	4315 (24.5)	17,260 (24.5)	
75–79	5372 (30.5)	21,488 (30.5)	
80–84	3567 (20.2)	14,268 (20.2)	
85+	497 (2.8)	1988 (2.8)	
Sex			1.000
Male	7049 (40.0)	28,196 (40.0)	
Female	10,585 (60.0)	42,340 (60.0)	
Income			1.000
1 (lowest)	3599 (20.4)	14,396 (20.4)	
2	2020 (11.5)	8080 (11.5)	
3	2409 (13.7)	9636 (13.7)	
4	3185 (18.1)	12,740 (18.1)	
5 (highest)	6421 (36.4)	25,684 (36.4)	
Region of residence			1.000
Urban	6222 (35.3)	24,888 (35.3)	
Rural	11,412 (64.7)	45,648 (64.7)	
Obesity[†]			<.001[*]
Underweight	941 (5.3)	2948 (4.2)	
Normal	7084 (40.2)	25,567 (36.3)	
Overweight	4178 (23.7)	18,103 (25.7)	
Obese I	4921 (27.9)	21,678 (30.7)	
Obese II	510 (2.9)	2240 (3.2)	
Smoking status			.001[*]
Nonsmoker	13,876 (78.7)	55,631 (78.9)	
Past smoker	1772 (10.1)	7862 (11.2)	
Current smoker	1986 (11.3)	7043 (10.0)	
Alcohol consumption			.026
< One time a wk	13,610 (77.2)	52,147 (73.9)	
≥ One time a wk	4024 (22.8)	18,389 (26.1)	
CCI score			<.001[*]
0	6473 (36.7)	39,980 (56.7)	
1	4147 (23.5)	13,134 (18.6)	
2	2655 (15.1)	7577 (10.7)	
3	2004 (11.4)	4403 (6.2)	
≥ 4	2355 (13.4)	5442 (7.7)	
Extrapyramidal and movement disorders	3302 (18.7)	4914 (7.0)	<.001[*]
Other degenerative diseases of the nervous system	1567 (8.9)	2438 (3.5)	<.001[*]
Head trauma histories	4886 (27.7)	14,049 (19.9)	<.001[*]
CRS with/without polyp	201 (1.1)	818 (1.2)	.825
CRS with nasal polyp	94 (0.5)	427 (0.6)	.263
CRS without nasal polyp	107 (0.6)	391 (0.6)	.406

CCI = Charlson comorbidity index calculated without dementia, CRS = Chronic Rhinosinusitis.

[*] Chi-squared test. Significance at $P < .05$.

[†] 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).

scores between participants with sinusitis (27.5 ± 1.8) and those without sinusitis (27.9 ± 2.0) ($P = .28$).[20]

Another suggestion is hematogenous spreading of infections. Periodontal bacteria have been identified as a potential risk factor for dementia. A meta-analysis showed that periodontal parameters were significantly higher in patients with dementia than in subjects without cognitive decline.[21] In a recent study, it was hypothesized that pathological germs and related inflammatory processes may transcend to the paranasal sinuses and finally penetrate the cortex by hematogenous spreading.[22] However, the study showed that only bacterial loads and inflammation levels were higher in dementia patients than in controls and did not demonstrate the direct spread of infection through the sinuses. Notably, all of this evidence suggests only possibilities.

Few studies on the relationship between CRS and neurodegenerative dementia have been conducted, and the relationship is still unclear. A study utilizing data from the Taiwan Longitudinal Health Insurance Database 2000 showed that subjects with dementia had a higher prevalence and risk of prior CRS (aOR = 1.44, 95% CI = 1.25–1.66) than controls,[23] in contrast with our

Table 2

Crude and adjusted odds ratios (95% confidence interval) for CRS total/CRS with nasal polyp/CRS without nasal polyp in dementia and control groups.

	Odds ratios			
Characteristics	**Crude**[†]	***P*-value**	**Adjusted**[†,‡]	***P*-value**
CRS with/without nasal polyp				
Dementia	0.98 (0.84–1.15)	.825	0.96 (0.82–1.13)	.653
Control	1.00		1.00	
CRS with nasal polyp				
Dementia	0.88 (0.70–1.10)	.263	0.91 (0.72–1.15)	.433
Control	1.00		1.00	
CRS without nasal polyp				
Dementia	1.10 (0.88–1.36)	.406	1.02 (0.81–1.27)	.882
Control	1.00		1.00	

[*] Conditional logistic regression model, Significance at $P < .05$.

[†] Models stratified by age, sex, income, and region of residence.

[‡] Models adjusted for obesity, smoking, alcohol consumption, extrapyramidal and movement disorders, other degenerative diseases of the nervous system, head trauma histories, and CCI scores.

Table 3

Subgroup analyses of crude and adjusted odds ratios (95% confidence interval) for CRS total/CRS with nasal polyp/CRS without nasal polyp in dementia and control groups according to age and sex.

	Odds ratios			
Characteristics	**Crude**[†]	***P*-value**	**Adjusted**[†,‡]	***P*-value**
CRS with/without nasal polyp, age < 75 yr old, men (n = 16,645)				
Dementia	1.04 (0.77–1.40)	.807	1.11 (0.81–1.51)	.520
Control	1.00		1.00	
CRS with/without nasal polyp, age < 75 yr old, women (n = 24,345)				
Dementia	1.15 (0.88–1.51)	.314	1.08 (0.81–1.44)	.588
Control	1.00		1.00	
CRS with/without nasal polyp, age ≥ 75 yr old, men (n = 18,600)				
Dementia	0.63 (0.41–0.95)	.028[*]	0.60 (0.39–0.92)	.018[*]
Control	1.00		1.00	
CRS with/without nasal polyp, age ≥ 75 yr old, women (n = 28,580)				
Dementia	1.02 (0.75–1.39)	0.899	1.00 (0.73–1.37)	1.000
Control	1.00		1.00	
CRS with polyp, age < 75 yr old, men (n = 16,645)				
Dementia	0.91 (0.60–1.38)	.648	1.06 (0.68–1.64)	.805
Control	1.00		1.00	
CRS with polyp, age < 75 yr old, women (n = 24,345)				
Dementia	1.12 (0.75–1.67)	.584	1.08 (0.71–1.63)	.734
Control	1.00		1.00	
CRS with polyp, age ≥ 75 yr old, men (n = 18,600)				
Dementia	0.47 (0.26–0.86)	.015[*]	0.48 (0.26–0.89)	.019[*]
Control	1.00		1.00	
CRS with polyp, age ≥ 75 yr old, women (n = 28,580)				
Dementia	1.00 (0.64–1.57)	1.000	1.02 (0.65–1.61)	.934
Control	1.00		1.00	
CRS without polyp, age < 75 yr old, men (n = 16,645)				
Dementia	1.20 (0.79–1.82)	.396	1.18 (0.75–1.83)	.477
Control	1.00		1.00	
CRS without polyp, age < 75 yr old, women (n = 24,345)				
Dementia	1.18 (0.81–1.70)	.388	1.09 (0.74–1.60)	.672
Control	1.00		1.00	
CRS without polyp, age ≥ 75 yr old, men (n = 18,600)				
Dementia	0.88 (0.49–1.56)	.650	0.77 (0.43–1.39)	.385
Control	1.00		1.00	
CRS without polyp, age ≥ 75 yr old, women (n = 28,580)				
Dementia	1.04 (0.68–1.59)	.861	0.99 (0.64–1.53)	.956
Control	1.00		1.00	

[*] Conditional logistic regression model, significance at $P < .05$.

[†] Models stratified by age, sex, income, and region of residence.

[‡] Models adjusted for obesity, smoking, alcohol consumption, extrapyramidal and movement disorders, other degenerative diseases of the nervous system, head trauma histories, and CCI scores.

results. Discrepancies in how subjects were selected or how CRS was diagnosed may be a cause of the different results. In the Taiwan study, the authors included both vascular dementia and Alzheimer disease and identified CRS patients using only the ICD code. In addition, while the authors selected a control group matched for age and sex, we minimized potential biases between dementia and controls by matching age, sex, income, and region of residence. A high income, good socioeconomic status, and living in the city can affect access to medical care. A previous study of data in the Taiwan Longitudinal Health Insurance Database in 2005 found that CRS patients mostly lived in urban regions and had a higher monthly income than non-CRS patients.[24]

The results suggesting that there is no link between CRS and dementia can be explained by several factors. First, cognitive dysfunction can be improved after the application of sinus-specific therapies, including surgery. A prospective study in the US reported that appropriate medical therapy improved several measures of cognitive dysfunction in patients with CRS.[25] In addition, in a multicenter study, patients with CRS with nasal polyps reported significant improvements in cognitive scores after endoscopic sinus surgery.[26] The declines in inflammation and cytokines following medical treatment or surgery may be 1 factor driving improvements in cognition. Second, it is difficult for an infection to spread directly to the brain through the sinuses due to the blood-brain barrier. There has been no definitive evidence of infection as the pathophysiological mechanism of dementia. Furthermore, the present study was performed with adjustment for variable covariates, including the CCI, extrapyramidal and movement disorders, and other degenerative diseases of the nervous system. The incidence of comorbidities associated with chronic inflammation may influence the association between CRS and neurodegenerative dementia. Therefore, this association may not be significant when possible confounding factors are attenuated by adjusting for comorbidities.

There are several limitations to this study. First, there were no cognitive function test results, so we could not classify the patients according to the severity of dementia. However, the Korean National Health Insurance Service – Cohort data were validated to identify dementia.[27] Second, the prevalence of CRS was relatively low. In many epidemiological studies, the definition of CRS is based on symptoms usually without an endoscopic examination or radiology. The European position paper on rhinosinusitis and nasal polyps (EPOS) 2020 stated that the definition of CRS on the basis of only symptoms will overestimate the prevalence due to overlap with allergic rhinitis and nonallergic rhinitis.[28] A previous Korean population study found that the prevalence of symptom-based CRS was 10.8%, but it was 1.2% when diagnosed by symptoms plus endoscopy.[29] In the present study, similar to the previous study, the prevalence of CRS with/without nasal polyps was 1.2% (1,019/88,170). It is possible that bias was minimized by selecting patients who underwent head and neck computed tomography evaluations.

In conclusion, CRS was not related to the risk of neurodegenerative dementia in the adult Korean population.

Author contributions

All authors: review and approval of the final manuscript
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Formal analysis: Jee Hye Wee, Dae Myoung Yoo.
Funding acquisition: Jee Hye Wee, Hyo Geun Choi.
Supervision: Soo Hwan Byun, Seok Jin Hong, Min Woo Park, Hyo Geun Choi.
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Writing – original draft: Jee Hye Wee, Dae Myoung Yoo.
Writing – review & editing: Soo Hwan Byun, Seok Jin Hong, Min Woo Park, Hyo Geun Choi.

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