Association between the use of electronic cigarettes and the prevalence of chronic rhinosinusitis and allergic rhinitis: a nationwide cross-sectional study*

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Abstract

Background: Whether the use of electronic cigarettes (ECs) is associated with upper airway diseases, including chronic rhinosinusitis (CRS) and allergic rhinitis (AR), remains unclear.

Methods: We analyzed data from the nationwide cross-sectional surveys: the Korea National Health and Nutrition Examination Survey VI (2013–2015), VII (2016–2018), and VIII (2019). Logistic regression analysis was performed to assess the association between EC use and CRS or AR.

Results: Among a total of 38,413 participants, 6.4% were former EC users and 2.5% were current EC users. Former EC users and current EC showed a significantly increased OR for CRS or AR compared with never EC users. In the subgroup analysis, the "current CC (conventional cigarette)-current EC" and the "current CC-formal EC" group had a significantly higher OR for CRS or AR than the "current CC-never EC" group. In addition, former CC smokers who currently use ECs showed a significantly higher OR for AR than former CC smokers without EC use.

Conclusions: EC use is significantly associated with a high prevalence of CRS and AR in the adult population. These results indicate that the use of ECs may increase the risk of upper airway disease.

Key words: allergic rhinitis, chronic rhinosinusitis, electronic cigarette, smoking

Introduction

Chronic rhinosinusitis (CRS) and allergic rhinitis (AR) are the most common chronic inflammatory diseases of the upper airway worldwide [(1,2)]. They cause a substantial socioeconomic burden and negatively affect patients' quality of life. Although the exact pathophysiology of CRS and AR remains to be elucidated, several non-infectious environmental factors are known to play a role in the development of CRS and AR. A significant association has been reported between CRS and conventional cigarette (CC) exposure [(3,4)]. In addition, it has been shown that many occupational factors are linked to CRS [(4)]. Environmental factors associated with AR similarly include CC smoking, occupational irritants, air pollution, and animal exposure [(2)].

Electronic cigarettes (ECs) are newly developed devices that generate an aerosol by heating a liquid containing flavors, nicotine, propylene glycol (PG), vegetable glycerin (VG), and water [(5)]. ECs are designed to deliver nicotine to the brain without the combustion of tobacco [(6)]. As ECs have been introduced as a healthier alternative to CC smoking, they have appealed to CC smokers or non-smokers. Recently, the use of ECs has increased dramatically, particularly in the younger population [(6-8)]. However, little is known about the effect of ECs on human health.
In particular, whether EC use is associated with upper airway diseases, including CRS and AR, remains unclear.
In the present study, we analyzed data from a large nationwide survey in South Korea and investigated the association between

EC use and the prevalence of CRS or AR in adults. We also examined whether additional EC use is linked to a high prevalence of CRS or AR among former and current CC smokers.

Methods

Study participants and data collection

This study obtained data from the Korean National Health and Nutrition Examination Survey (KNHANES) VI (2013–2015), VII (2016–2018), and VIII (2019). The KNHANES is an annual nationwide survey conducted by the Korean Centers for Disease Control and Prevention since 1998. KNHANES extracts samples using a stratified multistage clustered probability sampling design and represents the non-industrialized South Korean population. The survey sample weights were constructed regarding the survey design, non-response rate, and post-stratification, adjusted for age and sex, for the survey population to be representative of the entire South Korean population. Among the total 55,327 participants, individuals who were under 19 years of age and individuals with missing values for any parameter (age, body mass index [BMI], sex, income, education level, smoking history, alcohol consumption, hypertension, diabetes mellitus [DM], asthma, atopic dermatitis, and pulmonary tuberculosis) were excluded. Finally, 38,413 participants were included in the study (Figure 1). All study participants agreed to participate in the survey, and informed consent was obtained from all participants or their legal guardians. This study was reviewed and approved by the Institutional Review Board (IRB) of the Korea Centers for Disease Control and Prevention (IRB No. 2013-07CON-03-4C, 2013-12EXP-03-5C, 2015-01-02-6C) and Severance Hospital, Seoul, South Korea (IRB No. 4-2021-0787).

Definition of variables

Participants were considered to have physician-diagnosed CRS (or AR) if they responded positively to, "Have you been diagnosed with CRS (or AR) by a physician?" The presence of other medical conditions was similarly determined by a self-reported physician's diagnosis. The experience of EC (or CC) use was determined by the questionnaire, "Have you ever used an EC (or CC)?" A "current EC user" (or "current CC smoker") was defined when their answer to the question, "Are you using ECs (or CCs) currently?" was "daily" or "frequently." If a participant answered that he or she had ever used ECs (or CCs) but not at the time of the survey, he or she was classified as a "former EC user" (or a "former CC smoker"). Participants who had never used ECs (or CCs) were classified as "never EC user" (or "never CC smoker").

Statistical analysis

SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. The KNHANES was designed using a multistage clustered probability sampling method. To obtain a nationally representative sample of the non-institutionalized South Korean population, all statistical analyses in the present study applied a complex survey design and sampling weight. Statistical significance was set at $P < 0.05$. The differences in general characteristics of the participants according to the presence of CRS or AR were analyzed with a t-test using the complex samples general linear model for continuous variables and the Pearson chi-square test with Rao-Scott adjustment for categorical variables. Logistic regression analysis with adjustments for possible confounders was performed to evaluate the association between EC use and the prevalence of CRS or AR.

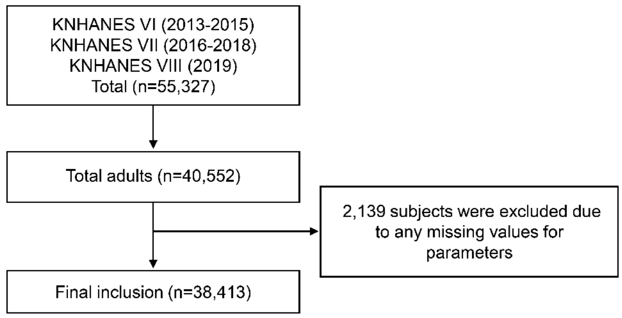

Figure 1. A flowchart of participant inclusion. Among the total 55,327 participants from the Korean National Health and Nutrition Examination Survey (KNHANES) VI (2013–2015), VII (2016–2018), and VIII (2019), individuals who were under 19 years of age and individuals with missing values for any parameter (age, body mass index, sex, income, education level, smoking history, alcohol consumption, hypertension, diabetes mellitus, asthma, atopic dermatitis, and pulmonary tuberculosis) were excluded. Finally, 38,413 participants were included in the study.

Results

General characteristics of the study population

In the KNHANES VI (2013-2015), VII (2016–2018), and VIII (2019), a total of 55,327 individuals were investigated. Of these, 38,413 individuals were included in the current study. A flowchart of participant enrollment is presented in Figure 1. The mean age of the study population was 46.6 years, and 49.3% of the participants were men. The prevalence rates of CRS and AR were 7.3% and 15.4%, respectively. Of all participants, 21.1% were former CC smokers and 21.9% were current CC smokers. In addition, 6.4% were former EC users, and 2.5% were current EC users. The characteristics of the study population are presented in Table 1. Participants with CRS were younger (mean age of CRS vs. non-CRS, 42.1 ± 0.28 vs. 47.0 ± 0.12; P<0.001) and had higher incomes (high income, 52.0% vs. 49.9%; P=0.029) and education levels (high education level, 84.3% vs. 75.6%; P<0.001) than those without CRS, while there was no significant difference in BMI (23.9 ± 0.07 vs. 23.9 ± 0.02; P=0.962) and sex composition (female, 50.5% vs. 50.8%; P=0.158) between the two populations. In addition, EC use (P<0.001), but not CC smoking (P=0.141),

Table 1. Characteristics of the study population according to the presence of CRS and AR.

Parameter	Total	CRS		P value[a]	AR		P value[a]
	(n=38,413)	(-), n=35,772	(+), n=2,641		(-), n=33,142	(+), n=5,367	
Age, years	46.6 ± 0.11	47.0 ± 0.12	42.1 ± 0.28	<0.001	47.8 ± 0.12	39.9 ± 0.16	<0.001
BMI	23.9 ± 0.02	23.9 ± 0.02	23.9 ± 0.07	0.962	23.9 ± 0.02	23.5 ± 0.04	<0.001
Sex				0.158			<0.001
Female	50.7 (0.2)	50.8 (0.2)	50.5 (0.9)		49.5 (0.2)	57.3 (0.6)	
Male	49.3 (0.2)	49.2 (0.2)	49.5 (0.9)		50.5 (0.2)	42.7 (0.6)	
Income				0.029			0.079
Low	49.9 (0.4)	50.1 (0.4)	48.0 (1.0)		50.1 (0.4)	48.9 (0.8)	
High	50.1 (0.4)	49.9 (0.4)	52.0 (1.0)		49.9 (0.4)	51.1 (0.8)	
Education				<0.001			<0.001
Low	23.7 (0.3)	24.3 (0.3)	15.7 (0.6)		25.8 (0.3)	12.4 (0.4)	
High	76.3 (0.3)	75.6 (0.3)	84.3 (0.6)		74.2 (0.3)	87.6 (0.4)	
CC				0.141			<0.001
Never	57.0 (0.2)	56.9 (0.2)	57.7 (0.9)		56.2 (0.2)	61.7 (0.6)	
Former	21.1 (0.2)	21.1 (0.2)	21.8 (0.7)		21.4 (0.2)	19.8 (0.5)	
Current	21.9 (0.2)	22.0 (0.2)	20.5 (0.8)		22.5 (0.2)	18.5 (0.5)	
EC				<0.001			<0.001
Never	91.1 (0.2)	91.3 (0.2)	88.5 (0.6)		91.3 (0.2)	89.7 (0.4)	
Former	6.4 (0.1)	6.2 (0.1)	8.6 (0.6)		6.3 (0.1)	6.9 (0.3)	
Current	2.5 (0.1)	2.5 (0.1)	3.0 (0.3)		2.4 (0.1)	3.3 (0.2)	
Alcohol consumption				<0.001			<0.001
None	9.2 (0.1)	9.4 (0.1)	6.5 (0.4)		9.8 (0.2)	5.9 (0.3)	
<1/month	32.3 (0.2)	32.2 (0.2)	33.6 (0.8)		32.1 (0.2)	33.2 (0.6)	
1/month≤	58.5 (0.3)	58.4 (0.3)	59.8 (0.8)		58.1 (0.3)	60.9 (0.6)	
Hypertension	18.6 (0.2)	19.1 (0.2)	12.8 (0.5)	<0.001	20.2 (0.2)	10.3 (0.3)	<0.001
Diabetes Mellitus	7.3 (0.1)	7.5 (0.1)	4.7 (0.3)	<0.001	8.0 (0.1)	3.5 (0.2)	<0.001
Asthma	3.0 (0.1)	2.7 (0.1)	6.6 (0.5)	<0.001	2.2 (0.1)	7.3 (0.3)	<0.001
Atopic dermatitis	3.5 (0.1)	3.3 (0.1)	5.6 (0.4)	<0.001	2.7 (0.1)	8.1 (0.3)	<0.001
Tuberculosis	3.5 (0.1)	3.6 (0.1)	3.1 (0.4)	<0.001	3.6 (0.1)	2.9 (0.2)	<0.001

Abbreviations: CRS, chronic rhinosinusitis; AR, allergic rhinitis; BMI, body mass index; CC, conventional cigarette; EC, electronic cigarette. Data are presented as mean ± standard error or weighted percentage (standard error). [a] Statistical analyses were performed using a t-test using the complex samples general linear model or the Pearson chi-square test with Rao-Scott adjustment.

was significantly associated with CRS. Furthermore, participants with CRS had more frequent alcohol intake than those without CRS (P<0.001). Significantly lower frequencies of hypertension (12.8% vs. 19.1%; P<0.001), DM (4.7% vs. 7.5%; P<0.001), and pulmonary tuberculosis (3.1% vs. 3.6%; P<0.001) were observed in patients with CRS. In contrast, asthma (6.6% vs. 2.7%; P<0.001) and atopic dermatitis (5.6% vs. 3.3%; P<0.001) were more prevalent in patients with CRS.

When we next compared participants with AR and those without AR, age (AR vs. non-AR, 39.9 ± 0.16 vs. 47.8 ± 0.12; P<0.001) and BMI (23.5 ± 0.04 vs. 23.9 ± 0.02; P<0.001) were significantly lower in participants with AR. In addition, a higher education level (high education level, 87.6% vs. 74.2%; P<0.001) was observed in participants with AR, whereas income (high income, 51.1% vs. 49.9%; P=0.079) did not differ between the two populations. Similar to the case of CRS, EC use (P<0.001) and alcohol intake (P<0.001) were significantly associated with AR. Intriguingly, significantly lower frequencies of current and former CC users were observed in participants with AR than in those without AR (P<0.001). Patients with AR had a significantly higher prevalence of asthma (7.3% vs. 2.2%; P<0.001) and atopic dermatitis (8.1% vs. 2.7%; P<0.001), whereas hypertension (10.3% vs. 20.2%; P<0.001), DM (3.5% vs. 8.0%; P<0.001), and pulmonary tuberculosis (2.9% vs. 3.6%; P<0.001) were less com-

Table 2. Characteristics of the study population according to status of EC use.

Parameter	Never user (n=35,792)	Former user (n=1,896)	Current user (n=725)	P value [a]
Age, years	47.8 ± 0.12	37.1 ± 0.25	36.3 ± 0.34	<0.001
BMI	23.8 ± 0.02	24.5 ± 0.07	24.7 ± 0.12	<0.001
Sex				<0.001
Female	54.4 (0.2)	12.8 (0.6)	13.8 (1.1)	
Male	45.6 (0.2)	87.2 (0.6)	86.2 (1.1)	
Income				0.093
Low	49.8 (0.4)	51.8 (1.0)	48.4 (1.6)	
High	50.2 (0.4)	48.2 (1.0)	51.6 (1.6)	
Education				<0.001
Low	25.1 (0.3)	9.7 (0.5)	9.0 (1.0)	
High	74.9 (0.3)	90.3 (0.5)	91.0 (1.0)	
CC				<0.001
Never smoker	62.4 (0.2)	1.9 (0.3)	1.5 (0.3)	
Former smoker	21.3 (0.2)	21.8 (0.8)	14.5 (1.0)	
Current smoker	16.3 (0.2)	76.3 (0.8)	84.0 (1.1)	
Alcohol consumption				<0.001
None	9.9 (0.2)	1.3 (0.2)	1.7 (0.4)	
<1/month	33.8 (0.2)	17.9 (0.7)	15.9 (1.1)	
1/month≤	56.3 (0.2)	80.9 (0.7)	82.4 (1.2)	
CRS	7.1 (0.1)	9.7 (0.6)	8.6 (0.9)	<0.001
AR	15.2 (0.2)	16.6 (0.7)	20.4 (1.3)	<0.001
Hypertension	19.5 (0.2)	10.5 (0.5)	9.0 (0.7)	<0.001
Diabetes Mellitus	7.5 (0.1)	5.0 (0.4)	4.5 (0.6)	<0.001
Asthma	3.0 (0.1)	2.7 (0.3)	4.6 (0.8)	<0.001
Atopic dermatitis	3.3 (0.1)	5.2 (0.4)	6.5 (0.7)	<0.001
Tuberculosis	3.6 (0.1)	2.6 (0.3)	2.3 (0.4)	<0.001

Abbreviations: BMI, body mass index; CC, conventional cigarette; EC, electronic cigarette; CRS, chronic rhinosinusitis; AR, allergic rhinitis. Data are presented as mean ± standard error or weighted percentage (standard error). [a] Statistical analyses were performed using a t-test using the complex samples general linear model or the Pearson chi-square test with Rao-Scott adjustment.

mon in patients with AR.

The detailed general characteristics according to the presence of CRS and AR are presented in Table 1.

Characteristics of participants according to EC status

Table 2 presents the characteristics of the study participants according to EC status. Age was significantly lower in current EC users than in never EC users and former EC users (current vs. former vs. never, 36.3 ± 0.34 vs. 37.1 ± 0.25 vs. 47.8 ± 0.12; P<0.001). In contrast, BMI was the highest in current users (24.7 ± 0.12 vs. 24.5 ± 0.07 vs. 23.8 ± 0.02; P<0.001). Current and former EC users were more likely to be male (P<0.001) and had a higher education level (P<0.001). In addition, current EC users showed a higher rate of CC smoking (P<0.001) and alcohol consumption (P<0.001). Current EC users were more likely to have asthma (4.6% vs. 2.7% vs. 3.0%; P<0.001) and atopic dermatitis (6.5% vs. 5.2% vs. 3.3%; P<0.001) than never EC users and former EC users, whereas the prevalence of hypertension (9.0% vs. 10.5% vs. 19.5%; P<0.001), DM (4.5% vs. 5.0% vs. 7.5%; P<0.001), and pulmonary tuberculosis (2.3% vs. 2.6% vs. 3.6%; P<0.001) was lower in current EC users than in never EC users and former EC users. Moreover, current and former EC users showed a significantly higher prevalence of CRS (8.6% vs. 9.7% vs. 7.1%; P<0.001) and AR (20.4% vs. 16.6% vs. 15.2%; P<0.001) than never EC users.

The association of EC use with the prevalence of CRS and AR

We next performed logistic regression analysis to examine the association between EC use and CRS prevalence (Table 3 and Figure 2). Without adjusting for potential confounders, the odds ratio (OR) for CRS was significantly higher in former EC users

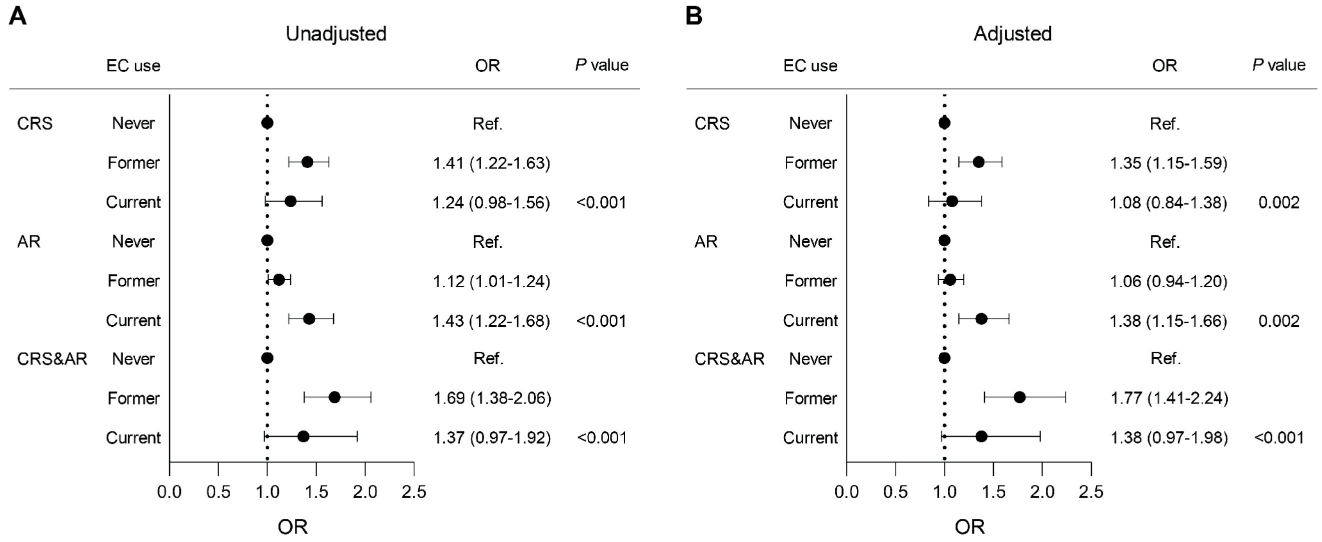

Figure 2. Association of EC use with the prevalence of CRS and AR. Forest plots showing the unadjusted (A) and adjusted (B) odds ratios (ORs) for each disease (CRS, AR, or both) according to status of EC use in logistic regression analysis. Ref., reference.

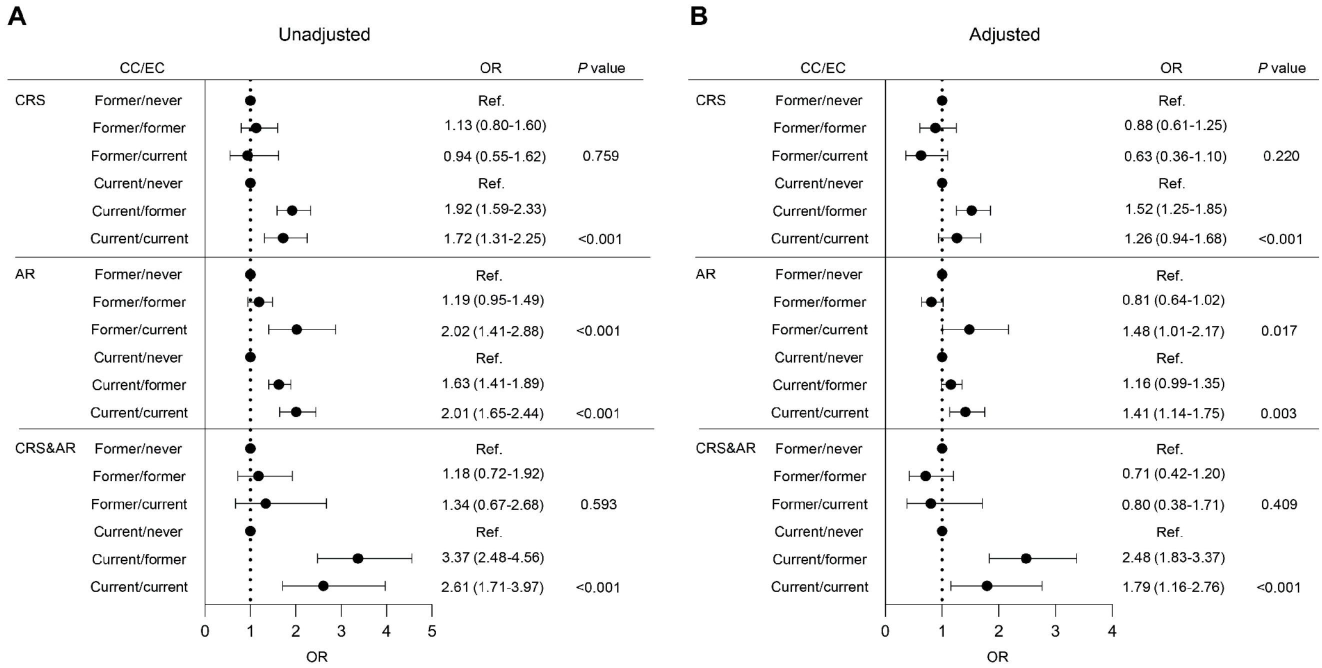

Figure 3. Association of CC and EC using status with the prevalence of CRS and AR. Forest plots showing the unadjusted (A) and adjusted (B) odds ratios (ORs) for each disease (CRS, AR, or both) according to CC and EC use in logistic regression analysis. Ref., reference.

(OR=1.41, 95% confidence interval [CI]=1.22–1.63) and current EC users (OR=1.24, 95% CI=0.98–1.56) than in never EC users (P<0.001). When adjusted for possible confounders (age, sex, BMI, income, education, CC smoking, alcohol consumption, asthma, atopic dermatitis, and AR), former EC users (adjusted OR=1.35, 95% CI=1.15–1.59), and current EC users (adjusted OR=1.08, 95% CI=0.84–1.38) also showed significantly increased ORs for CRS than never EC users (adjusted P=0.002). In the case of AR, the OR was also significantly higher in former EC users (OR=1.12, 95% CI=1.01–1.24) and current EC users (OR=1.43, 95% CI=1.22–1.68) than in never EC users (P<0.001). In addition, a significantly higher OR for AR remained stable (former EC users, adjusted OR=1.06, 95% CI=0.94–1.20; current EC users, adjusted OR=1.38, 95% CI=1.15–1.66; P=0.002) after adjusting for confounders (age, sex, BMI, income, education, CC smoking, alcohol consumption, asthma, atopic dermatitis, and CRS). When

Table 3. The association of EC use with the prevalence of CRS and AR.

	EC use status	Unadjusted		Adjusted	
		OR (95% CI)	P value	OR (95% CI)	P value
CRS	Never user	Ref		Ref	
	Former user	1.41 (1.22-1.63)		1.35 (1.15-1.59)	
	Current user	1.24 (0.98-1.56)	<0.001	1.08 (0.84-1.38)	0.002[a]
AR	Never user	Ref		Ref	
	Former user	1.12 (1.01-1.24)		1.06 (0.94-1.20)	
	Current user	1.43 (1.22-1.68)	<0.001	1.38 (1.15-1.66)	0.002[b]
CRS and AR	Never user	Ref		Ref	
	Former user	1.69 (1.38-2.06)		1.77 (1.41-2.24)	
	Current user	1.37 (0.97-1.92)	<0.001	1.38 (0.97-1.98)	<0.001[c]

Abbreviations: CRS, chronic rhinosinusitis; AR, allergic rhinitis; EC, electronic cigarette; OR, odds ratio; CI, confidence interval; Ref, reference

[a] the covariates used were age, sex, body mass index, income, education, conventional cigarette use, alcohol consumption, asthma, atopic dermatitis, and allergic rhinitis.

[b] the covariates used were age, sex, body mass index, income, education, conventional cigarette use, alcohol consumption, asthma, atopic dermatitis, and chronic rhinosinusitis.

[c] the covariates used were age, sex, body mass index, income, education, conventional cigarette use, alcohol consumption, asthma, and atopic dermatitis.

we investigated the association between EC use and co-prevalence of CRS and AR, former EC users (unadjusted OR=1.69, 95% CI=1.38–2.06; adjusted OR=1.77, 95% CI=1.41–2.24) and current EC users (unadjusted OR=1.37, 95% CI=0.97–1.92; adjusted OR=1.38, 95% CI=0.97–1.98) showed significantly higher ORs than never EC users in both unadjusted (P<0.001) and adjusted models (adjusted P<0.001). Collectively, these results indicate that EC use is associated with a high prevalence of CRS and AR.

Subgroup analysis of ever-CC smokers

In the present study, we found that the majority of total EC users, including former and current EC users, had an experience of CC smoking (former or current CC smokers) (e-Table 1). Thus, we next performed a subgroup analysis of ever-CC smokers (former and current CC smokers) to investigate the effects of additional EC use on CRS and AR in this population (Table 4 and Figure 3). Among current CC smokers, current EC users (adjusted OR=1.26, 95% CI=0.94–1.68) and former EC users (adjusted OR=1.41, 95% CI=1.14–1.75) showed significantly higher ORs of CRS than never EC users (adjusted P<0.001). In contrast, there was no significant association between the use status of EC and the prevalence of CRS among former CC smokers (adjusted P=0.220). In the case of AR, the "current CC-current EC" group (adjusted OR=1.41, 95% CI=1.14–1.75) and the "current CC-former EC" group (adjusted OR=1.16, 95% CI=0.99–1.35) showed significantly higher ORs than the "current CC-never EC" group (adjusted P=0.003). In addition, current EC use (adjusted OR=1.48, 95% CI=1.01–2.17) was associated with a high prevalence of AR than in former CC smokers (adjusted P=0.017). Similarly, the ORs for co-prevalence of CRS and AR were significantly higher in the "current CC-current EC" group (adjusted OR=1.79, 95% CI=1.16–2.76, P<0.001) and the "current CC-formal EC" group (adjusted OR=2.48, 95% CI=1.83–3.37, P<0.001) than the "current CC-never EC" group. Among former CC smokers, there was no significant association between the use status of EC and co-prevalence of CRS and AR (adjusted P=0.409).

Altogether, these data indicate that additional EC use may increase the risk of CRS and AR in current CC smokers and the risk of AR in former smokers.

Discussion

Various environmental factors are known to be involved in the development of CRS and AR. However, the effect of ECs, a novel tobacco product, on the pathogenesis of CRS and AR remains to be elucidated. In the present study, we demonstrated that EC use is significantly associated with a high prevalence of CRS and AR in the adult population using nationwide cross-sectional survey data. Furthermore, we found that former CC smokers with current EC use showed a significantly higher OR for AR than those without EC use. Together, these findings indicate that EC use may have harmful effects on respiratory health by increasing the risk of upper airway diseases. Our results add new knowledge to the current understanding of the effects of EC on human health.

The upper airway acts as a front-line barrier against inhaled respiratory pathogens, allergens, and irritants [9]. The mucosal immune system plays a critical role in maintaining the homeostasis of the nasal cavity and paranasal sinuses [9]. Nasal epithelial

Table 4. The association of CC and EC use with the prevalence of CRS and AR.

	EC use status	Unadjusted		Adjusted	
		OR (95% CI)	P value	OR (95% CI)	P value
CRS	Former/never	Ref		Ref	
	Former/former	1.13 (0.80-1.60)		0.88 (0.61-1.25)	
	Former/current	0.94 (0.55-1.62)	0.759	0.63 (0.36-1.10)	0.220[a]
	Current/never	Ref		Ref	
	Current/former	1.92 (1.59-2.33)		1.52 (1.25-1.85)	
	Current/current	1.72 (1.31-2.25)	<0.001	1.26 (0.94-1.68)	<0.001[a]
AR	Former/never	Ref		Ref	
	Former/former	1.19 (0.95-1.49)		0.81 (0.64-1.02)	
	Former/current	2.02 (1.41-2.88)	<0.001	1.48 (1.01-2.17)	0.017[b]
	Current/never	Ref		Ref	
	Current/former	1.63 (1.41-1.89)		1.16 (0.99-1.35)	
	Current/current	2.01 (1.65-2.44)	<0.001	1.41 (1.14-1.75)	0.003[b]
CRS and AR	Former/never	Ref		Ref	
	Former/former	1.18 (0.72-1.92)		0.71 (0.42-1.20)	
	Former/current	1.34 (0.67-2.68)	0.593	0.80 (0.38-1.71)	0.409[c]
	Current/never	Ref		Ref	
	Current/former	3.37 (2.48-4.56)		2.48 (1.83-3.37)	
	Current/current	2.61 (1.71-3.97)	<0.001	1.79 (1.16-2.76)	<0.001[c]

Abbreviations: CRS, chronic rhinosinusitis; AR, allergic rhinitis; EC, electronic cigarette; OR, odds ratio; CI, confidence interval; Ref, reference

[a] the covariates used were age, sex, body mass index, income, education, conventional cigarette use, alcohol consumption, asthma, atopic dermatitis, and allergic rhinitis.

[b] the covariates used were age, sex, body mass index, income, education, conventional cigarette use, alcohol consumption, asthma, atopic dermatitis, and chronic rhinosinusitis.

[c] the covariates used were age, sex, body mass index, income, education, conventional cigarette, alcohol consumption, asthma, and atopic dermatitis

cells produce cytokines that activate various immune cells upon triggering by environmental factors, including smoking and occupational irritants [1,2]. Considering that ECs produce toxic substances, such as aldehydes and reactive oxygen species [8,10], it is highly likely that EC use may stimulate nasal epithelial cells and subsequently induce mucosal inflammation. In this regard, the relationship between EC use and chronic inflammatory diseases of the upper airway needs to be examined. To the best of our knowledge, this is the first study to investigate the association between EC use and the prevalence of CRS or AR in the adult population.

Notably, we found that most current EC users had a history of CC smoking. These findings are in line with previous studies from other countries [11,12]. In the subgroup analysis, former CC smokers who currently use EC showed a significantly higher OR of AR than former CC smokers without EC use. These results indicate that ECs may not be a healthy alternative to CCs, as previously thought. Moreover, current dual (CC and EC) users were found to have a significantly higher OR for CRS or AR than current CC smokers without EC use. Similar to our findings, a previous study analyzing survey data from South Korean adolescents reported that current dual users tended to show a higher risk of current AR than current CC smokers without EC use [13]. These data may suggest that EC compounds could enhance the harmful effects of CC on respiratory health. Considering that a previous proteomic analysis of bronchial epithelial cells revealed differential biological effects between EC and CC [14], it would be of interest to examine whether there is a synergistic adverse effect of EC and CC on the respiratory mucosa.

In recent years, several studies have investigated the effects of ECs on the respiratory system. It has been shown that intracellular expression of MUC5AC, a major mucin protein, in human bronchial epithelial cells is increased by aerosolized PG and VG exposure [14]. In line with this, ex vivo proteomic analyses revealed upregulation of MUC5AC, but not MUC5B, in the bronchial epithelial cells from EC users than those from non-smokers [14].

Similar results were observed in the previous study analyzing induced sputum samples from EC users and non-smokers [15]. Considering that increased mucin concentration and altered MUC5AC/MUC5B ratio are frequently observed in patients with chronic respiratory diseases [16], these data may indicate the harmful effects of EC use on respiratory health. In addition, nasal scrape samples from EC users show decreased expression of immune-related genes [17], and MUC5AC expression is upregulated in the nasal epithelial cells following in vitro or in vivo stimulation with PG and VG [14,18]. Furthermore, EC vapor inhibits ciliary beating in the nasal epithelium [19]. Given that immune perturbation and mucociliary dysfunction are key features of CRS, it seems plausible that EC-induced dysregulation of the nasal epithelial cells may underlie the development of CRS, and consequently explain the significant association between EC use and the high prevalence of CRS. Although a growing body of experimental evidence suggests detrimental effects of EC on respiratory health, real-world data are still insufficient. Toxicological studies with long-term follow-up of EC users are needed to verify the chronic effects of EC. In addition, further investigations using in vivo animal models would provide mechanistic insights into EC-induced mucosal inflammation and the subsequent development of respiratory diseases.

Given that mechanisms underlying the pathogensis of CRS without nasal polyps (CRSsNP) and with nasal polyps (CRSwNP) are known to be distinct [20], an association of EC use with the prevalence of CRS may be different according to the CRS phenotype. However, the current survey did not provide data regarding endoscopic findings. Whether EC use promotes NP formation should be addressed in future studies. Deeper investigations on the effect of EC compounds on immune responses in upper airway mucosa would help answer this question.

Since the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guideline is the standard diagnostic criteria for CRS in South Korea, it can be assumed that the physician-diagnosed CRS in this study was mostly based on the patients' symptoms. Indeed, the prevalence of CRS in the present study was similar to the prevalence in the previous study assessing CRS based on symptoms and endoscopic findings in the South Korean population [21]. In addition, a previous study reported that the prevalence of self-reported physician-diagnosed CRS was highly correlated with the prevalence of EPOS-diagnosed CRS [3]. Nevertheless, further studies using the symptom-based diagnosis of CRS should be performed to validate the significant association between EC use and high prevalence of CRS. In addition, it would be of interest to investigate which cardinal symptoms of CRS are closely linked to EC.

In the present study, we found no significant association between CC smoking status and CRS prevalence. This result is contradictory to previous studies reporting that CRS is more common in CC smokers than in non-smokers [3,4]. This discrepancy can be attributed to multiple factors. First, the questionnaires used to define the presence of CRS were different. While our study defined CRS as self-reported physician-diagnosed CRS, those studies defined CRS by symptom-based diagnosis based on the EPOS criteria. Whether this discrepancy in the survey method may affect the results needs to be investigated. Large-scale population studies using objective diagnostic tools, including nasal endoscopy or computed tomography, would enable us to determine the precise prevalence of CRS. Second, racial and geographical factors also need to be considered in relation to the inflammatory endotypes of CRS. It has been described that CRS in Western countries is primarily mediated by type 2 inflammation, whereas type 1/3 inflammation is more frequent in East Asia [22].

The present study had several limitations. First, this study cannot explain the direction of causality due to its cross-sectional nature. EC use may promote the development of CRS or AR by induction of immune perturbation in the upper airway mucosa. Conversely, the association may be due to patients changing to EC use to help with smoking cessation. To clarify this issue, long-term prospective cohort studies should be conducted in the future. Second, detailed information on the clinical features of CRS (e.g., the presence of nasal polyps and disease severity) and AR (e.g., symptom frequency and severity) are lacking. These clinical parameters are possible confounding factors but are uncontrollable in this study. Third, the subgroup defined in this study could be heterogeneous in terms of the amount of EC used. For instance, not only participants who used EC once in their lifetime but also previous heavy users may belong to "former EC users." Since the amount of EC use may affect the results, whether the prevalence of CRS and AR is higher in heavy users than in light users should be addressed in future studies. Nevertheless, this study had several strengths. First, we analyzed a large number of participants using unbiased data from a 7-year nationwide survey. Second, our study is the first to investigate the association between EC use and CRS and AR in adults.

Conclusion

In summary, we comprehensively analyzed nationwide survey data and demonstrated a significant association between EC use and the high prevalence of CRS and AR in the adult population. Furthermore, we found that additional EC use is associated with not only a high prevalence of CRS and AR in current CC smokers but also a high prevalence of AR in former smokers. Our current analysis provides valuable information that EC use may increase the risk of upper airway diseases. The mechanisms underlying these results should be addressed in future studies.

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Authorship contribution

M-SR: conceptualization, analysis, and writing; H-JC: analysis and editing; J-HY: conceptualization and review; C-HK: conceptualization, editing, and review.

Conflict of interest

The authors declare no conflicts of interests.

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