Gill Amarbir Singh (Orcid ID: 0000-0002-6776-0712)

Tobacco use increases the risk of chronic rhinosinusitis among patients undergoing endoscopic sinus surgery

[1,2]Amarbir S. Gill, MD
[3]Huong Meeks, PhD
[3,4]Karen Curtin, PhD
[5,6]Kerry Kelly, PhD
[1]Jeremiah A. Alt, MD PhD

[1]Division of Otolaryngology – Head and Neck Surgery, Department of Surgery; University of Utah, Salt Lake City, Utah, USA
[2]Department of Otolaryngology-Head and Neck Surgery, University of Michigan, Ann Arbor, Michigan, USA
[3]Pedigree and Population Resource, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA
[4]Department of Internal Medicine, University of Utah, Salt Lake City, Utah, USA
[5]Department of Chemical Engineering, University of Utah
[6]Utah Center for Nanomedicine, Nano Institute of Utah, University of Utah.

Conflict(s) of Interest: None

Disclosures:
Kerry Kelly: Co-founder and co-owner of Tetrad Network Sensor Solutions
Jeremiah A. Alt: Consultant for OptiNose, GM, Medtronic, and GSK

Corresponding author:
Amarbir S. Gill, MD
University of Michigan
Department of Otolaryngology – Head and Neck Surgery
1500 E. Medical Center Dr.
1904 TC, SPC 5312
Ann Arbor, MI 48109
Email: asingill@umich.edu

Word count: 2283

Key words: chronic rhinosinusitis, tobacco, endoscopic sinus surgery, smoking

Author Contributions

Amarbir S. Gill, MD: conceptualization, data interpretation, manuscript writing, revisions

Huong Meeks, PhD: data analysis, data interpretation, revisions

Karen Curtin, PhD: data analysis, data interpretation, revisions

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/coa.14013

Kerry Kelly, PhD: data interpretation, revisions

Jeremiah A. Alt, MD PhD: conceptualizations, data analysis, data interpretation, revisions

Acknowledgments

This study was supported by the Department of Surgery, "blinded for review". We thank the Pedigree and Population Resource of "blinded for review," "blinded for review" (funded in part by the "blinded for review" Cancer Foundation) for its role in the ongoing collection, maintenance, and support of the Utah Population Database (UPDB). We also acknowledge partial support for the UPDB through grant P30 CA2014 from the National Cancer Institute, "blinded for review" and from the "blinded for review" program in Personalized Health. We thank the "blinded for review" Center for Clinical and Translational Science (funded by NIH Clinical and Translational Science Awards) and "blinded for review" Information Technology Services and Biomedical Informatics Core for establishing the Master Subject Index between the UPDB and the "blinded for review" Health Sciences Center. This research was supported by the NCRR grant, "Sharing Statewide Health Data for Genetic Research" (R01 RR021746, G. Mineau, PI) with additional support from the Utah State Department of Health and the "blinded for review".

Background:
Although it has been postulated that tobacco use, as well as other environmental exposures, may contribute to chronic rhinosinusitis (CRS), the data remain limited. Here, we utilized a large state population database to assess the association between tobacco use and CRS prevalence among patients undergoing endoscopic sinus surgery (ESS).

Methods:
Employing a case-control study design, the Utah Population Database was queried for patients age > 18 with a diagnosis of CRS and tobacco use who underwent ESS between 1996 and 2018. Smoking status was compared between patients with CRS (n=34,350) and random population controls matched 5:1 on sex, birth year, birthplace, time residing in Utah, and pedigree (i.e., familial) information (n=166,020). Conditional logistic regression models were used for comparisons between CRS patients and their matched controls. All analyses were repeated, additionally adjusting for race, ethnicity, tobacco use, asthma history, and interaction between tobacco use and asthma history.

Results:
A total of 200,370 patients were included in the final analysis. Patients with CRS were significantly more likely to demonstrate a history of tobacco use than controls (19.6% vs. 15.0%) (p<0.001), with an adjusted odds ratio (aOR) of 1.42, 95% CI 1.37-1.47, (p<0.001). More patients with CRS and comorbid asthma used tobacco (19.5%) than controls with asthma (15.0%) (p<0.001).

Conclusion:
History of tobacco use may portend increased risk for the development of CRS among patients undergoing ESS compared to healthy controls.

Key points:

1. Tobacco use is among the many potential factors thought to contribute to an increased risk of chronic rhinosinusitis (CRS).
2. However, data is limited.
3. Studies surrounding CRS and tobacco use suffer from poor study design, small sample sizes, and inadequate definitions of CRS, leading to heterogeneity and conflicting results.
4. Most of these data are based on non-US populations and epidemiologic in nature.
5. Utilizing a case-control study design and a US-based population, the present investigation demonstrated that a history of tobacco use may portend an increased risk for the development of CRS among patients undergoing endoscopic sinus surgery compared to healthy controls.

Introduction

Chronic rhinosinusitis (CRS) is a common condition affecting approximately 1 in 7 Americans, with a severe impact on quality of life and a large societal cost.[1] The negative impact on patient

quality of life and health is similar or even more severe than congestive heart failure, angina, chronic obstructive pulmonary disease, and back pain.[2] Despite the impact that this condition has on individual health and society, the etiology remains unclear as it is a multifactorial disease with many predisposing factors.

Among the many potential factors thought to contribute to an increased risk of CRS are tobacco use, as well as other environmental exposures.[3] However, studies surrounding CRS and tobacco use have suffered from poor study design, small sample sizes and inadequate definitions of CRS, leading to significant heterogeneity and conflicting results. Moreover, prior studies have been performed primarily in non-US populations, such as South Korea, China and, most recently, the United Kingdom (UK).[4-10] Finally, prior studies have not accounted for the potential confounding impact of comorbid asthma when evaluating the role of tobacco use on CRS prevalence. Patients with asthma are more likely to be smokers of tobacco compared to the healthy public (up to 27%[11] vs 14%[12] in the general public), and the literature has repeatedly demonstrated that a large proportion of patients with CRS have concomitant asthma.[13]

We hypothesized that a history of tobacco use would increase the risk of CRS. Focusing on a large, US-based database, and utilizing a case-control study design, we sought to characterize this relationship between tobacco use and CRS and test the aforementioned hypothesis.

Methods

Utah Population Database (UPDB)

The UPDB contains 42 million records spanning several decades, representing 11 million individuals who have ever resided in Utah, as well as their ancestors identified from genealogical records. Of these, 7 million individuals are linked to statewide clinical data contributed by the Utah Department of Health and the University of Utah Healthcare system of clinics and hospitals. Records on hospitalizations, ambulatory surgeries, and emergency department visits span from 1996 to the present.[14] The institutional review board (IRB) of the University of Utah and the Utah Resource for Genetic and Epidemiologic Research approve this population-based investigation. An IRB waiver of consent and authorization were obtained. We utilized UPDB data resources for this study as previously described,[14-16] and followed the written reporting guideline for this study. The comprehensive and longitudinal nature the database provides a unique opportunity to assess the relationship between various risk factors, including tobacco use, and CRS as compared to individually-matched population controls, while maintaining anonymity of medical datasets linked to the UPDB by providing investigators with a non-identifying study identifier unique to each approved protocol.[17]

Study Population

Case definition

Electronic medical records within UPDB were queried for patients age 18 and older with an index diagnosis of CRS between 1996 and 2017.[15] Patients were included in the study if they satisfied the following criteria:

1. CPT (Current Procedural Terminology) endoscopy code 31231 AND at least one or more ICD-9/10 diagnosis codes for: chronic rhinosinusitis without nasal

polyposis (CRSsNP): ICD-9 473.0-473.9; ICD-10 J32.0-J32.9 or chronic rhinosinusitis with nasal polyposis (CRSwNP): ICD-9 471.x; ICD-10 J33.0-J33.

2. CPT sinus surgery code: 30115, 30110, 31233, 31237, 31254, 31255, 31256, 31267, 31276, 31287, 31288, 31253, 31257, 31259

Of note, patient diagnoses/procedures in 2015 were excluded due to the inability to link these health records to other administrative records. Cases were excluded if they had the following known diagnoses that can be secondary causes of CRS: cystic fibrosis (ICD-9 277.x, ICD-10 E84.x), malignant sinonasal neoplasms (ICD-9 160.0-160.9, ICD-10 C30.0), inverted papilloma (ICD-9 212.0, ICD-10 D14.0), and a history of head or facial trauma (ICD-9 801.0-804.9; ICD-10 S01-S09), cerebrospinal fluid leak (ICD-9 349.81; ICD-10 G96.0), ganulomatosis with polyangitis (ICD-9 446.4; ICD-10 M31.3x), sarcoidosis (ICD-9 135.x; ICD-10 D86.x), churg-strauss syndrome (ICD-9 446.4; ICD-10 M30.1), HIV/AIDS (any HIV illness) (ICD-9 42; ICD-10 B20.x), injury to blood vessels of the head and neck (Carotid ICD-9 900.00-900.03, multiple vessels ICD-9 900.82, specified vessels ICD-9 900.89, and CSF rhinorrhea ICD-9 349.81; ICD-10 S15.x, J34.89), or history of aspirin exacerbated respiratory disease (ICD-9 V14.6, ICD-10 Z88.6). Patients were excluded if there was no documentation of patient gender, or if the date of last follow up in the UPDB preceded the date of first surgery. This excluded patient records that may have documentation errors and ensure that we have adequate follow-up.

Control selection

Control patients (i.e., no history of CRSwNP or CRSsNP) were randomly selected from the Utah population and individually matched to cases in a 5:1 target ratio (actual 4.8:1) based on sex,

birth year, birthplace (i.e., Utah or other), time residing in Utah, and pedigree (i.e., familial) information in relation to CRSwNP or CRSsNP cases. We required controls to reside in Utah at least until the matching case's first CRS diagnosis. This requirement was necessary to ensure that the controls did not have any diagnosis history of CRS in Utah. Matching by "familial information" indicates that cases and controls were matched by the minimum of pedigree information (i.e., if cases were singleton, controls could be singleton; if cases were not singleton, controls had to have at least a first degree relative who was informative; that is, alive and living in Utah after 1/1/1996). The control subject randomization was performed using sampling without replacement. Risk factors associated with occurrence of CRS were compared between cases and controls.

Demographics and exposures.

The following demographic information was collected for each patient: age at index case diagnosis, gender, race/ethnicity, birthplace (in Utah or outside of Utah). Exposure status for diagnosis history of allergies, asthma, and tobacco use were determined from electronic medical records in UPDB from 1996-2017. A diagnosis of tobacco use was searched utilizing the following codes for tobacco/nicotine use: ICD-9 V15.82 and ICD-10 Z87.891. Patients with asthma were defined as anyone who were diagnosed with ICD-9 493.x or ICD-10 J45.x. The presence of allergy diagnoses was confirmed using ICD-9 477 or ICD-10 J30.

Study Outcome

The primary outcome of this study was diagnosis of CRS requiring ESS, as defined above from the medical record (1996-2017), among individuals with and without a diagnosis history of tobacco use.

Statistical Analysis

Demographic characteristics and tobacco smoking status was compared across cases and controls, using t-tests for continuous variables and chi-squared tests for categorical variables. Conditional logistic regression models were used for comparisons between CRS patients and their matched controls. All analyses were repeated, additionally adjusting for race, ethnicity, tobacco use, asthma history, and interaction between tobacco use and asthma history. Statistical analysis was performed using R software version 4.0.1.

Results

Demographics

A total of 200,370 patients (34,350 CRS and 166,020 controls) were included in the final analysis (Table 1). The mean age at 1st CRS diagnosis was 43.9 with 58.3% of CRS patients demonstrating nasal polyposis. A larger proportion of the CRS cases were White/Caucasian and non-Hispanic/Latino compared to controls ($p<0.001$). Similarly, significantly more CRS patients exhibited a history of asthma, allergy, and tobacco use ($p<0.001$).

Tobacco use among controls vs. patients with CRS

A significantly larger amount of CRS patients demonstrated a personal history of tobacco use (19.5%) than matched controls (15.0%) ($p<0.001$) (Table 2). This association between tobacco use and a CRS diagnosis was seen in both males and females, as well as in CRSsNP and

CRSwNP (Table 2). The risk of CRS in the setting of tobacco use demonstrated an unadjusted odds ratio (OR) of 1.38 (confidence interval (CI) 1.34-1.42, $p<0.001$) (Table 3). Compared to tobacco non-users without a history of asthma, the CRS risk among tobacco users without a history of asthma was 1.42-fold, while the CRS risk among smokers with an asthma was 3.60-fold (Supplemental Table 1, Appendix Table 1). Among non-smokers with asthma, CRS risk was 5.21-fold (Supplemental Table 1, Appendix Table 1). Finally, among the CRS with asthma (CRS-A) cases, there was a greater proportion of patients with a personal history of tobacco use (23.3%) compared to controls with asthma (15.6%) (Table 1).

Discussion

Most of the current data examining the relationship between active smoking and CRS is based in epidemiologic studies (mainly from Asia and the UK). The impact of findings from these investigations is hampered by inherent limitations related to survey style epidemiologic studies, including incomplete diagnostic criteria to characterize CRS.[18] The variable definition of CRS across this literature has resulted in significant heterogeneity.[18] Most studies do not have physician diagnoses, but rather incorporate self-reported diagnoses, which can significantly overestimate the true prevalence of disease.[9] Furthermore, findings from existing studies are often contradictory - some demonstrate an association between tobacco smoking and CRS prevalence,[4-8] while others do not.[9,10,19] Finally, few (limited) attempts have even been made to examine this relationship in the US population.[20] It is important to acknowledge these limitations in the existing literature and work to address them; if overlooked, they can lead to overreaching conclusions about the definitive nature of the positive association between tobacco smoking and CRS prevalence.[21]

In the present study, we used physician diagnoses of CRS based on ICD-9 and ICD-10 codes to fill in the knowledge gap left behind by study design deficits and a lack of US based investigations in the prior literature. Our study was unique in that it was able to achieve a large sample size without the traditional design of a survey based epidemiologic survey, due to the incorporation of a large, statewide database, as well as implementation of a study design that accounted for comorbid asthma. These study design differences may explain why, unlike some of the survey based, epidemiologic studies, our data demonstrate a significant association between tobacco use and prevalence of CRS with or without comorbid asthma, with an adjusted OR of 1.42, representing an over 40% increase in risk.

The use of self-reported or non-physician CRS diagnoses, or otherwise limited implementation of recommended subjective and objective diagnostic criteria for CRS,[22,23] has the potential to misconstrue the true prevalence of disease and is also subject to recall bias. Nevertheless, this is a common limitation of survey-based studies, which represent most of the current data on CRS and tobacco use. Indeed, several large survey studies in Europe and Asia have utilized this study design to conclude that CRS is more common among tobacco users and non-users (i.e., tobacco use is an independent risk factor for development of CRS).[4-8] However, these studies suffer from the aforementioned limitations to varying degrees.

Only a single database study was undertaken in the US by Lieu et al in 2000; although the authors noted a relative risk (RR) of 1.18 associated with cigarette smoking, this study was again significantly hindered by reliance on a self-reported diagnosis of CRS (i.e., symptoms of

"sinusitis or sinus problems" in the last 12 months). Chen et al performed a similar national database study in Canada and found an association between active smoking and CRS, but again, the study design was hindered by a self-reported diagnosis of CRS.

It is less common to come across studies that have successfully incorporated physician and/or complete diagnostic criteria in their evaluation of CRS and tobacco use. The two major studies to have done so utilized the Chronic Rhinosinusitis Epidemiology Study (CRES) data in the UK, incorporating the EPOS 2012 symptomatic guidelines and either endoscopic or CT evidence of CRS to render a physician diagnosis of CRS. Both studies, with limited sample sizes ranging from 1400-1700 patients, demonstrated no significant association between tobacco smoking and a diagnosis of CRS.[10] An earlier study out of Korea by Min et al. similarly combined a large epidemiology study design with both subjective and objective (nasal endoscopy) diagnostic criteria of CRS in a population of 9000 Korean participants to likewise conclude a lack of association between tobacco smoking and prevalence of CRS.[19]

In contrast to the present investigation, these 3 studies, which also utilized comprehensive criteria/physician diagnoses for CRS, demonstrated no significant relationship between CRS and tobacco use. It is important to note that although the results from our study differ from those outlined in the CRES studies and by Min et al., they are in alignment with the larger collection of non-US epidemiologic studies.[4-8] A possible reason for this observation may lie in the significantly larger sample size, longitudinal nature (1996 to 2017 in the present study vs. 2007-2013 in CRES studies and 1991 in Min et al.)[9,10,19] and/or different baseline levels of smoking in the respective populations. For example, our study included 166,000 matched non-CRS controls

and an additional 34,000 patients with a CRS diagnosis; this is a much larger sample size than either the CRES or Min et al. studies.[9,10,19] It is possible that if the differences between CRS patients and healthy controls are small, a larger sample size such as ours is necessary to tease out these differences. Furthermore, all patients included in our analysis underwent ESS for their CRS. It is possible that these cases represent more severe disease that cannot be managed medically, which may be unique from the patient population examined in the CRES studies.

There are several key limitations to our study that should be acknowledged. First, the ICD-9 and -10 codes used to diagnose tobacco use include all forms of tobacco consumption, including smoking, chewing, snuffing, etc. Existing data in the literature demonstrates that of the individuals in the US who use tobacco, the vast majority smoke (14% of the US population), rather than consume it in a smokeless fashion (2.4% of the US population).[12,24] Nevertheless, the present manuscript interprets our data as tobacco used in any form and does not imply that *only* smoking tobacco is associated with risk of developing CRS. Second, we were limited by our database, in our ability to characterize duration of use, as well as former vs current tobacco use. Third, we cannot ignore the potential for inaccurate coding at the time the time of initial diagnostic documentation. However, the CRS diagnoses codes used here have been previously validated through chart review.[15,16] Further, although ICD-9 codes tobacco codes were shown to be effective in identifying an individual's smoking status,[25] we acknowledge there is potential for underreporting of tobacco use,. Fourth, the rates of tobacco use in the state of Utah are not representative of the remainder of the US, as the prevalence of cigarette smoking is the lowest in the state of Utah compared to the rest of the US (7.9% vs. 14% in 2019).[12] It is possible that in areas that have higher rates of tobacco use, the association with a CRS diagnosis may be even

greater. Finally, due to the large sample size of the present study, there is a potential for statistical over-powering, which may highlight statistical differences that are not necessarily clinically relevant. Despite these limitations, the large sample size of the present investigation, along with a case-control study design and incorporation of physician, rather than self-reported diagnoses of CRS, help fill a knowledge gap regarding the impact of tobacco use on the prevalence of CRS. Future studies should consider evaluating the role of tobacco use on revision rates of ESS in CRS to further understand the impact of tobacco on CRS outcomes.

Conclusion

The risk of a CRS diagnosis is increased by more than 40% among tobacco users undergoing ESS compared to matched controls, independent of asthma status.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Anand VK. Epidemiology and economic impact of rhinosinusitis. Ann Otol Rhinol Laryngol Suppl 2004; 193:3-5.
2. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg 1995; 113:104-109.
3. Kennedy DW. Pathogenesis of chronic rhinosinusitis. Ann Otol Rhinol Laryngol Suppl 2004; 193:6-9.
4. Hastan D, Fokkens WJ, Bachert Cet al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. Allergy 2011; 66:1216-1223.
5. Thilsing T, Rasmussen J, Lange B, Kjeldsen AD, Al-Kalemji A, Baelum J. Chronic rhinosinusitis and occupational risk factors among 20- to 75-year-old Danes-A GA(2) LEN-based study. Am J Ind Med 2012; 55:1037-1043.
6. Ahn JC, Kim JW, Lee CH, Rhee CS. Prevalence and Risk Factors of Chronic Rhinosinusitus, Allergic Rhinitis, and Nasal Septal Deviation: Results of the Korean National Health and Nutrition Survey 2008-2012. JAMA Otolaryngol Head Neck Surg 2016; 142:162-167.
7. Lee WH, Hong SN, Kim HJet al. Effects of cigarette smoking on rhinologic diseases: Korean National Health and Nutrition Examination Survey 2008-2011. Int Forum Allergy Rhinol 2015; 5:937-943.
8. Shi JB, Fu QL, Zhang Het al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. Allergy 2015; 70:533-539.
9. Hutson K, Clark A, Hopkins Cet al. Evaluation of Smoking as a Modifying Factor in Chronic Rhinosinusitis. JAMA Otolaryngol Head Neck Surg 2021; 147:159-165.
10. Philpott CM, Erskine S, Hopkins Cet al. Prevalence of asthma, aspirin sensitivity and allergy in chronic rhinosinusitis: data from the UK National Chronic Rhinosinusitis Epidemiology Study. Respir Res 2018; 19:129.
11. Croisant S. Epidemiology of asthma: prevalence and burden of disease. Adv Exp Med Biol 2014; 795:17-29.
12. Extinguishing the Tobacco Epidemic in Utah. Office on Smoking and Health NCfCDPaHPM, 2021. https://www.cdc.gov/tobacco/about/osh/state-fact-sheets/utah/. Accessed June 2, 2021. .
13. Castagnoli R, Licari A, Brambilla I, Tosca M, Ciprandi G, Marseglia GL. An update on the role of chronic rhinosinusitis with nasal polyps as a co-morbidity in severe asthma. Expert Rev Respir Med 2020:1-9.
14. Utah Population Database. Huntsman Cancer Institute. https://uofuhealth.utah.edu/huntsman/utah-population-database/. Accessed October 30, 2020.
15. Smith KA, Orlandi RR, Oakley G, Meeks H, Curtin K, Alt JA. Long-term revision rates for endoscopic sinus surgery. Int Forum Allergy Rhinol 2019; 9:402-408.
16. Oakley GM, Curtin K, Orb Q, Schaefer C, Orlandi RR, Alt JA. Familial risk of chronic rhinosinusitis with and without nasal polyposis: genetics or environment. Int Forum Allergy Rhinol 2015; 5:276-282.
17. Smith KRM, G. P. The Utah Population Database. The Legacy of Four Decades of Demographic Research. Historical Life Course Studies 2021; 11:48-73.

18. Orlandi RR, Kingdom TT, Smith TLet al. International Consensus Statement on Rhinology and Allergy: Rhinosinusitis. Int Forum Allergy Rhinol 2020.
19. Min YG, Jung HW, Kim HS, Park SK, Yoo KY. Prevalence and risk factors of chronic sinusitis in Korea: results of a nationwide survey. Eur Arch Otorhinolaryngol 1996; 253:435-439.
20. Lieu JE FA. Confirmations and surprises in the association of tobacco use with sinusitis. 2000; 126:940-946.
21. Christensen DN, Franks ZG, McCrary HC, Saleh AA, Chang EH. A Systematic Review of the Association between Cigarette Smoke Exposure and Chronic Rhinosinusitis. Otolaryngol Head Neck Surg 2018; 158:801-816.
22. Fokkens WJ, Lund VJ, Mullol Jet al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology 2012; 50:1-12.
23. Rosenfeld RM, Piccirillo JF, Chandrasekhar SSet al. Clinical practice guideline (update): adult sinusitis. Otolaryngol Head Neck Surg 2015; 152:S1-S39.
24. Smokeless Tobacco Product Use in the United States. Office on Smoking and Health 2021. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/smokeless/use_us/index.htm#adult-national. Accessed June 2, 2021.
25. Wiley LK, Shah A, Xu H, Bush WS. ICD-9 tobacco use codes are effective identifiers of smoking status. J Am Med Inform Assoc 2013; 20:652-658.

Table 1: Baseline demographic data comparing patients with chronic rhinosinusitis (CRS) with their matching controls.

	Controls (N = 166,020)	CRS (N = 34,350)	*p*-value
Gender			0.737
- Female	84,662 (51.0%)	17,482 (50.9%)	
- Male	81,358 (49.0%)	16,868 (49.1%)	
Race			< 0.001
- White/Caucasian	149,123 (89.8%)	31,945 (93.0%)	
- African American	730 (0.4%)	81 (0.2%)	
- Asian	1,716 (1.0%)	216 (0.6%)	
- American Indian/Alaska Native	1,082 (0.7%)	46 (0.1%)	
- Native Hawaiian/Pacific Islander	609 (0.4%)	57 (0.2%)	
- Other/Multiple Races	6199 (3.7%)	1129 (3.3%)	
- Not Available	6561 (4.0%)	876 (2.6%)	
Ethnicity			< 0.001
- Not Hispanic/Latino	123,576 (74.4%)	27,095 (78.9%)	
- Hispanic/Latino	16,519 (10.0%)	2490 (7.2%)	
- Not available	25,925 (15.6%)	4765 (13.9%)	
Asthma	10,646 (6.4%)	7837 (22.8%)	< 0.001
Allergy	3010 (1.8%)	2476 (7.2%)	< 0.001
Tobacco Use	24,946 (15.0%)	6699 (19.5%)	< 0.001
Born in Utah			< 0.001
- Yes	99,008 (59.6%)	20,521 (59.7%)	
- No	51,159 (30.8%)	11,541 (33.6%)	
- Unknown	15,853 (9.5%)	2288 (6.7%)	
Nasal polyposis			<0.001
-Yes	0 (0)	20,026 (58.3%)	
-No	166,020 (100.0%)	14,324 (41.7%)	

Note: Demographic characteristics of CRS vs controls were compared using t-tests for continuous variables and chi-square tests for categorical variables.

Table 2: Tobacco use among patients with chronic rhinosinusitis (CRS) vs. matching controls with respect to sex and nasal polyposis.

Personal use of tobacco	5:1 Controls		CRS		*p*-value	CRSsNP		*p*-value	CRSsNP		*p*-value
	N	%	N	%		N	%		N	%	
Total subjects	166,020	100.0	34,350	100.0		14,310	100		20,040	100	
Gender					0.737			0.826			0.802
- Men	81,358	49.0	16868	49.1		6588	46.0		10,280	51.3	
- Women	84,662	51.0	17482	50.9		7722	54.0		9760	48.7	
Tobacco use					< 0.001			< 0.001			< 0.001
- Exposed	24,946	15.0	6699	19.5		2707	18.9		3992	19.9	
- Unexposed	141,074	85.0	27651	80.5		11,603	81.1		16,048	80.1	
Tobacco use in men					< 0.001			< 0.001			< 0.001
- Exposed	13,410	16.5	3627	21.5		1349	20.5		2278	22.2	
- Unexposed	67,948	83.5	13241	78.5		5239	79.5		8002	77.8	
Tobacco use in women					< 0.001			< 0.001			< 0.001
- Exposed	11,536	13.6	3072	17.6		1358	17.6		1714	17.6	
- Unexposed	73,126	86.4	14410	82.4		6364	82.4		8046	82.4	

Note: p-values were calculated from chi-square tests comparing CRS patients to their matching controls. CRSsNP=chronic rhinosinusitis without nasal polyposis; CRSwNP=chronic rhinosinusitis with nasal polyposis.

Table 3: Association of chronic rhinosinusitis (CRS) with history of tobacco use – an *unadjusted* logistic regression analysis accounting for matching on sex and birth year.

	All patients*			Men*			Women*		
	Risk of CRS vs controls								
	OR	95% CI	*p* -value	OR	95% CI	*p* -value	OR	95% CI	*p* -value
Likelihood ratio test	413.2, p < 2e-16			239.1, p < 2e-16			175.3, p < 2e-16		
Tobacco history									
Exposed	1.38	1.34-1.42	<0.001	1.40	1.34-1.46	<0.001	1.35	1.30-1.41	<0.001
Unexposed	Reference			Reference			Reference		
	Risk of CRSsNP vs. controls								
	OR	95% CI	*p* -value	OR	95% CI	*p* -value	OR	95% CI	*p* -value
Likelihood ratio test	147.3, p < 2e-16			75.81, p < 2e-16			71.64, p < 2e-16		
Tobacco history									
Exposed	1.35	1.29-1.41	<0.001	1.36	1.27-1.46	<0.001	1.34	1.25-1.43	<0.001
Unexposed	Reference			Reference			Reference		
	Risk of CRSwNP vs. controls								
	OR	95% CI	*p* -value	OR	95% CI	*p* -value	OR	95% CI	*p* -value
Likelihood ratio test	267.2, p < 2e-16			164.4, p < 2e-16			103.9, p < 2e-16		
Tobacco history									
Exposed	1.40	1.34-1.45	<0.001	1.43	1.35-1.50	<0.001	1.37	1.29-1.45	<0.001
Unexposed	Reference			Reference			Reference		

Note: Unadjusted (i.e., accounting for sex and age) conditional logistic regression models were used for comparison between CRS patients (i.e., all CRS cases, CRS without nasal polyposis (CRSsNP), CRS with nasal polyposis (CRSwNP)) and their matching controls. OR=odds ratio; CI=confidence interval.

*See Table 2 for sample size for each of these categories

Appendix Table 1: Expansion of Supplemental Table 1 Parameters.

a) All CRS patients

Covariate	Est	SE	Z	P-value	RR	LL	UL
Tobacco use: Yes (vs No)	0.35	0.02	19.57	0.000	1.42	1.37	1.47
White: No (vs Yes)	-0.38	0.03	-12.90	0.000	0.69	0.65	0.73
White: Unknown (vs Yes)	-0.37	0.04	-9.26	0.000	0.69	0.64	0.75
Hispanic: Yes (vs No)	-0.40	0.02	-16.78	0.000	0.67	0.64	0.70
Hispanic: Yes (vs Unknown)	-0.07	0.02	-3.59	0.000	0.93	0.90	0.97
Asthma: Yes (vs No)	1.65	0.02	84.21	0.000	5.21	5.01	5.41
Tobacco use x Asthma	-0.72	0.04	-18.65	0.000			

b) Male CRS patients only

Covariate	Est	SE	Z	P-value	RR	LL	UL
Tobacco use: Yes (vs No)	0.36	0.02	14.88	0.000	1.43	1.36	1.50
White: No (vs Yes)	-0.36	0.04	-8.55	0.000	0.70	0.65	0.76
White: Unknown (vs Yes)	-0.47	0.06	-8.47	0.000	0.63	0.56	0.70
Hispanic: Yes (vs No)	-0.51	0.04	-14.23	0.000	0.60	0.56	0.64
Hispanic: Yes (vs Unknown)	-0.13	0.03	-5.03	0.000	0.87	0.83	0.92
Asthma: Yes (vs No)	1.75	0.03	54.59	0.000	5.74	5.39	6.11
Tobacco use x Asthma	-0.68	0.06	-11.46	0.000			

c) Female CRS patients only

Covariate	Est	SE	Z	P-value	RR	LL	UL
Tobacco use: Yes (vs No)	0.35	0.03	12.94	0.000	1.42	1.34	1.49
White: No (vs Yes)	-0.40	0.04	-9.76	0.000	0.67	0.62	0.73
White: Unknown (vs Yes)	-0.24	0.06	-4.17	0.000	0.79	0.70	0.88
Hispanic: Yes (vs No)	-0.30	0.03	-9.48	0.000	0.74	0.70	0.79
Hispanic: Yes (vs Unknown)	0.00	0.03	-0.13	0.898	1.00	0.95	1.05
Asthma: Yes (vs No)	1.59	0.02	64.12	0.000	4.91	4.67	5.15
Tobacco use x Asthma	-0.77	0.05	-14.70	0.000			

d) All CRSsNP patients

Covariate	Est	SE	Z	P-value	RR	LL	UL
Tobacco use: Yes (vs No)	0.33	0.03	11.95	0.000	1.39	1.32	1.47
White: No (vs Yes)	-0.46	0.05	-9.96	0.000	0.63	0.58	0.69
White: Unknown (vs Yes)	-0.40	0.06	-6.44	0.000	0.67	0.59	0.76
Hispanic: Yes (vs No)	-0.49	0.04	-13.28	0.000	0.61	0.57	0.66
Hispanic: Yes (vs Unknown)	-0.12	0.03	-4.21	0.000	0.88	0.84	0.94
Asthma: Yes (vs No)	1.42	0.03	45.13	0.000	4.14	3.89	4.40
Tobacco use x Asthma	-0.67	0.06	-10.79	0.000			

e) Male CRSsNP patients only

Covariate	Est	SE	Z	P-value	RR	LL	UL
Tobacco use: Yes (vs No)	0.33	0.04	8.58	0.000	1.39	1.29	1.50
White: No (vs Yes)	-0.47	0.07	-6.91	0.000	0.62	0.54	0.71
White: Unknown (vs Yes)	-0.51	0.09	-5.71	0.000	0.60	0.51	0.72
Hispanic: Yes (vs No)	-0.59	0.06	-10.21	0.000	0.55	0.50	0.62
Hispanic: Yes (vs Unknown)	-0.19	0.04	-4.49	0.000	0.83	0.76	0.90
Asthma: Yes (vs No)	1.45	0.05	26.52	0.000	4.25	3.82	4.73
Tobacco use x Asthma	-0.65	0.10	-6.36	0.000			

f) Female CRSsNP patients only

Covariate	Est	SE	Z	P-value	RR	LL	UL
Tobacco use: Yes (vs No)	0.33	0.04	8.35	0.000	1.39	1.29	1.51
White: No (vs Yes)	-0.45	0.06	-7.23	0.000	0.64	0.57	0.72
White: Unknown (vs Yes)	-0.28	0.09	-3.24	0.001	0.75	0.64	0.89
Hispanic: Yes (vs No)	-0.42	0.05	-8.63	0.000	0.66	0.60	0.72
Hispanic: Yes (vs Unknown)	-0.06	0.04	-1.58	0.113	0.94	0.87	1.02
Asthma: Yes (vs No)	1.41	0.04	36.51	0.000	4.09	3.79	4.41
Tobacco use x Asthma	-0.69	0.08	-8.65	0.000			

g) All CRSwNP patients

Covariate	Est	SE	Z	P-value	RR	LL	UL
Tobacco use: Yes (vs No)	0.37	0.02	15.57	0.000	1.44	1.38	1.51
White: No (vs Yes)	-0.32	0.04	-8.48	0.000	0.73	0.67	0.78
White: Unknown (vs Yes)	-0.35	0.05	-6.75	0.000	0.71	0.64	0.78
Hispanic: Yes (vs No)	-0.33	0.03	-10.70	0.000	0.72	0.68	0.76
Hispanic: Yes (vs Unknown)	-0.03	0.02	-1.12	0.262	0.97	0.93	1.02
Asthma: Yes (vs No)	1.80	0.03	71.35	0.000	6.04	5.75	6.34
Tobacco use x Asthma	-0.75	0.05	-15.16	0.000			

h) Male CRSwNP patients only

Covariate	Est	SE	Z	P-value	RR	LL	UL
Tobacco use: Yes (vs No)	0.38	0.03	12.24	0.000	1.46	1.37	1.55
White: No (vs Yes)	-0.29	0.05	-5.43	0.000	0.75	0.68	0.83
White: Unknown (vs Yes)	-0.45	0.07	-6.30	0.000	0.64	0.56	0.73
Hispanic: Yes (vs No)	-0.46	0.05	-10.04	0.000	0.63	0.58	0.69
Hispanic: Yes (vs Unknown)	-0.10	0.03	-2.84	0.004	0.91	0.85	0.97
Asthma: Yes (vs No)	1.91	0.04	47.88	0.000	6.75	6.24	7.29
Tobacco use x Asthma	-0.70	0.07	-9.55	0.000			

i) Female CRSwNP patients only

Covariate	Est	SE	Z	P-value	RR	LL	UL
Tobacco use: Yes (vs No)	0.36	0.04	9.90	0.000	1.44	1.34	1.54
White: No (vs Yes)	-0.36	0.05	-6.62	0.000	0.70	0.63	0.78
White: Unknown (vs Yes)	-0.21	0.08	-2.77	0.006	0.81	0.70	0.94
Hispanic: Yes (vs No)	-0.21	0.04	-4.99	0.000	0.81	0.75	0.88
Hispanic: Yes (vs Unknown)	0.04	0.04	1.26	0.208	1.05	0.98	1.12
Asthma: Yes (vs No)	1.72	0.03	52.84	0.000	5.59	5.24	5.96
Tobacco use x Asthma	-0.81	0.07	-11.78	0.000			