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Sex differences in healthcare utilization for chronic rhinosinusitis: a prospective cohort study

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Abstract

Background An understanding of future healthcare needs of patients with chronic rhinosinusitis (CRS) is essential for patients and providers to make informed treatment decisions. Data on the predictors of long-term CRS-related healthcare utilization are limited. While there is evidence of sex differences in CRS, it is unknown whether the factors associated with long-term healthcare needs differ by sex.

Objective The objectives of this study were to evaluate associations between CRS symptoms and CRS-related healthcare utilization and how these associations differ by sex.

Methods We conducted a prospective study of 7,847 subjects, utilizing questionnaire and electronic health record data to assess CRS-related healthcare utilization. Individuals who met CRS symptom criteria were categorized into one of four symptom profiles in 2014: obstruction and discharge; pain or pressure without smell loss; smell loss without pain or pressure; and pain or pressure and smell loss. Healthcare utilization (2014–2019) was classified into one of six categories based on CRS-related clinical encounters and diagnostic imaging: minimal overall utilization, no CRS-related utilization; one-year of CRS-related utilization; repeated CRS-related utilization; episodic CRS-related utilization; and discontinued utilization. We evaluated associations between symptom profiles and utilization categories using multinomial logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI), assessing effect modification by sex using cross-product terms.

Results Of the 7,847 subjects, 62.7% were women and 37.3% were men. Among women, there was no association between CRS symptoms in 2014 and repeated CRS-related healthcare utilization (versus discontinued CRS-related utilization), whereas men with CRS symptoms had nearly twice the odds (OR 1.81 CI: 1.02, 3.20) of repeated utilization. Women who had CRS with pain and pressure, had higher odds of discontinued CRS-related utilization. This was not observed for other symptom profiles.

Conclusion Healthcare utilization patterns for CRS varied by symptoms and sex. Women with facial pain/pressure were uniquely at risk for discontinuation of CRS-related care, providing further evidence of sex differences among individuals reporting sinonasal symptoms.

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Keywords Chronic rhinosinusitis, Healthcare utilization, Prospective cohort, Sex

Introduction

Chronic rhinosinusitis (CRS) is a highly prevalent condition [1], with estimated annual healthcare costs greater than \$14.4 billion [2]. There has been a movement towards more personalized CRS disease management because CRS is a heterogeneous condition, with a range of symptom patterns, co-occurring conditions, and response to treatment [1, 3, 4]. The long-term healthcare needs of individuals with CRS are poorly understood and are also likely to be heterogeneous. Patients at high risk of long-term CRS healthcare needs may benefit from increased care coordination among specialists, primary care providers, and pharmacists [5]. An understanding of future healthcare needs of patients with CRS is essential for patients and providers to make informed and tailored treatment decisions [6]. However, predictors of long-term CRS healthcare needs remain underexplored.

Healthcare utilization for CRS can continue for many years for some patients. Reported sinus surgery revision rates range from 4 to 24% of patients, with durations between surgeries varying from one to ten years [7, 8]. Studies examining long-term healthcare utilization in CRS are limited, as they have generally been restricted to one year or confined to surgical patients who are more likely to have more severe disease. Additionally, these studies have been based on CRS diagnoses, not symptoms, and have therefore been unable to account for the heterogeneity in symptoms [9–12].

CRS symptoms and comorbidities vary by sex [1, 3]. Symptoms of pain and pressure in the absence of smell loss is more common in women [1], whereas nasal obstruction is more common among men [3]. Women have a higher prevalence of comorbid headache [3], whereas men have a higher prevalence of nasal polyps [3, 13]. Studies showed that at pre-surgery, women presented with worse symptom severity but had comparable or better scores on objective measures (e.g., computed tomography (CT)) than men [14, 15]. Whether these findings are due to differences in CRS pathophysiology or are driven by care-seeking behavior [16] is unknown. To better understand the mechanisms behind these differences and inform more personalized approaches to care, sex needs to be incorporated into CRS research [17]. No study has explored whether there are sex differences in long-term CRS-related healthcare utilization patterns or whether symptoms associated with long-term CRS-related healthcare utilization differ by sex.

We studied six years of healthcare utilization for sinonasal symptoms among the Chronic Rhinosinusitis Integrative Study Program (CRISP) cohort [1]. The CRISP cohort is a group of 7,847 patients, with and without

CRS symptoms, from a Pennsylvania health system. The objectives of this study were (1) to evaluate whether CRS symptom profiles and demographic features are associated with CRS-related healthcare utilization; and (2) to determine whether associations between symptoms and utilization differ between men and women.

Methods

Study overview

We conducted a prospective cohort study on a previously described cohort, who responded to the baseline sinonasal questionnaire in the CRISP study (i.e., CRISP1 baseline cohort) [1]. We merged questionnaire data with electronic health record (EHR) data from 2001 to 2019 to examine the associations between baseline sinonasal symptoms and demographic features and healthcare utilization for sinonasal symptoms over the subsequent six year period and to determine whether these associations differ between men and women. The study was approved by Geisinger's Institutional Review Board (#2019–0547).

Study sample and recruitment

The CRISP1 baseline cohort included the 7,847 respondents to a sinonasal symptom questionnaire sent to 23,700 Geisinger patients in 2014 [1]. The Geisinger population is representative of the general population in the region [18]. For the baseline questionnaire, we used stratified random sampling and oversampling of racial and ethnic minorities and patients with EHR evidence of CRS, nasal polyps, or asthma from adult primary care patients [1]. Respondents were then sent four additional questionnaires, one for each season from fall 2014 through summer 2015, and then a fifth questionnaire in 2020. The participation rate for the first survey was 33% and was above 58% for each of the follow-up surveys.

Data sources

We used questionnaire data to assess sinonasal symptoms, diagnoses, and comorbid disease. EHR data included sociodemographic data, diagnoses, medications, procedures (e.g., endoscopic sinus surgery [ESS]), diagnostic tests/results (e.g., sinus CT scans), and their dates from 2001 to 2019.

Identification of individuals with CRS symptoms

We used the previously published CRISP1 baseline questionnaire [1] (2014) to identify individuals with evidence of CRS according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) epidemiologic criteria for CRS [19]. We classified individuals as meeting CRS criteria if they had at least two of six symptoms

(i.e., nasal obstruction, anterior nasal discharge, posterior nasal discharge, smell loss, facial pain, facial pressure) most or all of the time for at least three months, with at least one of the symptoms including nasal obstruction or discharge. Individuals were classified as having “current CRS” if they met these criteria at the time of the baseline questionnaire, “past CRS” if they reported a history of these symptoms but did not meet the criteria at the time of the questionnaire, and “never CRS” if they reported no history of meeting CRS symptom criteria. We then categorized individuals who met the CRS symptom criteria into previously described, mutually exclusive symptom profiles of baseline symptoms: obstruction and discharge with no other symptoms (obstruction/discharge); pain or pressure without smell loss (pain/pressure); smell loss without pain or pressure (smell loss); and pain or pressure and smell loss (pan-symptomatic) [1].

Comorbid conditions and sinus surgery

Respondents were classified as having the comorbid disease (asthma, allergic rhinitis, migraine) at the time of the baseline questionnaire if (1) they reported on a questionnaire that they had been told by a doctor that they had the disease before 2014, or (2) they had at least two diagnoses associated with encounters or medication orders in the EHR before the date of the baseline questionnaire. We captured ESS history using the questionnaire and EHR data.

Outcome measurement

For each of the years from 2014 to 2019, we noted whether CRS-related healthcare utilization occurred using questionnaire and EHR data. For each year, we assigned a ‘1’ if the individual had any of the following in that year: clinical encounter with a diagnosis of CRS or nasal polyps, sinus CT scan, or sinus endoscopy; a ‘0’ if the individual had at least one encounter at Geisinger, but no encounters related to CRS (i.e., did not meet the criteria for ‘1’); and an ‘X’ if the individual had no encounters with Geisinger in that year. We assigned individuals to one of six mutually-exclusive patterns over the six-year period (Additional file 1). Participants were categorized as having minimal overall utilization if they had at least four years without a Geisinger encounter or no Geisinger encounter in 2018 and 2019. Among those with appreciable overall utilization, participants were classified as having: no CRS-related utilization: no CRS-related utilization in any year; one-year of CRS-related utilization: a single year with CRS-related utilization; repeated CRS-related utilization: at least two adjacent years of CRS-related utilization separated by no more than one year without CRS-related utilization, and followed by no more than a one-year gap in CRS-related utilization (e.g., year assignments 011110); episodic CRS-related utilization: at

least two total years of CRS-related utilization separated by at least two years without CRS-related utilization (e.g., year assignments 001001); and discontinued utilization: at least two years of CRS-related utilization, with no greater than a one year gap, followed by at least two years without CRS-related utilization and no additional years of CRS-related utilization (e.g., year assignments 001100). Because discontinued utilization required at least two prior years of CRS-related utilization, individuals in this category had more CRS-related utilization than those in the no-CRS related utilization and one-year of CRS-related utilization categories.

Statistical analysis

The primary goal of the analysis was to evaluate the associations between baseline CRS symptom profiles, demographic features, and CRS utilization patterns. We used multinomial logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for each utilization pattern, compared to discontinued CRS-related utilization as the reference group. The base model included age (years), sex (female, male), smoking status (current, former, never), race (White, all other races, which combined races into a single category due to the small proportion of individuals who identified as non-White), ethnicity (Hispanic, non-Hispanic), and Medical Assistance as a surrogate for socioeconomic status (ever, never) [20]. We also adjusted for baseline comorbid disease status (yes/no) for asthma, allergic rhinitis, and migraine. We centered continuous variables and used quadratic and cubic terms when needed to allow for non-linearity.

Next, we added baseline CRS symptom status (i.e., current, past, never) to the base model. Then, in a separate model, we added a categorical variable to capture the CRS symptom profiles (obstruction/discharge, pain/pressure, smell loss, pan-symptomatic at the time of the baseline survey, past CRS symptoms, never CRS symptoms) to the base model. These models enabled us to examine associations between demographic features (e.g., sex), symptoms, and CRS-related utilization.

The secondary goal of this analysis was to determine whether sex, comorbid disease, or ESS (prior to baseline questionnaire) modified associations between CRS symptoms and utilization patterns. We evaluated effect modification by adding cross-product terms of these variables with CRS symptom status and CRS symptom patterns in separate models.

Sensitivity analyses

To distinguish general health utilization patterns that may be influenced by gender from utilization specific to CRS, we replicated the analysis of effect modification by sex for migraine symptoms. We used the ID Migraine, a

migraine symptom assessment included in the baseline questionnaire [21, 22], to create a binary category for presence of migraine symptoms within the year prior to the baseline questionnaire. We then created the six-year utilization patterns for migraine, based on years with a diagnosis of migraine or a migraine medication order. We conducted multinomial logistic regression for each of the migraine utilization patterns using the same sociodemographic covariates as in the CRS base model, with the addition of the baseline migraine symptom status. We evaluated effect modification of associations of migraine symptoms with utilization by sex by adding a cross-product term for migraine symptoms and sex.

Results

Study sample characteristics

The mean (SD) age of baseline questionnaire respondents was 55.04 (16.09) years. Most were female (62.7%) and White (90.4%) (Table 1) [1]. Up to the date of the questionnaire, 61.2% of respondents had at least one CRS diagnosis in the EHR. In the six years after the baseline questionnaire, 1,245 of the 7,847 respondents [15.9%] had minimal utilization recorded in the EHR (Table 1). From 2014 to 2019, more than half of the 7,847 respondents (53.4%) had no CRS-related utilization, 4.3% discontinued CRS-related utilization, 3.0% had episodic CRS-related utilization, and 7.0% had repeated utilization (Table 1).

At baseline, of the 7,847 respondents, 23.9% met the criteria for current CRS symptoms, 26.6% reported symptoms only in the past, and 49.0% did not have a history of meeting CRS symptom criteria. Among respondents, 7.8% reported obstruction and discharge without other symptoms, 8.8% reported pain and/or pressure without smell loss, 4.2% reported smell loss without pain or pressure, and 3.0% reported that they had smell loss with pain, pressure, or both. There was a history of ESS, self-reported or in the EHR, in 882 respondents (11.2%) before 2014.

Associations of CRS symptoms with utilization

Individuals who met CRS symptom criteria at baseline were less likely to have six years of follow-up with no CRS-related utilization (OR=0.25 CI=0.18, 0.34) and only one year of CRS-related utilization (OR=0.53 CI=0.38, 0.73) than discontinued utilization (Table 2). Baseline symptom status was not associated with episodic or repeated CRS-related utilization when compared to discontinued utilization. Similar patterns were observed, regardless of CRS symptom profile.

Associations of sex with utilization

Women were more likely to have a single year of CRS-related utilization than have discontinued utilization

(OR=1.40 CI=1.08, 1.82). Sex was not associated with other utilization patterns. However, sex did modify associations between CRS symptoms and utilization (Table 3). Among women, those who met CRS symptom criteria in 2014 had lower odds of episodic versus discontinued utilization (OR=0.52 CI=0.29, 0.94), whereas, among men, those who met CRS criteria in 2014 had higher odds, though the association did not cross an inferential threshold (OR=1.61 CI=0.78, 3.30). Similarly, the association between CRS symptom status and repeated versus discontinued utilization, differed by sex. Among women, there was no association between CRS symptoms and repeated utilization (OR=0.75 CI=0.45, 1.25), whereas men who met CRS criteria in 2014 had nearly twice the odds of repeated utilization (OR=1.81 CI=1.02, 3.20).

Sex only modified the association of one of the four CRS symptom profiles – facial pain/pressure – and utilization (Table 3). Women who had CRS with pain or pressure (without smell loss), had lower odds of episodic versus discontinued utilization (OR=0.44 CI=0.23, 0.87). No association was observed among women with other symptom combinations. An association with utilization was not observed among men with pain or pressure (OR=1.90 CI=0.67, 5.40). To explore this finding, we compared the proportion of individuals with migraine (a condition with symptoms of pain and pressure) across healthcare utilization categories, by sex (Fig. 1). Migraine was more common in women and most common among those who discontinued CRS-related healthcare utilization. Unlike in CRS, there was no evidence of effect of the association between symptoms and utilization by sex (Additional file 2).

Associations of comorbid conditions and surgery history with utilization

Individuals who had asthma, allergic rhinitis, or migraine, were all less likely to have no CRS-related utilization (versus discontinued) than individuals without these conditions. Individuals with asthma also had lower odds of having CRS-related utilization for only a single year (OR 0.63 CI: 0.49, 0.81) and episodic CRS-related utilization (OR 0.65 CI: 0.45, 0.92) versus discontinued CRS-related utilization. Individuals with ESS before the 2014 questionnaire had twice the odds of repeated versus discontinued utilization (OR 2.00 CI:1.44, 2.78). There was no evidence that comorbid disease or ESS modified associations between CRS symptoms and utilization (results not shown).

Discussion

We conducted the first study, to our knowledge, to evaluate long-term CRS-related healthcare utilization by symptoms and in a cohort with and without a history of

Table 1 Description of CRISP1 baseline cohort at time of the baseline questionnaire in 2014 by CRS-related utilization patterns from 2014–2019

Variable	Full cohort	Minimal utilization	No CRS-related utilization	CRS-related utilization in one year	Episodic CRS-related utilization	Discontinued CRS-related utilization	Repeated CRS-related utilization
Number (%)	7847 (100)	1245 (15.9)	4,194 (53.4)	1,293 (16.5)	234 (3.0)	334 (4.3)	547 (7.0)
Age (years), n (%) ¹							
18 to < 30	639 (8.1)	177 (14.2)	328 (7.8)	78 (6.0)	16 (6.8)	21 (6.3)	19 (3.5)
30 to < 45	1420 (18.1)	188 (15.1)	759 (18.1)	252 (19.5)	52 (22.2)	63 (18.9)	106 (19.4)
45 to < 55	1660 (21.2)	177 (14.2)	946 (22.6)	291 (22.5)	57 (24.4)	75 (22.5)	114 (20.8)
55 to < 65	1904 (24.3)	193 (15.5)	1036 (24.7)	360 (27.8)	61 (26.1)	90 (27.0)	164 (30.0)
65 or older	2224 (28.3)	510 (41.0)	1125 (26.8)	312 (24.1)	48 (20.5)	48 (20.5)	144 (26.3)
Sex, n (%)							
Female	4921 (62.7)	693 (55.5)	2658 (63.4)	877 (67.8)	149 (63.7)	208 (62.3)	336 (61.4)
Male	2926 (37.3)	552 (44.3)	1536 (36.6)	416 (32.2)	85 (36.3)	126 (37.7)	211 (38.6)
Race, n (%)							
White	7442 (94.8)	1155 (92.8)	3929 (93.7)	1256 (97.1)	229 (97.9)	330 (98.8)	543 (99.3)
Non-White	405 (5.2)	90 (7.2)	265 (6.3)	37 (2.9)	5 (2.1)	4 (1.2)	4 (0.7)
Ethnicity, n (%)							
Non-Hispanic	7437 (94.8)	1151 (92.4)	3939 (93.9)	1251 (96.8)	227 (97.0)	328 (98.2)	541 (98.9)
Hispanic	410 (5.2)	94 (7.6)	255 (6.1)	42 (3.2)	7 (3.0)	6 (1.8)	6 (1.1)
Smoking, n (%) ¹							
Current	1142 (14.6)	202 (16.2)	586 (14.0)	194 (15.0)	38 (16.2)	56 (16.8)	66 (12.1)
Former	2399 (30.6)	402 (32.3)	1241 (29.6)	407 (31.5)	76 (32.5)	111 (33.2)	162 (29.6)
Never	4306 (54.9)	641 (51.5)	2367 (56.4)	692 (53.5)	120 (51.3)	167 (50.0)	319 (58.3)
Med Assistance, n (%) ¹	1129 (14.4)	162 (13.0)	581 (13.8)	209 (16.2)	47 (20.1)	58 (17.4)	72 (13.2)
Sinus surgery, n (%) ¹	882 (11.2)	66 (5.3)	299 (7.1)	198 (15.3)	51 (21.8)	71 (21.3)	197 (36.0)
Asthma, n (%) ¹	2441 (31.1)	344 (27.6)	1128 (26.9)	459 (35.5)	89 (38.0)	160 (47.9)	261 (47.7)
Allergic rhinitis, n (%) ¹	4932 (62.8)	658 (52.9)	2460 (58.7)	935 (72.3)	176 (75.2)	256 (76.7)	447 (81.7)
Migraine headache, n (%) ¹	2493 (31.8)	270 (21.7)	1244 (29.7)	516 (39.9)	98 (41.9)	152 (45.5)	213 (38.9)
CRS, n (%) ²							
Current	1873 (23.9)	253 (20.3)	726 (17.3)	421 (32.6)	96 (41.0)	139 (41.6)	238 (43.5)
Past	2088 (26.6)	307 (24.7)	1043 (24.9)	363 (28.1)	71 (30.3)	112 (33.5)	192 (35.1)
Never	3842 (49.0)	670 (53.8)	2408 (57.4)	504 (39.0)	66 (28.2)	79 (23.6)	115 (21.0)
Unknown	44 (0.56)	15 (1.2)	17 (0.4)	5 (0.4)	1 (0.4)	4 (1.2)	2 (0.4)
Obstruction/discharge, n (%) ³							
Current	619 (7.9)	83 (6.7)	266 (6.3)	131 (10.1)	31 (13.3)	42 (12.6)	66 (12.1)
Past	649 (8.3)	93 (7.5)	364 (8.7)	103 (8.0)	19 (8.1)	29 (8.7)	41 (7.5)
Other symptom profile	2737 (34.9)	399 (32.1)	1156 (27.6)	555 (42.9)	118 (50.4)	184 (55.1)	325 (59.4)
Never CRS	3842 (49.0)	670 (53.8)	2408 (57.4)	504 (39.0)	66 (28.2)	79 (23.7)	115 (21.0)
Pain/pressure, n (%) ³							
Current	689 (8.8)	81 (6.5)	260 (6.2)	168 (13.0)	38 (16.2)	60 (18.0)	82 (15.0)
Past	906 (11.6)	115 (9.2)	466 (11.1)	161 (12.5)	33 (14.1)	47 (14.1)	84 (15.4)
Other symptom profile	2410 (30.7)	379 (30.4)	1060 (25.3)	460 (35.6)	97 (41.4)	148 (44.3)	266 (48.6)
Never CRS	3842 (49.0)	670 (53.8)	2408 (57.4)	504 (39.0)	66 (28.2)	79 (23.7)	115 (21.0)
Smell loss, n (%) ³						19 (5.7)	
Current	331 (4.2)	51 (4.1)	120 (2.9)	71 (5.5)	20 (8.6)	14 (4.2)	50 (9.1)
Past	211 (2.7)	49 (3.9)	87 (2.1)	28 (2.2)	5 (2.1)	222 (66.5)	28 (5.1)
Other symptom profile	3463 (44.1)	475 (38.2)	1579 (37.7)	690 (53.4)	143 (61.1)	79 (23.7)	354 (64.7)
Never CRS	3842 (49.0)	670 (53.8)	2408 (57.4)	504 (39.0)	66 (28.2)		115 (21.0)
Pan-symptomatic, n (%) ³							
Current	234 (3.0)	38 (3.1)	80 (1.9)	51 (3.9)	7 (3.0)	18 (5.4)	40 (7.3)
Past	322 (4.1)	50 (4.0)	126 (3.0)	71 (5.5)	14 (6.0)	22 (6.6)	39 (7.1)

Table 1 (continued)

Variable	Full cohort	Minimal utilization	No CRS-related utilization	CRS-related utilization in one year	Episodic CRS-related utilization	Discontinued CRS-related utilization	Repeated CRS-related utilization
Other symptom profile	3449 (44.0)	487 (39.1)	1580 (37.7)	667 (51.6)	147 (62.8)	215 (64.4)	353 (64.5)
Never CRS	3842 (49.0)	670 (53.8)	2408 (57.4)	504 (39.0)	66 (28.2)	79 (23.7)	115 (21.0)

Abbreviations: CRS chronic rhinosinusitis, EPOS European Position Paper on Rhinosinusitis and Nasal Polyps

¹As of 2014 questionnaire

²CRS: *Current*: Met EPOS CRS symptom criteria in the preceding 3 months at the time of the baseline questionnaire; *Past*: Met EPOS CRS symptom criteria before 2014 but not at the time of the baseline questionnaire; *Never*: Did not report EPOS CRS symptoms ever in lifetime

³Symptom profiles: *Obstruction/discharge*: obstruction and discharge most of the time, but no other symptoms; *Pain/pressure*: facial pain and/or pressure with at least one cardinal symptom (obstruction and/or discharge); *Smell loss*: smell loss with at least one cardinal symptom, but without pain or pressure; *Pain-symptomatic*: smell loss with pain and/or pressure and at least one cardinal symptom

Table 2 Adjusted¹ associations of CRS-related utilization patterns from 2014–2019 among respondents to the CRISP1 questionnaire

Variable	Discontinued CRS-related utilization	Minimal healthcare utilization	No CRS-related utilization	CRS-related utilization in one year (ref.)	Episodic CRS-related utilization	Repeated CRS-related utilization
Number, total	334	1245	4,194	1,293	234	547
	Odds ratio (95% confidence interval)					
Sex						
Female	Reference	1.00 (0.76, 1.31)	1.27 (0.99, 1.62)	1.40 (1.08, 1.82)	1.11 (0.77, 1.61)	1.07 (0.80, 1.43)
Male (ref)						
Sinus surgery ²	Reference	0.36 (0.25, 0.53)	0.43 (0.32, 0.59)	0.82 (0.60, 1.12)	1.16 (0.76, 1.78)	2.00 (1.44, 2.78)
Asthma ²	Reference	0.53 (0.41, 0.70)	0.50 (0.39, 0.64)	0.63 (0.49, 0.81)	0.65 (0.45, 0.92)	0.93 (0.70, 1.23)
Allergic rhinitis ²	Reference	0.70 (0.52, 0.95)	0.71 (0.53, 0.94)	1.02 (0.75, 1.38)	1.61 (0.70, 1.61)	1.32 (0.93, 1.88)
Migraine ²	Reference	0.51 (0.38, 0.69)	0.69 (0.53, 0.89)	0.85 (0.65, 1.12)	0.82 (0.56, 1.19)	0.74 (0.54, 1.00)
CRS ³	Reference					
Current		0.42 (0.30, 0.59)	0.25 (0.18, 0.34)	0.53 (0.38, 0.73)	0.85 (0.54, 1.34)	1.10 (0.75, 1.61)
Past		0.57 (0.40, 0.80)	0.41 (0.30, 0.56)	0.56 (0.40, 0.77)	0.77 (0.48, 1.22)	1.02 (0.69, 1.49)
Never (ref)		1.0	1.0	1.0	1.0	1.0
CRS symptom profile ⁴	Reference					
Obstruction/discharge	1.0	0.40 (0.25, 0.63)	0.28 (0.18, 0.42)	0.53 (0.34, 0.81)	0.90 (0.50, 1.61)	0.99 (0.61, 1.62)
Pain/pressure	1.0	0.35 (0.22, 0.52)	0.21 (0.14, 0.30)	0.47 (0.32, 0.71)	0.75 (0.43, 1.31)	0.93 (0.59, 1.48)
Smell loss	1.0	0.51 (0.22, 0.97)	0.31 (0.18, 0.55)	0.67 (0.38, 1.20)	1.31 (0.63, 2.74)	1.51 (0.81, 2.81)
Pain/pressure/smell loss	1.0	0.60 (0.31, 1.17)	0.23 (0.13, 0.42)	0.50 (0.27, 0.93)	0.46 (0.18, 1.20)	1.51 (0.78, 2.91)
Past	1.0	0.57 (0.40, 0.80)	0.41 (0.30, 0.56)	0.55 (0.40, 0.77)	0.76 (0.48, 1.21)	1.01 (0.69, 1.50)
Never (reference)	1.0	1.0	1.0	1.0	1.0	1.0

Abbreviations: CRS chronic rhinosinusitis, EPOS European Position Paper on Rhinosinusitis and Nasal Polyps, ref reference group

¹Adjusted for age, age-centered squared, age-centered cube, race, ethnicity, and Medical Assistance

²As of 2014 questionnaire

³CRS: *Current*: Met EPOS CRS symptom criteria in the preceding 3 months at the time of the baseline questionnaire; *Past*: Met EPOS CRS symptom criteria before 2014 but not at the time of the baseline questionnaire; *Never*: Did not report EPOS CRS symptoms ever in lifetime

⁴Symptom profiles: *Obstruction/discharge*: obstruction and discharge most of the time, but no other symptoms; *Pain/pressure*: facial pain and/or pressure with at least one cardinal symptom (obstruction and/or discharge); *Smell loss*: smell loss with at least one cardinal symptom, but without pain or pressure; *Pain, pressure, smell loss*: smell loss with pain and/or pressure and at least one cardinal symptom

sinus surgery. Given the growing evidence of sex differences in CRS, we explored whether associations between symptoms and utilization differed by sex, as associations observed in women may not be generalizable to men. We found that women with sinonasal symptoms were more likely to discontinue care for CRS over six years, while men with symptoms were more likely to continue care. ESS was associated with higher odds of repeated utilization over the six-year study period. This study provides

insight into the long-term burden of CRS and additional evidence of the heterogeneity of CRS symptom profiles and sex [1, 13–15]. A more complete understanding of the sex-specific risks of repeated CRS-related healthcare utilization is a necessary step towards more personalized CRS care, informing treatment decisions and care coordination.

Women who met CRS symptom criteria were at increased risk of discontinued CRS-related utilization

Table 3 Adjusted associations¹ of discontinued CRS-related utilization (versus discontinued CRS-related utilization) patterns by sex from 2014–2019 among respondents to the CRISP1 questionnaire

CRS symptom status	Comparison	Adjusted odds ratio (95% confidence interval) Discontinued vs. Episodic		
		Test for interaction (sex x symptom profile)	Women	Men
CRS ²	Episodic versus discontinued			
Current		$p = 0.014$	0.52 (0.29, 0.94)	1.61 (0.78, 3.30)
Past		$p = 0.008$	0.44 (0.24, 0.82)	1.53 (0.76, 3.08)
Never (ref)				
CRS symptom profile	Episodic versus discontinued			
Obstruction/discharge		$p = 0.144$	0.60 (0.28, 1.27)	1.45 (0.57, 3.68)
Pain/pressure		$p = 0.018$	0.44 (0.23, 0.87)	1.90 (0.67, 5.40)
Smell loss		$p = 0.257$	0.88 (0.34, 2.30)	2.04 (0.66, 6.29)
Pain/pressure/smell loss		$p = 0.784$	0.34 (0.11, 1.00)	0.48 (0.05, 4.60)
Past		$p = 0.007$	0.44 (0.24, 0.81)	1.52 (0.75, 3.07)
Never (ref)				
CRS ²	Repeated versus discontinued			
Current		$p = 0.020$	0.75 (0.45, 1.25)	1.81 (1.02, 3.20)
Past		$p = 0.170$	0.77 (0.45, 1.31)	1.31 (0.74, 2.31)
Never (ref)				
CRS symptom profile ³	Repeated versus discontinued			
Obstruction/discharge		$p = 0.204$	0.72 (0.38, 1.40)	1.38 (0.65, 2.95)
Pain/pressure		$p = 0.078$	0.66 (0.37, 1.18)	1.67 (0.69, 4.06)
Smell loss		$p = 0.104$	0.91 (0.39, 2.13)	2.49 (1.02, 6.05)
Pain/pressure/smell loss		$p = 0.284$	1.08 (0.49, 2.39)	2.39 (0.70, 8.27)
Past		$p = 0.170$	0.78 (0.46, 1.32)	1.31 (0.75, 2.32)
Never (ref)				

Abbreviations: CRS chronic rhinosinusitis, EPOS European Position Paper on Rhinosinusitis and Nasal Polyps, ref reference group

¹Adjusted for age, sex, race, ethnicity, smoking status, and Medical Assistance

²CRS: *Current*: Met EPOS CRS symptom criteria in the preceding 3 months at the time of the baseline questionnaire; *Past*: Met EPOS CRS symptom criteria before 2014 but not at the time of the baseline questionnaire; *Never*: Did not report EPOS CRS symptoms ever in lifetime

³Symptom profiles: *Obstruction/discharge*: obstruction and discharge most of the time, but no other symptoms; *Pain/pressure*: facial pain and/or pressure with at least one cardinal symptom (obstruction and/or discharge); *Smell loss*: smell loss with at least one cardinal symptom, but without pain or pressure; *Pain, pressure, smell loss*: smell loss with pain and/or pressure and at least one cardinal symptom

after at least two years of CRS-related care, versus episodic or repeated utilization. Conversely, men who met CRS were more likely to have repeated utilization. In prior studies, women have reported higher levels of CRS symptoms than men, despite less-extensive radiologic evidence of disease [3]. One potential reason that discontinuation of utilization was observed among symptomatic women, but not men, may be that women who were symptomatic at baseline may have had less extensive disease (per radiographic criteria) than the symptomatic men in this cohort and, therefore, may be less likely to require long-term CRS-related healthcare. This would also explain why men with CRS symptoms were more likely to have repeated utilization, but women were not. Alternatively, guideline-based symptom criteria for CRS may not adequately capture symptoms experienced by women. In a prior study, we found that 14.9% of men and 9.9% of women had Lund-Mackay scores of 4 or greater, meeting the radiologic criteria for CRS. However, only 7.5% of men and 1.6% of women met both radiologic and

symptom criteria, a decrease of 49% for men and 84% for women [4].

Women with CRS symptom patterns that included facial pain and pressure were at an increased risk of discontinued CRS-related utilization. This was not true of men or of any other symptom pattern. Facial pain and pressure are also symptoms of migraine headache, a condition more common in women than in men [23] and frequently misclassified as sinus headache [3]. Indeed, the presence of facial pain may decrease the likelihood of a diagnosis of CRS [24]. Migraine and CRS can co-occur, and thus it can be difficult to attribute symptoms to one or the other condition [25]. We found that individuals who discontinued CRS-related care had the highest proportion of individuals with migraine headache. The discontinuation of CRS-related care among symptomatic women observed in the present study may reflect that women are more likely to have conditions that mimic CRS symptoms resulting in more short-term sinus-directed care before pivoting toward care directed at an alternative cause of their symptoms [3].

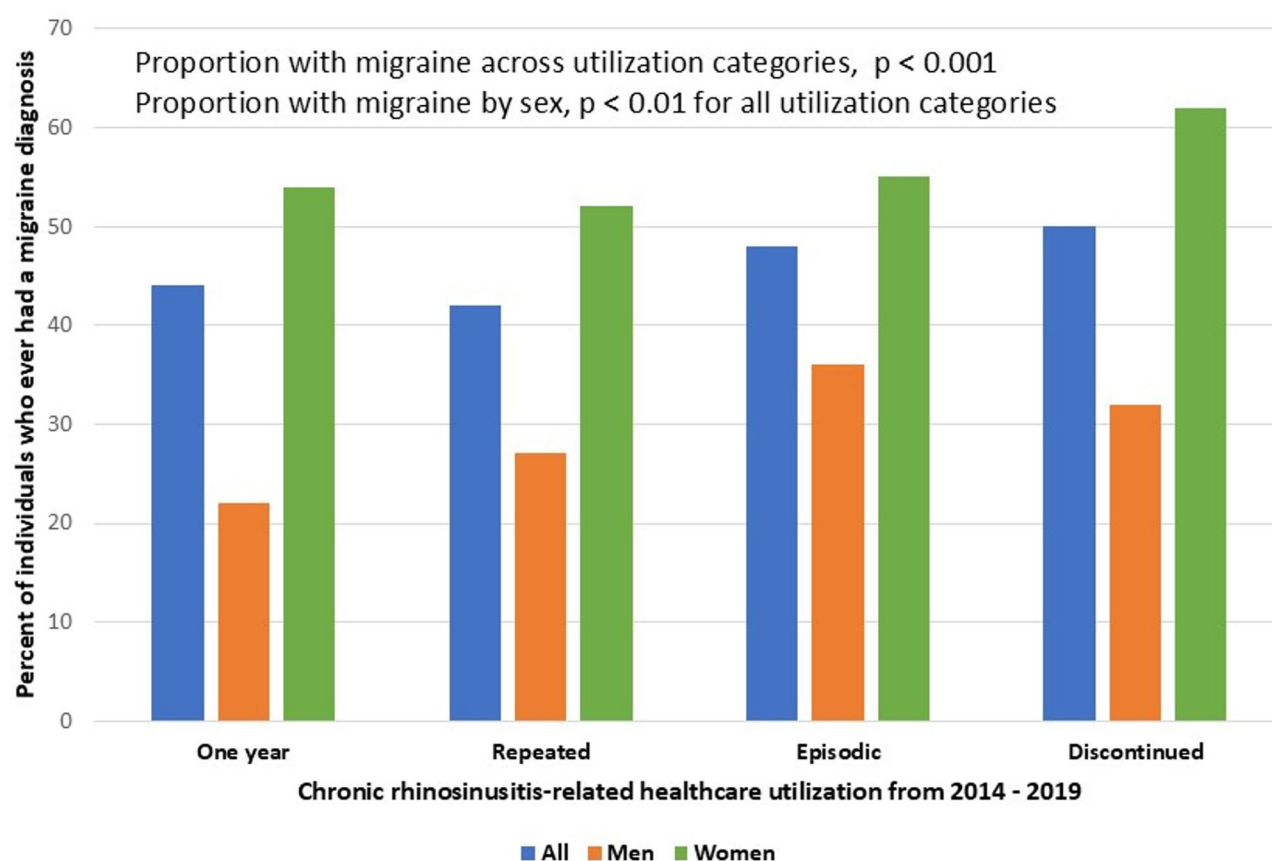


Fig. 1 Percent of respondents to the Chronic Rhinosinusitis Integration Study (CRISP) baseline questionnaire with a self-reported doctor diagnosis of migraine or a migraine diagnosis in the electronic health record as of 2014, by sex and by CRS-related utilization category

Our findings on sex contribute to a growing body of work showing sex differences in CRS. Ference and colleagues attributed sex differences in CRS symptom severity and co-occurring disease (e.g., asthma) to a variety of factors, including anatomic size and hormones [3]. CRS is a chronic inflammatory condition and sex hormones play important roles in regulating inflammatory responses [26]. These same factors could, in part, explain differences in long-term CRS-related utilization, given that differences in symptom severity and co-occurring disease, for example, could influence healthcare utilization patterns. Alternatively, our findings may be detecting utilization behavior driven, not by pathophysiological differences alone, but also by gender-related characteristics (e.g., access to care and care-seeking behavior [16]). For example, women are more likely than men to report that they would visit a physician in response to both a physical and mental health concern [27]. It may be that men with CRS were more likely to have repeated care, because they initially sought care at a later and more severe stage of disease. To better understand the mechanism driving our findings, we attempted to assess the role of gender by evaluating effect modification by sex

on associations between migraine headache and utilization. In migraine, sex did not modify utilization the way it did in CRS, providing some evidence that our findings reflect true sex differences in features of CRS. Prior studies have reported sex differences in migraine utilization, but these prior studies were based on self-report, not EHR data, and did not assess long-term utilization trajectories [28–30].

ESS was associated with double the odds of repeated CRS-related utilization, consistent with the well-documented need for revision ESS [8]. This finding could reflect surgical follow-up [31] or ESS may be a surrogate for more severe CRS [31]. ESS did not alter the trajectory of long-term utilization of CRS-related care among those with CRS symptoms at baseline. If an individual had CRS symptoms, a history of ESS did not put them at a lower risk of repeated utilization over the following six years. Thus, when presenting the option of surgery to patients, clinicians should discuss the potential need for long-term management of this chronic disease.

This study had several limitations. First, this study was conducted in a single health system and there may be care practices unique to Geisinger that would influence

utilization patterns. However, Geisinger has more than 100 clinics and 1700 physicians throughout a 40-county region, thus there is likely variation in diagnostic and treatment approaches across the system. Second, our study sample was primarily non-Hispanic White, reflecting the region Geisinger serves. Findings may not be generalizable to a more demographically diverse population. As previously noted, we used oversampling of racial and ethnic minorities and patients with EHR evidence of CRS. Therefore, the proportions of individuals in each of the utilization categories should not be interpreted as prevalence estimates in the general population. Third, we did not have gender data. Whereas sex likely plays a role in disease pathophysiology, gender can differentially affect access to care [32]. We did not include prescription orders for CRS treatment in our utilization measure, given that the treatments for CRS (i.e., antibiotics and steroids) are indicated for many different conditions. It was not always feasible to determine that the indications for these orders were for CRS. However, we did include clinical encounters that likely reflected medical management of CRS. Finally, individuals were classified as having CRS based on symptoms only, consistent with EPOS epidemiologic criteria [19]. To be considered as symptomatic, individuals had to report that the symptom occurred most or all of the time in the last three months. These criteria do not differentiate by CRS with and without nasal polyps. While we used orders for CTs and endoscopies as part of the utilization metric, results of these procedures were not used to determine CRS status.

One of the strengths of this study was the combination of EHR and symptom data. Prior studies of CRS utilization have generally used diagnoses to determine CRS status, an approach that does not account for the heterogeneity of CRS symptoms [9–12]. The longitudinal CRS-related utilization provides unique insight into the long-term burden of CRS care. Finally, because our study sample included individuals with and without a history of sinus surgery, we were able to study the full spectrum of disease.

Conclusions

The association between CRS symptoms and long-term healthcare utilization patterns differed by sex. Symptomatic women were more likely to discontinue care for CRS than go on to have episodic or repeated care, while men were more likely to have years of continued care. Women that reported facial pain and pressure were uniquely at an increased risk of discontinued CRS-related utilization. This finding should trigger a discussion of the value of the facial pain-pressure criterion in the diagnosis of CRS among women. The growing evidence of sex differences supports exploration of the value of delivering sex-specific treatment strategies in CRS.

Abbreviations

CRS	Chronic rhinosinusitis
CT	Computed tomography
EHR	Electronic health record
CRISP	Chronic Rhinosinusitis Integrative Study Program
ESS	Endoscopic sinus surgery
CT	Computed tomography
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
OR	Odds ratio
CI	Confidence interval
SES	Socioeconomic status

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

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Data availability

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request and with approval from the Geisinger Institutional Review Board.

Declarations

Ethics approval and consent to participate

Geisinger Institutional Review Board approved this study and approved a waiver of consent. This study adhered to the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

R. Kern serves as a senior consultant for Lyra Therapeutics and has received consulting fees from Sanofi-Regeneron and GSK. B. Tan has received consulting fees from Sanofi-Regeneron. R.P. Schleimer receives royalties from patents licensed by Johns Hopkins University to Allakos; he has received consulting fees from Intersect ENT, Merck, GSK, Sanofi Regeneron, AstraZeneca/Medimmune, Genentech, Actobio Therapeutics, Lyra Therapeutics, Astellas Pharma, Allakos, and Otsuka; and he owns stock in Allakos. A.T. Peters has received research grants or contracts from Sanofi Regeneron, Optinose, and AstraZeneca and consulting fees from SanofiRegeneron, AstraZeneca, Optinose, and GSK. The remaining authors declare that they have no relevant conflicts of interest.

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