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Longitudinal Evaluation of Chronic Rhinosinusitis Symptoms in a Population-based Sample

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Abstract

Background—Chronic rhinosinusitis (CRS) is a prevalent and disabling condition of the nose and sinuses. The natural history of CRS symptoms in a general population sample has not been previously studied.

Objective—In a general population-based sample from Pennsylvania, we used two questionnaires mailed six months apart to estimate the prevalence of, and identify predictors for, stability or change in symptoms over time.

Methods—We mailed the baseline and 6-month follow-up questionnaires to 23,700 primary care patients and 7801 baseline responders, respectively. We categorized nasal and sinus symptoms using European Position Paper on Rhinosinusitis (EPOS) epidemiologic criteria. We defined six symptom groups over time based on the presence of CRS symptoms at baseline and follow-up. We

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performed multivariable survey logistic regression controlling for confounding variables comparing persistent vs. non-persistent, recurrent vs. stable past, and incident vs never.

Results—There were 4966 responders at follow-up; 558 had persistent symptoms, 190 recurrent symptoms and 83 new symptoms meeting EPOS criteria for CRS. The prevalence of persistent symptoms was 4.8% (95% CI = 3.8–5.8), while the annual cumulative incidence of new symptoms was 1.9% and of recurrent symptoms was 3.2%. More severe symptoms at baseline were associated with persistence, while minor symptoms, allergies, and multiple treatments were associated with development of new symptoms.

Conclusion—Less than half with nasal and sinus symptoms meeting CRS EPOS criteria in our general, regional population had symptom persistence over time, with symptom profiles at baseline and age of onset being strongly associated with stability of symptoms.

Keywords

Chronic rhinosinusitis; longitudinal epidemiology; incidence; persistence; recurrence

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disorder defined by the presence of two or more cardinal symptoms (obstruction, drainage [anterior or posterior], smell loss, and facial pain or pressure) for at least 12 weeks duration, confirmed by objective evidence using sinus CT scan or nasal endoscopy.[1] Epidemiologic studies in the US, using symptom criteria alone, reported a prevalence of 11.9%, similar to studies from Europe.[1, 2] CRS is a heterogeneous disease, presenting with a variety of symptom combinations.[2] There is growing interest in examining whether certain symptom clusters are more or less likely to persist or progress, as such knowledge could aid in disease management.[3–5]

A dynamic chronic episodic disease model has been proposed for CRS.[6] Chronic episodic diseases have periods of remission and relapse with longer symptom-free intervals, especially early in the disease course, but over time, as structural changes ensue (e.g., inflammation in sinuses or airways), symptoms can become less likely to remit and more likely to become progressively worse over time.[6, 7] Understanding symptom presentation over time is the first step in evaluating whether CRS evidences features of such a model.[8, 9] Conditions that follow this pattern, including asthma and migraine, reveal milder symptoms and more common remission of symptoms earlier in the disease course, and more persistent symptoms, often associated with structural changes, later in the disease course.[10–13] There is some evidence for this pattern in CRS. Studies have reported that the longer the duration after CRS diagnosis to sinus surgery, the worse the respiratory conditions, antibiotic and steroid use, and CRS-related visits, postoperatively.[14, 15] Longer disease duration was also associated with the burden of symptoms and radiographic findings.[16] However, the natural history of the early disease course has not been sufficiently studied.

We describe here findings from a longitudinal general population-based study of nasal and sinus symptoms over six months using CRS criteria for epidemiologic studies from the European Position Paper on Rhinosinusitis (EPOS).[1] Data from two questionnaires six

months apart allowed us to identify six groups of patients based on EPOS CRS criteria at each time point: persistent, non-persistent, recurrent, stable past, incident, and never. For these patients representing the entire spectrum of nasal and sinus symptoms, we describe symptom profiles, report prevalence of these six longitudinal symptom subgroups in the source population, and identify predictors of these subgroups.

METHODS

Study Overview

We mailed self-administered questionnaires to a stratified random sample of primary care patients of the Geisinger Clinic in approximately 40 counties of central and northeastern Pennsylvania in April 2014 and again in October 2014. Data was collected on the cardinal EPOS symptoms, other nasal and sinus symptoms, symptom frequency and severity, lower respiratory symptoms, comorbidities, and treatment. The study was approved by the Institutional Review Board at the Geisinger Health System.

Study Population and Subject Selection

Selection methods have been previously reported.[2] In brief, a baseline questionnaire[2] was sent to a random sample of 23,700 patients stratified by electronic health record (EHR) information into three groups (based on diagnostic codes for CRS, asthma or allergy, and none of these) and by race/ethnicity (Table E1, Online Repository). A total of 7847 persons returned the baseline questionnaire. A second questionnaire was mailed approximately six months later to 7801 baseline respondents.

The Six Month Follow-up Questionnaire

The follow-up questionnaire paralleled the baseline questionnaire[2] but with additional questions that assessed the duration of symptoms, interim surgery, allergy symptoms, and lower respiratory symptoms over the prior six months. The 87 questions required 10–15 minutes to complete. The follow-up questionnaire was mailed in October 2014 with a return envelope and a $1 bill as an incentive, and resent to non-respondents in January 2015.

Identification of Longitudinal Symptom Subgroups

CRS as defined by EPOS epidemiologic criteria requires at least two of four symptoms for at least three months duration, one of which must be either nasal obstruction or discharge.[1] We used the EPOS epidemiologic criteria as this is the standard for study of CRS in large-scale epidemiologic studies. [1, 2, 17–19] We defined three groups at baseline as those meeting criteria for current CRS (fulfilling EPOS criteria in the three months prior, with symptoms at least most of the time on a five level frequency scale [never, once in a while, some of the time, most of the time, all of the time]), past CRS (fulfilling EPOS criteria in lifetime but not current), and never CRS.[2] The two questionnaires together allowed the identification of six symptom groups: (1) **persistent**, current CRS at baseline and follow-up; (2) **non-persistent**, current CRS at baseline but not follow-up; (3) **recurrent**, past CRS at baseline and current at follow-up; (4) **stable past**, past CRS at baseline and not current at follow-up; (5) **incident**, never CRS at baseline and current at follow-up; and (6) **never**, never CRS at baseline and not current at follow-up.

Definitions of Predictor Variables

All predictor variables were derived from the baseline questionnaire. Age of onset of nasal and sinus symptoms was evaluated in five categories (0–15, 16–30, 31–45, 46–60 and >60 years). Self-reported physician diagnosis of hay fever and asthma, a symptom-based definition for asthma, and migraine headache were created as previously reported.[20–22] CRS treatment was measured for six different medications (antibiotics, oral and intranasal corticosteroids, oral and intranasal antihistamines, decongestants); these were evaluated alone (yes vs no) and as any of the treatments alone or in combination vs none. Self-reported surgery for CRS or nasal polyps was assessed at baseline. Quartiles for minor CRS symptoms were created by taking the mean of the five-level frequency responses to questions on headache, fever, coughing, bad breath, fatigue, ear fullness, ear pain, and ear pressure in the previous three months.[23–25] Quartiles for lower respiratory symptoms were similarly created based on responses to questions on wheezing, chest tightness, and shortness of breath. Quartiles for allergy symptoms were based on responses to questions on nasal itching, sneezing, eye itching, and eye tearing.

Definition of Symptom Subgroups at Baseline

Because the baseline questionnaire included 67 different symptom questions, we used two different approaches to identify symptom subgroups at baseline, one based on clinical criteria and the other based on formal data reduction methods using latent class analysis (LCA). Regarding the clinical groupings, among patients with current CRS at baseline, we identified four symptom subgroups using only nasal and sinus symptoms, based on the frequency of symptom combinations as well as symptoms previously linked to CRSsNP and CRSwNP.[26–28] The four groups were OBS/DC (obstruction and discharge only), PP (pain and/or pressure with obstruction and/or discharge), SL (smell loss with obstruction and/or discharge), and PPSL (pain and/or pressure, smell loss, and obstruction and/or discharge).[2]

LCA was next used to identify patient subgroups based on clustering of nasal and sinus, allergy, asthma, migraine headache, and fatigue symptoms. After removal of 379 respondents with excessive missing data (defined as missing entire or at least five questions in conceptual blocks of questions [EPOS symptoms, minor CRS symptoms, asthma, migraine, and fatigue questions]), multiple imputation for 28 ordinal variables was performed (Stata function mi impute ologit, StataCorp LP, College Station, TX). In order to have a minimum of 10 subjects per question level we performed LCA with nine questions each made binary (at least most of the time vs. less than most of the time, $2^9 = 512$ levels). A total of 20 combinations of 46 questions on CRS (core and minor symptoms), asthma, migraine and fatigue were evaluated in the various LCA models before selection of the final model (using Stata plugin version 1.1, http://methodology.psu.edu/downloads/lcastata). Schwarz Bayesian Information Criteria and entropy r-squared were computed to evaluate model fit, determine the number of latent classes, and select the final model. The final model identified four latent classes using five secondary CRS questions (both nasal passages have blockage, blow nose more than 10 times a day, mucus in throat that felt like lump or blockage, cannot smell anything, facial pain of at least 5 of 10 on severity scale) and one each for allergy (eye itching), asthma (breathing with whistling sound in chest), migraine headache (unusually sensitive to light during headaches), and fatigue (fatigue interferes with

physical functioning). The four latent classes were identifiable to us as “pan-symptomatic” (all nine symptoms were more common in this group compared to patients overall), “CRS nasal and sinus symptoms” (nasal and sinus symptoms were most common in this group, and photophobia much less common than overall), “less frequent symptoms” (all symptoms were less common in this group), and “headache symptoms” (facial pain, photophobia, and fatigue were more common in this group) (Table E2, Online Repository).

Statistical Analysis

The goals of the analysis were: 1) estimate the prevalence of the six longitudinal symptom subgroups in the source population; and 2) identify predictors of the longitudinal symptom subgroups. Analysis was performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). We first compared responders and non-responders on the follow-up questionnaire on demographic and selected clinical variables. We next compared patients in the six longitudinal subgroups on demographic and selected clinical variables. To estimate the prevalence of the longitudinal subgroups in the source population, we used SAS PROC SURVEYFREQ, and prevalence estimates with 95% confidence intervals are presented. This required the use of sampling and participation weights based on the EHR selection groups and race/ ethnicity and participation rates for each questionnaire calculated by inverse probability weighting (Table E1, Online Repository).[29, 30] Original weights were used for this analysis so prevalence estimates represented those in the source population. In the source population, the lifetime prevalence of meeting EPOS symptom criteria was calculated by summing weighted prevalence from each of the subgroups except the missing (n = 230) and never CRS.

Logistic regressions were next used to evaluate associations of predictors with longitudinal symptom subgroups. For regression analyses, we used the aforementioned weights in the PROC SURVEYLOGISTIC procedure, which reduced bias in effect estimates compared to logistic regression, and also appropriately estimated the standard errors. [31–33] In inferential analyses, we truncated one extreme weight to the next highest value as previously reported. [2, 22, 34] Three primary comparisons were made in the logistic models: persistent CRS vs. nonpersistent; recurrent CRS vs. stable past; and incident CRS vs. never CRS. These models were adjusted for age (centered and centered-squared to allow for non-linearity), sex, race/ ethnicity, smoking status, and Medical Assistance (a surrogate for family socioeconomic status). Statistical significance was considered at p-value < 0.05. Results are presented in text or tables but not in both locations.

RESULTS

Characteristics of the Study Population

A total of 63.7% of baseline questionnaire respondents also returned the six-month questionnaire (4966 of 7801) (Table I). Compared to six-month non-responders, responders were more likely to be older, white, not on Medical Assistance, and to have a CRS diagnosis code in the EHR (p < 0.0001). There were differences between non-responders and responders in their symptom subgroups at baseline (p = 0.02).

Description of Longitudinal Symptom Subgroups, and Unadjusted Associations

At baseline in the study population, 24.1% had current CRS, 26.4% had past CRS and 49.5% had never CRS. Among those with current CRS at baseline, 51.2% no longer met EPOS criteria six months later; 15.2% of those with past CRS at baseline met EPOS criteria at six months; and 3.5% of those with never CRS at baseline met EPOS criteria at six months (Table II). There were several patterns of age, sex, race/ethnicity, and EHR selection group with longitudinal symptom subgroups, but Medical Assistance status was most strongly associated. In unadjusted analysis, patients ever (vs. never) receiving Medical Assistance were more likely to have both recurrence (12.1%, p = 0.03) and new onset (14.5%, p = 0.003) of symptoms. The symptom groups at baseline were associated with persistent (vs. non-persistent) symptoms; among those with current CRS at baseline, 38.1% of those with OBS/DC symptoms had persistent symptoms compared with 49.8% of those with PP, 59.5% of those with SL, and 62.0% of those with PPSL (Table E3).

While significant smell loss was relatively uncommon at baseline [n (%) = 466 (9.4)] and six months ([370 (7.5)], it was the most persistent symptom. Of those with facial pain and/or pressure at baseline, 40.3% (n = 261) continued to have this symptom at follow-up; while 43.6% (548) of those with obstruction, 57.5% (984) of those with discharge, and 62.9% (293) of those with smell loss continued to have these symptoms at follow-up.

Prevalence of Longitudinal Symptom Subgroups and Annual Cumulative Incidence of CRS

In the source population, the lifetime prevalence of meeting EPOS symptom criteria for CRS was 27.5%. The prevalence of current CRS at follow-up was 7.8% (95% CI 6.51, 9.13), consisting of patients from the persistent, recurrent, and incident groups. The prevalence of persistent CRS was 4.8%, with an age peak at 50–59 years, and the persistent group was the largest group of those with current CRS at follow-up. Remitted CRS (stable past and nonpersistent) was more common than persistent CRS (Table III). Stable past (remission of at least 6 months) was more than twice as prevalent (14.2%, 95% CI 12.4–16.1) as non-persistent (remission lasting no more than 6 months) CRS (5.5%, 95% CI 4.5–6.5). Remitted CRS was highest among younger patients (<49 years) and declined with age. The cumulative CRS incidence was 1.1% over a mean (SD) of 7.1 (2.0) months, equivalent to approximately 1.9% per year. There was higher incidence with older ages and incidence was higher in men.

Adjusted Predictors of Longitudinal Symptom Subgroups

Persistent vs. non-persistent—Younger age of symptom onset was associated with CRS persistence (trend p-value 0.02). Patients who at baseline reported physician-diagnosed CRS [odds ratio: 1.56 (1.03–2.38)], migraine headache, were in the SL or PPSL groups, or were in the pan-symptomatic LCA class had higher odds of persistent (vs. non-persistent) CRS (Table IV). Patients in the second quartile of the lower respiratory symptoms index (vs. the first quartile) were more likely to have persistence. There was also a trend of increasing odds for persistence from the OBS/DC to the PP, SL, and PPSL groups. Asthma and hay fever were not associated with persistence.

Recurrent vs. stable past—Patients who at baseline reported migraine headache or were in the headache or CRS nasal and sinus symptom LCA classes had higher odds of recurrent (vs. stable past) CRS (Table IV). Patients who were using intranasal anti-histamines, or who had the highest symptoms scores on the minor CRS symptom index, lower respiratory symptom index, or allergy symptom index (fourth quartile versus the first quartile) also were more likely to have recurrence. There were also trends of increasing odds for recurrence across quartiles of the minor CRS symptom index, the lower respiratory symptom index, and the allergy symptom index. Some of the associations were quite strong, with odds ratios > 5.0.

Incident vs. never—Patients who at baseline reported migraine headache, were in the headache LCA class, had Medical Assistance or had any treatment had higher odds of incident (vs. never) CRS (Table IV). There were trends of increasing odds for incident disease across quartiles of the minor CRS symptom index and the allergy symptom index at baseline.

DISCUSSION

In this first longitudinal evaluation of nasal and sinus symptoms meeting EPOS epidemiological criteria in a regionally-representative patient sample, there was large fluctuation among patients who met the definition at baseline and six months later. Of those who met criteria for current CRS at baseline in our study sample, only 49% met criteria six months later. Among patients who met past CRS at baseline, 15.2% had recurrent symptoms meeting the definition of CRS six months later. Finally, we estimated an annual cumulative incidence of almost 2% in the source population. There were many clinical variables that were associated with each of the longitudinal symptom subgroups, primarily based on headache and symptom profiles of nasal and sinus, respiratory, and allergy symptoms. We believe that understanding the predictors of these longitudinal symptom subgroups may be helpful for medical and surgical management of CRS.

Younger age of onset and greater frequency and severity of CRS symptoms identified by both clinical (SL and PPSL groups) and data reduction (pan-symptomatic LCA group) approaches were associated with persistent symptoms. In contrast, remission was common and occurred more frequently in younger patients and in those with fewer symptoms at baseline. These findings are emerging evidence in support of a disease progression model for CRS symptoms.

The prevalence of the stable past group in the source population was 14.2%, almost twice as large as the non-persistent CRS group. Many of these patients had isolated nasal and sinus symptoms which did not meet EPOS criteria and 18.3% of these participants showed stability of these isolated symptoms over time. In the CRS LCA group, many had nasal and sinus symptoms that did not meet EPOS criteria for current CRS at baseline but were more likely to meet EPOS criteria at follow-up, thereby predicting recurrence.

The prevalence of current CRS based on EPOS symptoms declined from 11.9% at baseline to 7.8% six months later, in the source population. The persistent CRS group constituted

most of the current CRS at follow-up (62%). A European-based study of EPOS symptoms reported a similar drop (−3%) in symptom-based prevalence of CRS over time (median time between assessments was 287 days).[35] The decline in prevalence could be due to the change in seasons (baseline during spring, follow-up during autumn).[36]

Obstruction with discharge, in the absence of other CRS symptoms, was the most common symptom profile among those with current CRS at any time point. When symptoms persisted over time, the most common profile at follow-up was the same as that at baseline (result not shown). Most patients in the recurrent and incident CRS groups, who met EPOS criteria at follow-up, had at least one of obstruction or discharge at baseline.

Migraine headache was strongly associated with all three longitudinal symptom subgroup comparisons. This could indicate that migraine is co-morbid with CRS, that the pain symptoms of migraine were confused with sinus disease and spuriously contributed to meeting EPOS criteria, or that patients with pain syndromes are more likely to seek care and hence more likely to have the diagnosis of related conditions. Migraine is associated with rhinorrhea and nasal congestion due to sinonasal neurogenic stimulation in 50–60% of people, leading to misdiagnosis of CRS in the absence of objective evidence of sinus disease.[37, 38] However, migraine is also co-morbid with CRS[39] and can also influence timing of surgical management.[40] We suspect that co-morbidity and misdiagnosis may each be occurring.

This study provides the first estimate of annual cumulative incidence of EPOS CRS symptoms in a population-based sample. Cumulative incidence increased with age. It is possible that older patients were less likely to recall past nasal and sinus symptoms lasting at least three months on the baseline survey resulting in misclassification of recurrent cases as incident cases. Medical Assistance, asthma, migraine headache, the headache LCA group, more nasal and sinus treatments at baseline (intranasal steroids, intranasal anti-histamine or any treatment), more minor CRS symptoms, and more allergy symptoms were all associated with incident CRS. These data suggest that incident CRS was preceded by many symptoms that required treatment at baseline, but these did not yet meet EPOS criteria. By six months later, many of these patients met EPOS criteria. This is consistent with results from a previous EHR-based study, and likely reflects increased health care utilization prior to meeting CRS symptom criteria.[41]

The LCA identified symptom clustering at baseline that was associated with longitudinal symptom subgroups over time. The five nasal and sinus symptom questions used in the LCA assessed the same areas as EPOS symptoms, but incorporated both frequency and severity. The magnitude of the associations of the LCA groups with the longitudinal symptom subgroups were quite large: the pan-symptomatic group had over three times the odds of persistence; the headache group over 16 times the odds of recurrence and 10 times the odds of incidence; and the CRS nasal and sinus symptoms group over 11 times the odds of recurrence and almost nine times the odds of incidence. This provides evidence of construct validity for the LCA findings and again suggests that there are many patients with significant nasal and sinus symptoms who meet EPOS criteria in an episodic pattern. Prior studies have applied similar data-driven methods to identify symptom clustering in CRS, but to our

knowledge this is the first study to use this approach in a general population-based sample.[42, 43]

Strengths of this study included longitudinal evaluation of EPOS epidemiologic symptom criteria, a primary care sample representing the general population in the region, a relatively large sample size, and detailed nasal and sinus, respiratory, and allergy symptoms for frequency, severity, and duration. In addition, in contrast to prior studies, we were able to refer sample estimates back to the source population through weighted analysis. Limitations included lack of objective evidence of inflammation; the possibility of recall bias, more so for the baseline (lifetime recall) than the follow-up (six month recall) questionnaire, however, recall is unavoidable due to the definition of CRS extending over a 3 month period; and the differential loss to follow-up, with drop-out associated with age, race/ethnicity, and Medical Assistance. Potential biases in our study subjects due to sampling, participation rates and differential loss to follow-up were mitigated by accounting for stratified sampling and weights in the analysis. Our source population has a relative lack of race/ethnic diversity but we enriched our sample for race/ethnic minorities in the stratified random sampling design; approximately 19% of patients invited to participate were race/ethnic minorities. However, participation rates were lower and loss to follow-up rate was higher among race/ethnic minorities, accounting for our final relative lack of diversity, limiting generalizability. Regardless, our study population is representative of the general population of Pennsylvania and the estimates are applicable to the region studied.[2]

Conclusions

Less than half with nasal and sinus symptoms meeting EPOS criteria in our general, regional population were stable over time. Given that half the patients who met CRS criteria at baseline did not six months later, our data suggests that physicians should evaluate longer periods of persistence as well as specific patterns of symptoms and multiplicity of symptoms before surgical intervention. Patients with three months of nasal obstruction and drainage alone are not likely to persist unlike those who have additional symptoms to nasal obstruction or drainage like smell loss, or smell loss and facial pain. Patients who eventually met EPOS symptom criteria had extended periods of upper and lower airway symptoms preceding the meeting of the full definition, followed by periods of remission, or recurrence. In the source population, the lifetime prevalence of CRS was 27.5% and the estimated annual cumulative incidence was almost 2%. Symptom profiles at baseline and low socioeconomic status were strongly associated with longitudinal symptom subgroups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CRISP	Chronic Rhinosinusitis Integrative Studies Program
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
EHR	electronic health record
EPOS	European Position Paper on Rhinosinusitis
ICD-9	International Classification of Diseases
LCA	latent class analysis
OBS/DC	obstruction and discharge only
PP	pain and/or pressure with at least one cardinal symptom (obstruction and or discharge)
PPSL	pain and/or pressure, smell loss, and at least one cardinal symptom
SD	standard deviation
SL	smell loss with at least one cardinal symptom
USA	United States of America

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1. What is already known about this topic?

- CRS is a prevalent and disabling condition of the nose and sinuses.
- It is a heterogeneous disease, with a variety of symptom combinations.
- Its natural history in the general population has not been previously studied.

2. What does this article add to our knowledge?

- Less than half with symptoms meeting CRS EPOS epidemiologic criteria were stable over a six-month time period in the general population.
- Multiple and severe symptoms, earlier age of onset predict disease persistence, and not treatment.

3. How does this study impact current management guidelines?

- CRS symptoms have high lifetime prevalence.
- Symptom profiles at baseline were associated with change in symptoms over 6 months.
- Understanding this variation could lead to better understanding of CRS phenotypes and management.

Table I

Comparison of 6-month follow-up questionnaire responders and non-responders

Characteristic[a]	Responders (n = 4966)	Non-responders (n = 2835)	Responders vs. Non- responders (p-value)[b]
Age, years, mean (SD)[c]	57.1 (15.4)	51.4 (16.6)	< 0.001
Age categories, %[c]			< 0.001
< 49 years, n = 2612	28.0	43.1	
49 to 63 years, n = 2640	34.9	32.1	
> 63 years, n = 2549	37.2	24.8	
Sex, %			0.13
Female, n = 4891	63.3	61.6	
Male, n = 2910	36.7	38.4	
Race/ethnicity, %			< 0.001
White, n = 7054	92.7	86.4	
Non-white, n = 747	7.3	13.6	
Medical Assistance, ever, %[c]			< 0.001
No, n = 6892	91.5	82.8	
Yes, n = 909	8.5	17.2	
EHR selection groups, %[d]			< 0.001
CRS codes, n = 4777	63.1	58.1	
Asthma or allergy codes, n = 1833	22.5	25.3	
None of these codes, n = 1191	14.5	16.7	
EPOS symptom status at baseline, %[e]			0.97
Current CRS, n = 1871	24.2	24.0	
Past CRS, n = 2072	26.7	26.7	
Never CRS, n = 3814	49.1	49.3	
CRS EPOS symptom subgroup at baseline, %			0.02
OBS/DC, n = 618	35.0	29.6	
PP, n = 689	35.7	38.8	
SL, n = 330	18.2	16.7	
PPSL, n = 234	11.1	14.9	

[a] Percentages are reported as column %; 7847 returned baseline questionnaire, 7801 of these were mailed 6-month questionnaire

[b] p-values are based on t-test for continuous variables and chi-square test for categorical variables

[c] Status based on baseline questionnaire

[d] Primary care patients were selected and mailed to, based on evidence of CRS, asthma, and allergic conditions in EHR: CRS codes = two or more ICD-9 codes 471.x or 473.x or CPT codes for sinus surgery, sinus endoscopy or sinus CT; asthma or allergy codes = one ICD-9 code for 471.x or 473.x or two or more ICD-9 codes for asthma (493.x) or allergic rhinitis (477.x); none of these codes = does not meet criteria for above groups

[e] CRS status unknown due to missing data on 44 respondents. Current CRS = EPOS epidemiologic criteria fulfilled in the last 3 months; past CRS = EPOS epidemiologic criteria fulfilled in their lifetime but not in the last 3 months; never CRS = EPOS epidemiologic criteria not fulfilled ever

Abbreviations: CPT = Current Procedural Terminology; CRS = chronic rhinosinusitis; CT = computed tomography; EHR = electronic health record; EPOS = European Position Paper on Rhinosinusitis; ICD-9 = International Classification of Diseases; OBS/DC = obstruction and discharge only; PP = pain and/or pressure with at least one cardinal symptom (obstruction and or discharge); PPSL = pain and/or pressure, smell loss, and at least one cardinal symptom; SD: standard deviation; SL = smell loss with at least one cardinal symptom

Table II

Selected demographic variables by categories of follow-up status (current vs. not current CRS) on the 6-month questionnaire by baseline status (current, past, and never), resulting in six longitudinal symptom subgroups[a]

	CRS Current at Baseline n = 1143		CRS Past at Baseline n = 1249		CRS Never at Baseline n = 2344	
Characteristic[b]	**Follow-up Status Current CRS n = 558**	**Follow-up Status Not Current CRS n = 585**	**Follow-up Status Current CRS n = 190**	**Follow-up Status Not Current CRS n = 1059**	**Follow-up Status Current CRS n = 83**	**Follow-up Status Not Current CRS n = 2261**
Group label	Persistent	Non-persistent	Recurrent	Stable past	Incident	Never
Percent of responders, n = 4966	11.2	11.8	3.8	21.3	1.7	45.5
Percent of baseline status in each of two groups at follow-up	48.9	51.2	15.2	84.8	3.5	96.5
Age, years, mean (SD)[c]	54.9 (14.0)	54.4 (14.5)	54.4 (13.8)	55.0 (14.5)	60.0 (15.6)	58.6 (16.0)
Age categories, %[c]						
< 49 years, n = 1367	30.7	34.0	31.1	31.7	21.7	25.7
49 to 63 years, n = 1731	41.8	38.3	38.4	38.3	30.1	31.1
> 63 years, n = 1846	27.6	27.7	30.5	29.9	48.2	43.3
Female, %, n = 3145	67.4	69.4	64.7	63.8	54.2	60.6
White race/ethnicity, %, n = 4604	95.7	96.9	95.3	93.4	97.6	90.5
Medical Assistance, ever, %, n = 421[c]	14.2	12.7	12.1	7.4	14.5	6.3
Smoking status, %[c]						
Current, n = 611	16.7	16.4	15.8	10.9	12.0	10.5
Former, n = 1549	29.9	29.6	35.8	28.9	47.0	31.3
Never, n = 2806	53.4	54.0	48.4	60.2	41.0	58.2
EHR selection groups, %[d]						
CRS codes, n = 3131	82.1	77.1	76.8	70.4	73.5	49.0
Asthma or allergy codes, n = 1117	13.8	19.3	18.4	22.2	18.1	26.8

	CRS Current at Baseline n = 1143		CRS Past at Baseline n = 1249		CRS Never at Baseline n = 2344	
Characteristic[b]	**Follow-up Status Current CRS n = 558**	**Follow-up Status Not Current CRS n = 585**	**Follow-up Status Current CRS n = 190**	**Follow-up Status Not Current CRS n = 1059**	**Follow-up Status Current CRS n = 83**	**Follow-up Status Not Current CRS n = 2261**
None of these codes, n = 718	4.1	3.6	4.7	7.4	8.4	24.2
Sinus surgery in the past 6 months, %, n = 88	3.9	3.8	4.2	1.8	1.2	0.6

[a]Unknown CRS status at 6-month follow-up questionnaire, n = 230

[b]Percentages are reported as column %

[c]Status based on baseline questionnaire

[d]Primary care patients were selected and mailed to, based on evidence of CRS, asthma, and allergic conditions in EHR: CRS codes = two or more ICD-9 codes 471.x or 473.x or CPT codes for sinus surgery, sinus endoscopy or sinus CT; asthma or allergy codes = one ICD-9 code for 471.x or 473.x or two or more ICD-9 codes for asthma (493.x) or allergic rhinitis (477.x); none of these codes = does not meet criteria for above groups

Abbreviations: CPT = Current Procedural Terminology; CRS = chronic rhinosinusitis; CT = computed tomography; EHR = electronic health record; ICD-9 = International Classification of Diseases; SD = standard deviation

Table III

Estimated prevalence[a] (using sampling and participation weights) of the longitudinal symptom subgroups in the source population by age and sex based on 4736 responders to 6-month follow-up questionnaire

	Weighted Prevalence in Row, % (95% Confidence Interval)					
	Categories of Follow-up Status on 6-month Questionnaire					
Characteristic	**Persistent n = 558**	**Non-persistent n = 585**	**Recurrent n = 190**	**Stable Past n = 1059**	**Incident n = 83**	**Never n = 2261**
Age (years) at baseline						
≤ 40	3.3 (1.5–5.1)	7.1 (4.1–10.1)	1.2 (0.4–1.9)	20.8 (15.0–26.6)	0.5 (0.02–1.0)	66.8 (60.3–73.2)
40 to 49	5.4 (2.4–8.4)	7.0 (4.2–9.9)	2.6 (0.7–4.5)	15.7 (10.5–20.9)	0.8 (0.08–1.5)	65.4 (58.6–72.1)
50 to 59	8.0 (5.2–10.8)	6.5 (4.1–8.9)	1.6 (0.5–2.8)	17.2 (13.2–21.2)	0.9 (0.0–1.9)	63.4 (58.1–68.6)
60 to 69	4.2 (2.3–6.1)	4.7 (2.8–6.7)	2.4 (0.9–4.0)	11.5 (8.2–14.7)	1.1 (0.08–2.2)	71.8 (67.0–76.6)
≥ 70	2.6 (1.1–4.2)	3.2 (1.6–4.8)	1.7 (0.2—3.1)	8.6 (5.6–11.6)	2.0 (0.2–3.8)	75.7 (70.8–80.5)
Sex						
Female	4.7 (3.5–6.0)	6.4 (4.9–7.9)	2.0 (1.2–2.9)	15.2 (12.9–17.6)	1.0 (0.3—1.7)	67.1 (63.9–70.3)
Male	4.8 (3.1–6.7)	3.9 (2.9–4.8)	1.6 (0.6–2.6)	12.4 (9.6—15.2)	1.4 (0.4–2.4)	72.4 (69.1–76.7)
Overall	**4.8 (3.8–5.8)**	**5.5 (4.5–6.5)**	**1.9 (1.3–2.5)**	**14.2 (12.4–16.1)**	**1.1 (0.6–1.7)**	**69.0 (66.5–71.4)**

[a]Weighted on sampling proportions (based on electronic health record [EHR] selection groups and race/ethnicity) and participation rates at baseline and at six months; and accounted for stratified survey sampling; 230 persons whose status at follow-up could not be ascertained were excluded from the table.

Abbreviation: CRS = chronic rhinosinusitis

Table IV

Survey logistic regression[a] results of adjusted associations of selected predictor variables with longitudinal symptom subgroups

Predictors	Persistent vs. Non-persistent N: 558 vs. 585 OR (95% CI)	Recurrent vs. Stable Past N: 190 vs. 1059 OR (95% CI)	Incident vs. Never N: 83 vs. 2261 OR (95% CI)
Base model			
Age	1.01 (1.00, 1.03)	1.00 (0.98, 1.02)	1.00 (0.98, 1.03)
Age-squared	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Sex (female vs. male)	1.02 (0.66, 1.57)	1.17 (0.67, 2.04)	0.76 (0.37, 1.56)
Race/ethnicity (non-white vs. white)	1.72 (0.79, 3.77)	0.82 (0.33, 2.01)	0.44 (0.11, 1.82)
Medical Assistance (Y vs. N)	1.00 (0.54, 1.84)	1.82 (0.69, 4.79)	4.27 (1.52, 12.05)
Smoking status (vs. never)			
Current	0.58 (0.33, 1.03)	0.96 (0.39, 2.39)	0.75 (0.18, 3.08)
Past	1.05 (0.67, 1.66)	1.37 (0.77, 2.42)	2.12 (0.97, 4.63)
Predictors[b]			
Age of onset (vs. 0–15 years)			
16–30 years	0.67 (0.38–1.19)	0.79 (0.39–1.60)	
31–45 years	0.62 (0.33–1.16)	1.06 (0.48–2.31)	DNA
46–60 years	0.64 (0.30–1.36)	0.84 (0.34–2.08)	
>60 years	0.25 (0.09–0.68)	0.51 (0.11–2.29)	
Trend p value[c]	*0.02*	*0.63*	
Hay fever, physician-diagnosed (Y vs. N)	0.85 (0.57–1.27)	1.46 (0.86–2.49)	1.57 (0.78–3.16)
Asthma, physician-diagnosed (Y vs. N)	0.86 (0.55–1.36)	1.46 (0.84–2.54)	0.66 (0.26–1.69)
Asthma, symptom based (Y vs. N)[d]	1.10 (0.73–1.66)	1.34 (0.80–2.24)	3.87 (1.91–7.82)

Predictors	Persistent vs. Non-persistent N: 558 vs. 585 OR (95% CI)	Recurrent vs. Stable Past N: 190 vs. 1059 OR (95% CI)	Incident vs. Never N: 83 vs. 2261 OR (95% CI)
Migraine headache (Y vs. N)[e]	1.71 (1.05–2.78)	3.46 (1.84–6.51)	3.29 (1.18–9.18)
Any treatment (Y vs. N)[f]	0.95 (0.47–1.91)	0.87 (0.42–1.80)	2.49 (1.11–5.58)
Intranasal steroid (Y vs. N)	1.13 (0.75–1.72)	1.04 (0.61–1.76)	2.35 (1.12–4.94)
Intranasal anti-histamine (Y vs. N)	0.63 (0.38–1.03)	2.28 (1.13–4.60)	3.80 (1.27–11.31)
CRS surgery at baseline (Y vs. N)	1.15 (0.69–1.92)	0.96 (0.49–1.88)	0.61 (0.22–1.71)
LCA class at baseline (vs. less frequent symptoms)[g]			
Pan-symptomatic	3.15 (1.31–7.57)	DNA	DNA
Headache symptoms	1.07 (0.49–2.33)	16.91 (6.25–45.70)	10.18 (1.22–85.31)
CRS nasal and sinus symptoms	1.30 (0.68–2.51)	11.55 (4.01–33.22)	8.93 (0.87–91.34)
CRS EPOS subgroup at baseline (vs. OBS/DC)			
PP	1.17 (0.73–1.88)		
SL	2.51 (1.39–4.53)	DNA	DNA
PPSL	2.80 (1.38–5.67)		
Trend p value[c]	*<0.001*		
Minor CRS symptoms quartiles (vs. Q1)[h]			
Q2	0.49 (0.17–1.39)	0.81 (0.31–2.15)	1.91 (0.73–4.99)
Q3	0.37 (0.14–1.01)	1.43 (0.58–3.51)	3.50 (1.27–9.64)
Q4	0.73 (0.28–1.93)	3.35 (1.38–8.11)	7.06 (2.37–20.99)
Trend p value[c]	*0.39*	*<0.001*	*<0.001*
Lower respiratory symptoms quartiles (vs. Q1)[i]			
Q2	2.63 (1.27–5.45)	0.73 (0.31–1.75)	1.06 (0.39–2.90)
Q3	0.94 (0.50–1.78)	1.14 (0.55–2.35)	0.86 (0.32–2.28)
Q4	1.29 (0.72–2.29)	1.96 (1.01–3.79)	2.14 (0.88–5.21)

Predictors	Persistent vs. Non-persistent N: 558 vs. 585 OR (95% CI)	Recurrent vs. Stable Past N: 190 vs. 1059 OR (95% CI)	Incident vs. Never N: 83 vs. 2261 OR (95% CI)
Trend p value[c]	*0.93*	*0.046*	*0.29*
Allergy symptoms quartiles (vs. Q1)[j]			
Q2	1.14 (0.53–2.45)	1.22 (0.52–2.88)	1.44 (0.53–3.90)
Q3	0.94 (0.48–1.86)	1.94 (0.89–4.22)	4.69 (1.94–11.35)
Q4	1.63 (0.81–3.25)	5.55 (2.40–12.80)	5.31 (1.46–19.34)
Trend p value[c]	*0.14*	*<0.001*	*<0.001*

[a] Survey logistic regression was used for the analysis; weighted based on sampling proportions (based on electronic health record (EHR) selection groups and race/ethnicity) and participation rates at baseline (highest weighted group was weighted at the weight of the next highest weighted subgroup); accounted for stratified survey sampling; adjusted for age, age-centered squared, sex, race/ethnicity, smoking status and Medical Assistance; all predictors were derived from the baseline questionnaire

[b] Each predictor was added to the base model one variable at a time

[c] Trend p value was calculated by treating the variables as continuous

[d] Some, most or all of the time to at least one of four questions- non-viral wheezing, nocturnal wheezing, exercise induced wheezing and non-viral nocturnal cough in the past 12 months

[e] Migraine was based on previously validated scale utilizing three questions- disability, nausea and light sensitivity with headache

[f] The treatment choices were antibiotics, oral and intranasal steroids, oral and intranasal anti-histamine, decongestants.

[g] Latent Class Analysis (LCA) to quantitatively evaluate symptom clustering, with final model having 9 questions- 5 CRS questions and 1 each for allergy, asthma, migraine, fatigue

[h] Headache, fevers, coughing, bad breath, fatigue, ear fullness, ear pain, and ear pressure in the past 3 months: take mean of the 5-point rating scale responses to these questions and quartile

[i] Wheezing, chest tightness, shortness of breath in the past 3 months: take mean of the 5-point rating scale responses to these questions and quartile

[j] Nasal itching, sneezing, eye itching, eye tearing in the past 3 months: take mean of the 5-point rating scale responses to these questions and quartile

Abbreviations: CI = confidence interval; CRS = chronic rhinosinusitis; DNA = did not analyze because of small sample sizes; EPOS = European Position Paper on Rhinosinusitis; NE = not evaluable; OBS/DC = obstruction and discharge only; OR = odds ratio; PP = pain and/or pressure with at least one cardinal symptom (obstruction and or discharge); PPSL = pain and/or pressure, smell loss, and at least one cardinal symptom; SL = smell loss with at least one cardinal symptom