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Aspirin-Exacerbated Respiratory Disease: Association Between Patient Reported Sinus and Asthma Morbidity

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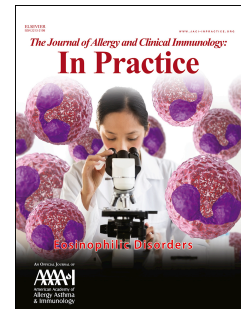
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Abstract:

Background: The association between sinonasal and pulmonary symptoms in aspirin-exacerbated respiratory disease (AERD) is not fully established.

Objective: To characterize sinonasal and asthma symptomatology, and to determine if reported sinonasal symptoms predict asthma severity.

Methods: Prospectively collected data from an AERD registry cohort was included from 2013-18. Sinonasal symptomatology measured by Sino-Nasal Outcomes Test (SNOT) 22-item total scores was used as the predictor variable, with Asthma Control Test (ACT) scores and percent predicted forced expiratory volume in one second (FEV1%) as primary outcomes. All instances of paired data on the same date were used. ACT was also evaluated with FEV1% as the outcome. Mixed effects regression was completed.

Results: From 1065 AERD registry subjects (mean age 48.1y, SD=12.8; 68.0% female, 29.8% male), mean SNOT-22 score was 42.3 (SD=24.12, n=1307 observations from 869 subjects), mean ACT score was 19.4 (SD=5.2, n=1511 observations from 931 subjects), and mean FEV1% was 82.8 (SD=19.6, n=777 observations from 307 subjects). SNOT-22 significantly predicted ACT scores ($p<0.0001$, 1185 paired observations from 845 subjects) and FEV1% ($p=0.018$, 485 observations from 246 subjects). Any ten-point increase in SNOT-22 was associated with a 0.87-point decrease in ACT and a 0.75% decrease in FEV1%. Any one-point increase in ACT was

associated with a 1.0% increase in FEV1% ($p < 0.0001$, 616 observations from 269 subjects). The most severe SNOT-22 symptoms were sense of smell/taste and blockage/congestion of nose.

Conclusion: SNOT-22 scores significantly predict ACT scores and FEV1%, and ACT scores significantly predict FEV1%. This study demonstrates an association between patient-reported rhinosinusitis and asthma symptom severity and subjective and objective measures of asthma severity.

For JACI In practice: Highlights box. Each Original Article will be accompanied by a highlights box that provides answers (no longer than 35 words) to the following questions:

1. *What is already known about this topic?*

Aspirin-exacerbated respiratory disease (AERD) is characterized by asthma, chronic rhinosinusitis with nasal polyps, and hypersensitivity to aspirin and other non-steroidal anti-inflammatory drugs.

2. *What does this article add to our knowledge?*

Chronic and severe sinonasal symptoms are a chronic cause of morbidity for patients with AERD. This study demonstrates a significant association between patient-reported rhinosinusitis symptom severity and subjective and objective asthma severity in AERD patients.

3. *How does this study impact current management guidelines*

AERD patients who report worsening sinonasal symptoms should be evaluated for asthma control and pulmonary function. Severity of sinonasal symptoms and asthma symptomatology is correlated. Further research is needed to confirm the hypothesis that improved sinonasal disease control would improve asthma symptomatology in patients with AERD.

Key words: (up to 10)

Outcomes, patient reported outcomes, asthma, aspirin-exacerbated respiratory disease, spirometry, sinusitis, chronic rhinosinusitis

120 **Abbreviations Used:**

121 ACT Asthma Control Test

122 AERD Aspirin-Exacerbated Respiratory Disease

123 FEV1% - Percent Predicted Forced Expiratory Volume in one second

124 LTC4 leukotriene C4

125 NSAID Non-Steroidal Anti-Inflammatory Drugs

126 PROMs Patient-Reported Outcome Measures

127 SNOT-22 Sino-Nasal Outcome Test 22

128

Introduction

Aspirin-exacerbated respiratory disease (AERD) is a chronic condition defined by the co-occurrence of asthma, chronic rhinosinusitis with nasal polyposis, and hypersensitivity to aspirin and all non-selective non-steroidal anti-inflammatory drugs (NSAIDs). Previously known as Samter's Triad, this disease is characterized by respiratory tissue eosinophilia and mast cell activation, with dysregulation of the 5-lipoxygenase–leukotriene C₄ (LTC₄) synthase pathway.(1,2) Drugs such as zileuton, which block the production of leukotrienes, are known to impact both sinonasal and asthma symptoms.(3,4) AERD affects 7% of adults with asthma and 8 to 26% of patients with chronic rhinosinusitis with nasal polyps.(5,6) This amounts to roughly 1.5 million patients in the United States, which is likely an underestimate as evidenced by a 10-year delay between onset of disease and diagnosis.(7) Patients with AERD tend to have a worse quality of life than patients with other chronic conditions, such as asthma and even cardiac disease, as these patients typically report a loss in productivity, missed school/work, and depression and/or anxiety.(8) There are also substantial costs associated with chronic rhinosinusitis,(9) likely to be more severe for patients with AERD. Successful diagnosis and management of AERD thus may have significant societal benefits in addition to improving a patient's quality of life.

Increasingly, Patient Reported Outcome Measures (PROMs) have been used as a clinical endpoint for both chronic rhinosinusitis and asthma. For chronic rhinosinusitis with or without polyps, use of a PROM such as the Sino-Nasal Outcome Test 22-item scale (SNOT-22) was recommended as an outcome metric for clinical trials.(10) Research on chronic rhinosinusitis has shown that SNOT-22 scores correlate with asthma severity in patients with both diagnoses.(11) Further research has shown that comorbid conditions such as depression and smoking are

152 associated with worse outcomes and increased disease severity based on the SNOT-22. Likewise,
153 there has been substantial uptake of PROMs for asthma, such as the Asthma Control Test
154 (ACT).(12)

155 A central pathophysiologic question in AERD is how the three diagnoses by which this
156 disease is defined inter-relate. For example, there is only limited data on how chronic sinonasal
157 symptomatology affects asthma severity and to what extent sinonasal and asthma severity are
158 correlated in this population. This data is important to clarify given recent findings, for example,
159 that endoscopic sinus surgery reduces respiratory reactivity during aspirin desensitization.(13,14)
160 Better understanding the interplay of these disease factors is important because it would also
161 suggest, for example, that sinonasal disease should be more aggressively controlled through
162 surgery or medical treatment to reduce asthma severity in patients where other asthma treatments
163 are insufficiently effective. Here we determine the association between patient-reported chronic
164 rhinosinusitis severity, as measured with the SNOT-22, with asthma control, as measured by the
165 ACT as well as objective pulmonary function testing. In particular, the relationship of SNOT-22
166 as a predictor of co-occurring asthma status is explored.

Methods

Study Design and Patient Population

This is a prospective longitudinal cohort study of AERD patients. Prospectively collected enrollment and follow-up data from the Brigham and Women's Hospital (BWH) AERD registry was included from 2013-18. Details of the registry have been previously published.⁽¹⁵⁾ Two groups of patients are in the registry: those receiving care at a Partners Healthcare institution (i.e. BWH, Massachusetts General Hospital, and affiliated institutions), and those receiving care outside of Partners Healthcare. For those within Partners network, an algorithm was previously developed to identify and recruit patients into the registry.⁽¹⁵⁾ Patients outside of Partners Healthcare can also enroll in the registry if they have been referred to the registry or have found it on their own. Their data is reviewed prior to enrollment to confirm the diagnosis and clinical data. For the outside patient cohort, enrollment data are typically available, but may be less complete, and there is often less longitudinal data.

Clinical and demographic data were extracted. These data points include gender, age, race/ethnicity, age at diagnosis of asthma, age at diagnosis of sinonasal polyposis, age at diagnosis of aspirin or NSAID allergy, number of lifetime polypectomies, patient reported outcomes (see below), pulmonary function testing results, and visit type. Visit type included enrollment visit into the registry, follow up visit, or aspirin desensitization visit. Enrollment visit into the registry does not necessarily occur at the time of diagnosis, as many patients are referred to our center after diagnosis and initial management or were pre-existing patients at the time the registry was established. This study was approved by the Partners Healthcare Institutional Review Board (IRB Protocol #2103P001659).

Patient-Reported Outcome Measures and Objective Measures

Two PROMs are routinely collected on patients in the registry at the time of enrollment and at all follow up and desensitization visits: SNOT-22 for sinonasal symptoms, and the ACT for asthma control.

The SNOT-22 is a valid and reliable instrument widely utilized for evaluation of chronic rhinosinusitis symptomatology.(16) It contains 22 Likert-scale items regarding sinonasal and associated symptomatology, each scored 0-5 with 0 being “no problem” and 5 being “problem as bad as it can be,” for a total score of 0 (no symptoms) to 110 (worst possible symptoms). The minimal clinically important difference for the SNOT-22 is estimated to be 8.9 points on the scale.(16) Mean SNOT-22 total scores, item scores, and domain scores were calculated. For SNOT-22 analysis, the four-domain model(17) was used for analysis and imputation when necessary.

The ACT is a 5-question Likert-scale PROM that is valid and reliable.(12) The five questions are scored the opposite way, with high scores indicating good control, and low scores indicating uncontrolled disease. The five questions are scored (1) all of the time to (5) none of the time, and ask about symptoms occurring in the past 4 weeks. Therefore, the total score ranges from 5 (worst possible) to 25 (no symptoms). The minimal important difference of the ACT is 3.(18) ACT scores are categorized as reflecting controlled asthma ($ACT \geq 20$), not well-controlled asthma ($ACT 16-19$), and uncontrolled asthma ($ACT \leq 15$).

Statistical Analysis

Mixed effect regression was performed to determine: (1) the effect of SNOT-22 total on ACT total; (2) the effect of SNOT-22 total on percent predicted forced expiratory volume in one second (FEV1%), and (3) the effect of ACT total on FEV1% predicted. All instances of paired data on the same date were used. The intraclass correlation coefficient among observations within patients was calculated for each data set.

Missing responses were handled as follows. For SNOT-22 scores, missing data were imputed based on other domain responses. If at least 50% or more of the questions in the domain were present, the missing scores were imputed by replacing the respondent's average score across completed items in that domain. If the respondent did not answer at least 50% in one of the four domains, the total score was set to missing and excluded from analysis. Missing ACT scores were omitted rather than imputed due to the lack of relevant domains. A threshold of $p < 0.05$ was used for statistical significance. All statistical analysis was completed with SAS 9.4 (Cary, NC).

Results

Patient Population

A total of 1065 subjects were in the AERD registry at the time of data extraction and therefore constituted the analytical sample. Demographic and clinical characteristics are listed in Table 1. The sample was majority female (68.0%; 29.8% male and 2.2% not reported) and Caucasian (89.2%; 2.8% race/ethnicity not available; 8.0% non-Caucasian). Mean ages at diagnosis of each of the three components of AERD were as follows: asthma 30.2 years (SD 14.1), polyps 34.8 years (SD 12.0), and aspirin or NSAID allergy 34.5 years (SD 12.8).

1307 SNOT-22 data from 869 subjects were available for analysis. 182 subjects out of 869 subjects (20.9%) had SNOT-22 more than once. The SNOT-22 mean score for all observations was 42.3 (Standard deviation [S.D.] 24.1). We completed a sensitivity analysis with complete SNOT-22 scores (N=1224 observations (93.6%, 1224/1307) from 813 subjects (93.6%, 813/869), excluding imputed or otherwise incomplete scores. These results were nearly identical (mean score of 42.2, SD 24.2). 1511 ACT data from 931 subjects were used for analysis. 207 subjects out of 931 subjects (22.2%) had ACT more than once.

Sinonasal Symptomatology: SNOT-22 Characterization at Registry Enrollment

790 subjects had enrollment SNOT-22 data. Mean total SNOT-22 score was 50.3 (SD 23.1) out of a maximum score of 110 (most severe). The five most severe individual symptoms were all sinonasal, including sense of smell/taste (mean 3.73/5, SD 1.58), blockage/congestion of nose (mean 3.28/5, SD 1.55), need to blow nose (mean 2.99/5, SD 1.47), post nasal drip (mean 2.90/5, SD 1.46), and thick nasal discharge (mean 2.87/5, SD 1.59). Facial pain/pressure, included in the otologic domain, was less severe (mean 1.84, SD 1.55) (**Table 2**). Using the four-

domain analysis for the SNOT-22(17) with proportion of maximum score for comparison, the most severe domain was sinonasal (55.4% of maximum domain severity score) followed by sleep (46.8% of maximum domain severity score). The otologic and emotional domains had lower mean symptom severity scores (32.5% and 28.9% of maximum domain severity scores, respectively) (**Table 3**).

Asthma Symptomatology: ACT Characterization

879 subjects had enrollment ACT data. Mean total enrollment ACT score was 18.77 (SD 5.37) out of a total score of 25 (no symptoms/least severe) (**Table 4**). ACT scores are categorized as reflecting controlled asthma ($ACT \geq 20$), not well-controlled asthma ($15 < ACT < 20$), and uncontrolled asthma ($ACT \leq 15$). Therefore, the mean score of the cohort reflected not well-controlled asthma.

Effect of SNOT 22 Scores on ACT Scores

To determine the association between patient reported outcomes for chronic sinusitis and asthma status in the AERD cohort, the effect of SNOT-22 on ACT scores was measured. A total of 1185 paired ACT and SNOT22 observations from 845 subjects were used for this analysis. Mixed effect regression was performed to assess the effect of SNOT-22 total on ACT total (Figure 1). The intraclass correlation coefficient among observations within patients was 46%. Any ten-point increase in SNOT-22 total score was significantly associated with a 0.8727 decrease in ACT ($p < 0.0001$) (**Table 5**). The SNOT-22 domain scores were each independently negatively correlated with ACT and statistically significant.

Effect of SNOT-22 on FEV1 % predicted

To determine the association between sinonasal patient-reported symptomatology and asthma status as measured by objective pulmonary function testing, the effect of SNOT-22 on FEV1% predicted was determined. A total of 485 paired FEV1% predicted and SNOT-22 observations from 246 subjects were used for this analysis. Mixed effect regression was performed to assess the effect of SNOT-22 total on FEV1% predicted (Figure 2). The intraclass correlation coefficient among observations within patients was 69.7%. Any ten-point increase in SNOT-22 total score was significantly associated with a 0.7529 decrease in FEV1% predicted ($p=0.0182$) (**Table 5**). The negative correlation of SNOT-22 domain scores with FEV1% reached statistical significance only the sleep and emotional domains, possibly due to smaller sample size of patients with SNOT-22 and FEV1% measures.

Effect of ACT Score on FEV1 % Predicted

To confirm that patient-reported asthma status and an objective measure of pulmonary function would be associated, the effect of ACT score on FEV1% predicted was analyzed. A total of 616 paired FEV1% predicted and ACT observations from 269 subjects were used for this analysis. Mixed effect regression was performed to assess the effect of ACT total on FEV1% predicted (Figure 3). The intraclass correlation coefficient among observations within patients was 66.2%. Any one-unit increase in ACT was significantly associated with a 1.0 increase in FEV1% predicted ($p<0.0001$) (**Table 5**).

Sensitivity Analyses

We completed multiple sensitivity analyses to account for possible confounding. First, we completed an analysis adjusting for potential confounders in the registry (Table 6). Age, gender, number of lifetime polypectomies (none, 1, 2, 3, 4 or more, and no information), years since nasal polyp diagnosis (0-10, 11-20, 21-30, 30 plus, and no information), and time since the first clinical evaluation in the registry were included in the adjusted model. This adjusted model showed the same relationships between SNOT-22, ACT, and FEV1% and remained significant. The effect sizes increased slightly in the adjusted model, demonstrating that these relationships are robust to potential confounders. We completed an additional analysis adjusting for smoking status, given the possibility that smoking could potentially exacerbate pulmonary status more than SNOT-22 scores. The results were very similar with clinically and statistically significant correlations between SNOT-22, ACT total score, and FEV1%. Given the somewhat skewed distribution of ACT scores, we also completed additional testing on ACT scores. The residual plot with ACT as a dependent variable was not worrisome for a violation of regression assumptions. For the results above we utilized repeated measure analysis which accounts for collinearity of responses within a participant. A sensitivity analysis using only “enrollment” values (only one measure per patient, at the time of registry enrollment) showed results that were essentially unchanged with significant correlations among the three measures as reported above.

Discussion

This study demonstrates that patient-reported increased sinonasal symptom severity in AERD patients is predictive of both worse patient-reported asthma control and worse lung function measured objectively. Specifically, sinonasal symptoms as measured with the SNOT-22 (high scores indicating worse symptoms) are inversely correlated with asthma symptoms as measured by ACT scores (low scores indicating worse symptoms) (**Figure 1**). Additionally, SNOT-22 symptoms were inversely correlated with pulmonary function, as measured by spirometry and FEV1% predicted (**Figure 2**).

Prior research on patients with chronic rhinosinusitis with or without polyps and with or without asthma have shown that a more severe SNOT-22 score is associated with worse asthma control.⁽¹¹⁾ This study additionally confirms a SNOT-22 score correlation with an objective measure of asthma severity (FEV1%). The correlation between sinonasal symptomatology and asthma symptomatology found in this study has important implications for clinical care of patients with AERD. Further research is needed to confirm the hypothesis that improved sinonasal disease control would improve asthma symptom severity in the AERD population.

For medical conditions such as AERD with a substantial symptom burden but low risk of mortality, PROMs can be useful tools in clinical trials and also in clinical care to quantify and track symptom burden over time.⁽¹⁹⁾ Response to intervention, such as surgery or pharmacologic treatment, for a disease with substantial symptom burden should include a reliable evaluation of symptomatology with a validated PROM. PROMs are increasingly being required for drug approval by the Food and Drug Administration. There is increasing evidence that PROMs are valuable measures for both chronic rhinosinusitis and asthma. The recent trial of dupilumab for chronic rhinosinusitis with nasal polyps, for example, demonstrated improvement

in SNOT-22 symptomatology as well as asthma control in patients with AERD and in patients with chronic rhinosinusitis with polyps.(20)

In this study, we also demonstrated the extremely high sinonasal and asthma symptom burden experienced by AERD patients. Loss of sense of smell and taste followed by nasal blockage and congestion were the most severe sinonasal symptoms noted by AERD patients on the SNOT-22 (**Table 2**). Overall, sinonasal and sleep symptoms dominated the symptom profile for this disease, with lower severity rankings for facial pain, otologic complaints or sadness/embarrassment (**Tables 2 and 3**). This constellation of symptoms – smell loss and nasal obstruction with limited or no facial pain – should prompt the physician to consider a diagnosis of AERD in a patient not yet diagnosed with that condition. Sinonasal symptomatology can have a significant impact on quality of life. In non-AERD patients, we have previously shown correlation of worse sinonasal symptomatology as measured by the SNOT-22 with depression, poor productivity, and poor health-related quality of life.(21,22) For asthma, ACT has been shown to have good diagnostic accuracy and assessment of controlled ($ACT \geq 20$) and not well-controlled asthma ($15 < ACT < 20$), but not for uncontrolled asthma ($ACT \leq 15$).(23) Patient-rated asthma control is an important predictor of asthma health-related quality of life.(24) Asthma symptom control is integral to management of the condition.

This study must be interpreted in the context of its limitations. The patients in this cohort had typically been diagnosed years before inclusion in the registry as evidenced by the gap between the mean age of the cohort at enrollment and the mean ages at diagnosis of each of the three disease components. Therefore, patients are often undergoing active treatment and enrollment symptoms do not represent an untreated disease state. The symptomatology reported by patients in this study generally reflects the chronic symptomatology of an actively treated

patient cohort. This registry does not have sufficient data on timing of surgery or aspirin desensitization in this cohort to reliably specify differences in PROMs based on specific treatments. Furthermore, the patient population is limited in racial and ethnic diversity. The patient registry in this study contains only 3.3% of African Americans, which is likely an underrepresentation of the AERD general patient population. African Americans with chronic rhinosinusitis have an increased prevalence of nasal polyposis, anosmia, and AERD, as well as a higher reoccurrence rate of nasal polyposis compared to white patients.(25) Contrarily, the number of patients who undergo surgery for AERD is nearly the same for all races, possibly demonstrating under-treatment of African American patients.(26) Additionally, African American patients with chronic rhinosinusitis with nasal polyposis have a disproportionate amount of emergency room visits and asthma hospitalizations.(26) Racial and ethnic differences in aspirin treatment outcomes in AERD patient have been previously reported.(27) Therefore our results must be assessed within the context of the limited diversity of our cohort. Further studies are needed with a more diverse patient population.

Women comprised 68.0% of patients in this study, which is an accurate representation of the greater AERD patient population. Our finding of a high proportion of women with AERD is consistent with our prior publications with this AERD registry, as well as the gender distribution of when computer algorithms were used to identify AERD patients who had not been previously diagnosed (40.9-43.8% male).(15) In previous studies, AERD is more common in women than men with a ratio of 2.3:1, and women were found to have more severe AERD, be more likely to require revision surgeries, and be more likely to be prescribed perioperative oral steroids.(28) The onset of AERD symptoms tends to occur significantly earlier for women, and the disease is more progressive in females than in males.(28) Currently, we have had 100% consent rate for

registry participation of our AERD patients seen in clinic. Like other registries or clinical cohorts, our study includes patients who presented for care or otherwise opted into the registry. Therefore, patients who have not sought medical care for AERD may not be included.

In conclusion, this study demonstrated substantial symptom burden of AERD patients. Sinonasal symptom severity as measured by the SNOT-22 was predictive of asthma symptom severity as measured by both the ACT and FEV1% in this large registry cohort of patients. Future research can examine the extent to which treatment of chronic sinusitis symptoms may reduce asthma symptoms in AERD patients.

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Figure Legends

Figure 1. Inverse association between SNOT-22 score and ACT. SNOT-22 scores, shown on the x-axis, are inversely correlated with ACT score, shown on the y-axis.

Figure 2: Inverse association between SNOT-22 score and FEV1%. SNOT-22 scores, shown on the x-axis, are inversely correlated with FEV1% predicted, shown on the y-axis.

Figure 3: Positive association between ACT score and FEV1%. ACT scores, shown on the x-axis, are positively correlated with FEV1% predicted, shown on the y-axis.

Tables

Table 1: Clinical and Demographic Characteristics, total

	Entire cohort in the registry	ACT and SNOT22 analysis cohort	SNOT22 and FEV1% analysis cohort	ACT and FEV1% analysis cohort
Total patients	1065	845	246	269
Age in years (mean $\pm$ SD)	48.1 (SD 12.8, n=1040)	48.5 (SD 12.8, n=842)	51.9 (SD 12.6)	51.2 (SD=13.0)
Gender				
Male	29.8% (n=317)	31.2% (n=264)	43.1% (n=106)	45.7% (n=123)
Female	68.0% (n=724)	68.5% (n=579)	56.5% (n=139)	53.9% (n=145)
Missing	2.2% (n=24)	0.3% (n=2)	0.4% (n=1)	0.4% (n=1)
Race				
Caucasian	89.2% (n=950)	91.3% (n=772)	89.9% (n=221)	89.5% (n=241)
Black or African American	3.0% (n=32)	2.8% (n=24)	5.3% (n=13)	5.2% (n=14)
Asian	1.5% (n=16)	1.7% (n=14)	2.0% (n=5)	1.9% (n=5)
Other	3.5% (n=37)	3.2% (n=27)	1.2% (n=3)	1.5% (n=4)
Not available	2.8% (n=30)	1.0% (n=8)	1.6% (n=4)	1.9% (n=5)
Age at diagnosis of asthma, mean years	30.2 (SD=14.0, n=924)	30.3 (SD=14.2, n=782)	33.9 (SD=14.4, n=232)	33.0 (SD=14.5, n=252)
Age at diagnosis of polyps, mean years	34.8 (SD=12.0, n=971)	35.1 (SD=12.2, n=814)	38.2 (SD=12.3, n=238)	37.4 (SD=12.5, n=261)
Age at diagnosis of aspirin or NSAID allergy, mean years	34.5 (SD=12.6, n=884)	34.6 (SD=12.6, n=746)	38.1 (SD=12.8, n=194)	37.4 (SD=13.3, n=218)
Number of lifetime polypectomies at time of enrollment, median, range	2 (0-50) (n=949)	2 (0-50) (n=800)	2 (0-15) (n=237)	2 (0-15) (n=262)
Smoking History				
Yes	31.0% (n=331)	33.6% (n=284)	29.3% (n=72)	29.3% (n=72)
No	62.0% (n=660)	65.0% (n=549)	68.7% (n=169)	68.7% (n=169)
Missing	7.0% (n=74)	1.4% (n=12)	2.0% (n=5)	2.0% (n=5)
On high-dose daily aspirin at follow-up visits	66.5% (n= 373/561 follow up visits)	66.5% (n= 373/561 follow up visits)	70.3% (n=315/475 follow up visits)	65.3% (339/519 follow up visits)
SNOT 22 score, mean, all presentations	42.3 (SD=24.1, n=1307 observations from 869 patients)	42.8 (SD=24.0, n=1185 observations from 845 patients)	36.6 (SD=21.9, n=485 observations from 246 patients)	34.4 (SD=21.3, N=634 observations from 269 patients)
SNOT 22 score, mean, enrollment only	50.3 (SD= 23.1, n=790 patients)	50.5 (SD= 23.2, n=746 patients)	47.3 (SD=20.4, n=177 patients)	47.3 (SD=20.7, n=169 patients)
ACT score, mean $\pm$ SD, all presentations	19.4 (SD= 5.2, n=1511 observations from 931 patients)	19.3 (SD= 5.2, n=1185 observations from 845 patients)	19.8 (SD=5.0, n=724 observation from 246 patients)	19.3 (SD=5.2, n=616 observations from 269 patients)
ACT score, mean $\pm$ SD, enrollment only	18.8 (SD= 5.4, n=879 patients)	18.8 (SD= 5.3, n=746 patients)	18.6 (SD=5.2, n=190 patients)	18.4 (SD=5.5, n=216 patients)
FEV1% predicted, mean $\pm$ SD, all presentations	82.8 (SD=19.6, N=777 observations)	82.6 (SD=19.4, n=695 observations)	82.0 (SD=18.9, n=485 observations)	82.1 (SD=19.9, n=616 observations)
FEV1% predicted, mean $\pm$ SD, enrollment only	84.2 (SD=19.1, N=284)	83.8 (SD=19.0, N=230)	84.2 (SD=18.2, N=177)	83.6 (SD=19.1, n=216)

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Table 2: SNOT-22 item statistics, registry enrollment encounters only. Items are listed most severe to least severe. The item maximum score of 5 (worst possible symptoms), with a minimum score of 0 (no symptoms).

SNOT-22 Item	Mean	SD	Domain
Sense of smell/taste	3.73	1.58	Sinonasal
Blockage/congestion of nose	3.28	1.55	Sinonasal
Need to blow nose	2.99	1.47	Sinonasal
Post nasal drip	2.90	1.46	Sinonasal
Thick nasal discharge	2.87	1.59	Sinonasal
Waking up tired	2.77	1.54	Sleep
Fatigue during the day	2.67	1.51	Sleep
Lack of a good night's sleep	2.54	1.64	Sleep
Runny nose	2.53	1.50	Sinonasal
Reduced productivity	2.29	1.57	Sleep
Waking up at night	2.28	1.60	Sleep
Reduced concentration	2.20	1.59	Sleep
Frustrated/restless/irritable	2.18	1.60	Sleep
Ear fullness	2.10	1.60	Otologic
Cough	1.96	1.43	Sinonasal
Sneezing	1.91	1.37	Sinonasal
Facial pain/pressure	1.84	1.55	Otologic
Difficulty falling asleep	1.76	1.62	Sleep
Sad	1.53	1.53	Emotional
Ear pain/pressure	1.46	1.47	Otologic
Embarrassed	1.35	1.56	Emotional
Dizziness	1.10	1.27	Otologic
TOTAL SCORE	50.28	23.12	

Table 3: SNOT-22 domain statistics, enrollment encounters only. Domains are listed most severe to least severe.

SNOT-22 Domain	Mean Score	SD	Maximum Possible Domain Score	% of Maximum Domain Score
Sinonasal	22.18	8.90	40	55.44%
Sleep	18.71	10.86	40	46.78%
Otologic	6.51	4.81	20	32.54%
Emotional	2.89	2.81	10	28.89%

Table 4: Asthma Control Test item characteristics, enrollment encounters only. Items are listed most severe to least severe. An item score of 1 is indicative of maximally severe symptoms, and 5 is no symptoms.

ACT Item	Mean Score	SD
Shortness of breath	3.49	1.38
Use of rescue inhaler or medication	3.57	1.32
How well asthma is controlled	3.71	1.04
Waking up at night	3.84	1.44
Productivity losses	4.16	1.07
Total Score	18.77	5.37

Table 5: Association of SNOT-22 total score, ACT total score, and FEV1% Predicted

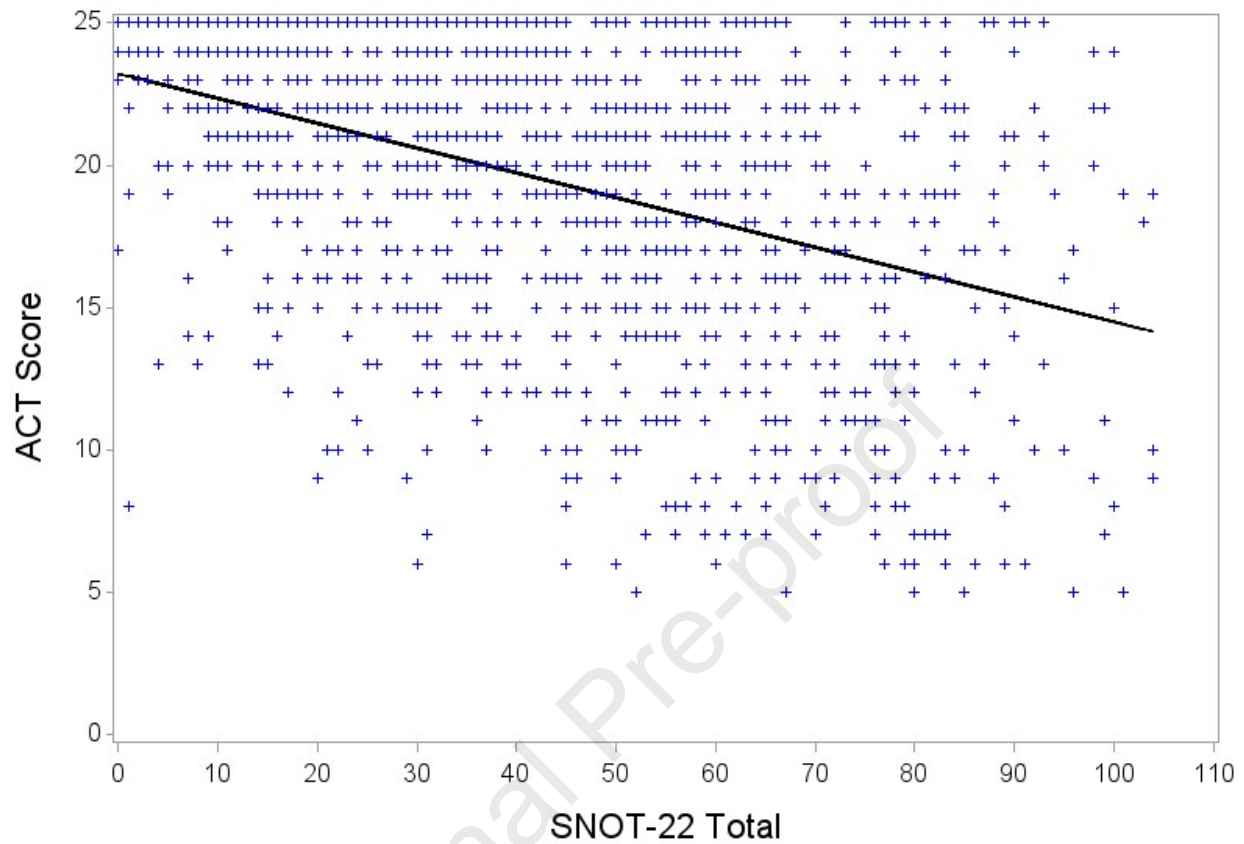
	Number of paired observations	Number of subjects	Coefficient (Standard Error)	P Value
SNOT-22 10-point increase and ACT	1185	845	-0.8727 (0.05813)	<0.0001
SNOT-22 10-point increase and FEV1 % Predicted	485	246	-0.7529 (0.3175)	0.0182
ACT one-point increase and FEV1 % Predicted	616	269	1.0311 (0.1187)	<0.0001

Table 6: Association of SNOT-22 total score, ACT total score, and FEV1% Predicted (Adjusted Analysis*)

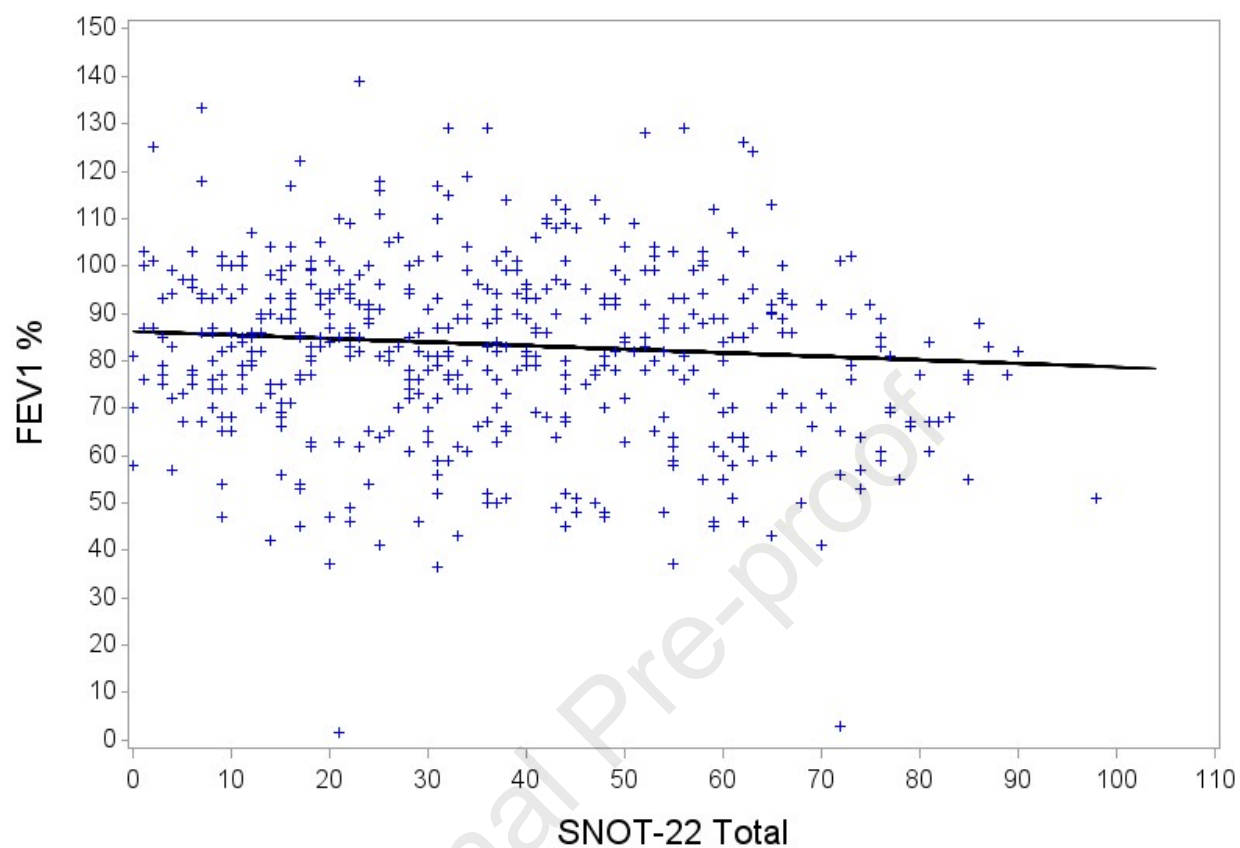
	Number of observations	Number of subjects	Coefficient (Standard Error)	P Value
SNOT-22 10-point increase and ACT	965	649	-0.9695 (0.06510)	<0.0001
SNOT-22 10-point increase and FEV1 % Predicted	475	239	-1.3813 (0.3824)	0.0003
ACT one-point increase and FEV1 % Predicted	607	261	1.1172 (0.1365)	<0.0001

*Age, gender, number of lifetime polypectomies (none, 1, 2, 3, 4 or more, and no information), years since nasal polyp diagnosis (0-10, 11-20, 21-30, 30 plus, and no information), smoking status, and time since the first clinical evaluation in the registry were included in the adjusted model.

Association between SNOT-22 and ACT



Association between SNOT-22 and FEV1%



Association between ACT and FEV1%

