

Original Article

Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin-Exacerbated Respiratory Disease

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What is already known about this topic? Aspirin-exacerbated respiratory disease (AERD) is characterized by the clinical triad of asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and an intolerance of medications that inhibit the cyclooxygenase 1 enzyme.

What does this article add to our knowledge? Before this study, the prevalence of AERD among patients with CRSwNP was not well defined. This study created one of the largest cohorts of patients with CRSwNP to date and more extensively characterized the clinical features of patients with AERD compared with patients with CRSwNP.

How does this study impact current management guidelines? Understanding the clinical characteristics of AERD will assist physicians in the appropriate medical management of this subgroup of patients with severe upper and lower airway disease.

BACKGROUND: Aspirin-exacerbated respiratory disease (AERD) comprises the triad of chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and intolerance to inhibitors of the cyclooxygenase-1 (COX-1) enzyme. The prevalence of AERD remains unclear, and few studies have compared the clinical characteristics of patients with AERD to those with CRSwNP alone, asthma alone, or both CRSwNP and asthma.

OBJECTIVE: To determine the prevalence of AERD within a tertiary care setting, and to identify unique clinical features that

could distinguish these patients from those with both CRSwNP and asthma or with CRSwNP alone.

METHODS: Electronic medical records of patients at Northwestern in Chicago, Illinois, were searched by computer algorithm and then manual chart review to identify 459 patients with CRSwNP alone, 412 with both CRSwNP and asthma, 171 with AERD, and 300 with asthma only. Demographic and clinical features including sex, atopy, and sinus disease severity were characterized.

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Abbreviations used

AERD- aspirin-exacerbated respiratory disease
 COX-1- cyclooxygenase 1
 CRS- chronic rhinosinusitis
 CRSwNP- chronic rhinosinusitis with nasal polyps
 CRSwNP + Asthma- chronic rhinosinusitis with nasal polyps and asthma
 CT- computed tomography
 EDW- Enterprise Database Warehouse
 OR- odds ratio
 PNIF- peak nasal inspiratory flow

RESULTS: The prevalence of AERD among patients with CRSwNP was 16%. Patients with AERD had undergone 2-fold more sinus surgeries ($P < .001$) and were significantly younger at the time of their first surgery (40 ± 13 years) than were patients with CRSwNP (43 ± 14 years; $P < .05$). Atopy was significantly more prevalent in patients with AERD (84%) or asthma (85%) than in patients with CRSwNP (66%, $P < .05$). More patients with AERD (13%) had corticosteroid-dependent disease than patients with both CRSwNP and asthma (4%, $P < .01$) or asthma (1%, $P < .001$).

CONCLUSIONS: AERD is common among patients with CRSwNP; even though patients with AERD have CRSwNP and asthma, the clinical course of their disease is not the same as of patients who have CRSwNP and asthma but are tolerant to COX-1 inhibitors. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: AERD; CRS; CRSwNP; Asthma; Samter's disease; Sinus

Chronic rhinosinusitis (CRS) is characterized by chronic inflammation of the sinonasal mucosa and is estimated to affect 31 million Americans.^{1,2} This disease is associated with a significant financial burden on the US health care system, with direct and indirect costs approximating \$22 billion annually.³ Only a fraction of patients with CRS develop nasal polyps, benign inflammatory outgrowths of the epithelial lining of the sinonasal mucosa.⁴ However, patients with chronic rhinosinusitis with nasal polyps (CRSwNP) on average have greater severity of clinical disease and impairment of quality of life when compared with patients with CRS without nasal polyps.⁵⁻⁹

It is estimated that 48% of patients with CRSwNP have comorbid asthma, which is thought to impact disease severity.^{1,10} In one study of 106 patients with CRS undergoing sinus surgery, those with asthma had significantly worse sinonasal inflammation and nasal polyps than did those without asthma.¹¹ In addition, in a cohort of patients with asthma, those with severe lung disease were more likely than patients with mild disease to undergo sinus surgery for nasal polyps.¹² Given these associations, further studies are needed to more directly address how asthma may impact CRSwNP and vice versa.

A subset of patients with CRSwNP and asthma is also intolerant of medications that inhibit the cyclooxygenase-1 (COX-1) enzyme. Over the years, patients with this clinical triad have been defined as having Samter's disease, Samter's triad, Widall's triad,

aspirin-exacerbated respiratory disease (AERD), or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease.¹³⁻¹⁵ In the present study, we use the term AERD to refer to those patients with CRSwNP and asthma who specifically develop upper and/or lower respiratory tract reactions to COX-1 inhibitors. Importantly, the true prevalence of AERD among patients with CRSwNP is not well defined, although AERD is thought to place an even higher clinical and financial burden on affected individuals.¹⁶

Numerous groups have advanced the understanding of the underlying mechanisms contributing to the pathogenesis of CRSwNP and AERD. In particular, AERD is uniquely characterized by a dysregulation in arachidonic acid metabolism, reflecting diminished levels of the anti-inflammatory prostanoid prostaglandin E2 and increased levels of 5-lipoxygenase products leukotriene C4, leukotriene D4, and leukotriene E4.¹⁷⁻¹⁹ Low expression levels of the prostaglandin E2 receptor, EP2, as well as aberrant downstream receptor signaling and induction of the IL-1 receptor, is also thought to be important.²⁰⁻²³ Aspirin challenges further reduce protective prostaglandin E2 and dramatically elevate leukotrienes from mast cells, eosinophils, and other cells as well as prostaglandin D2 derived from mast cells.²⁴⁻²⁶ Clinically, the development of a respiratory reaction to COX-1 inhibitors remains the major feature differentiating patients with AERD from those with CRSwNP. However, patients with AERD typically avoid taking aspirin and nonsteroidal anti-inflammatory drugs of their own accord. This leads to the question of whether, in the absence of COX-1 inhibitor use, there are other clinical or demographic differences between patients with AERD and patients with CRSwNP alone. Because all patients with AERD have asthma but not all patients with CRSwNP do, this study controlled for the presence of asthma by including a separate cohort of patients who had both CRSwNP and asthma (CRSwNP + Asthma).

By searching an electronic medical database of patients within our tertiary care facility, we assembled one of the largest cohorts of patients with CRSwNP available to date, encompassing 1059 unique patients. Within this cohort we identified patients with AERD and estimated the prevalence of this disease among patients with CRSwNP. Finally, we investigated various clinical characteristics to determine whether and how patients with AERD, in the absence of COX-1 inhibitor treatment, differ from patients with CRSwNP with or without comorbid asthma. Knowledge about how these conditions differ could provide important insights into the etiology or pathophysiology of these conditions, which could help inform prevention and treatment strategies.

METHODS

Identification of subjects

We identified patients with CRSwNP, asthma, and AERD using a mix of automated and manual chart reviews as described below. Additional details on our methods are described in this article's Online Repository at www.jaci-inpractice.org. The Northwestern University Internal Review Board approved this study.

To identify subjects with CRSwNP, we first conducted an automated search of the Northwestern University Enterprise Database Warehouse (EDW) to identify patients with acute or chronic sinusitis. Then, we manually reviewed the medical records of all patients identified with an *International Classification of Diseases*,

Ninth Revision code for nasal polyps to confirm the diagnosis of CRSwNP, asthma, and COX-1 inhibitor intolerance. Patients were diagnosed with AERD if they had a clinical history of CRSwNP, asthma, and COX-1 inhibitor intolerance. However, aspirin challenges to confirm the diagnosis of AERD have not yet been performed in most patients identified by clinical history. Finally, to identify patients who only had asthma, without CRSwNP, we conducted a separate automated EDW search.

Identification of subjects with allergic rhinitis

The presence of allergic rhinitis in the confirmed asthma, CRSwNP, and AERD cases was determined by manual chart review with additional detail provided in this article's Online Repository.

Determination of sinonasal disease severity

The severity of sinonasal inflammation in patients with CRSwNP was determined on the basis of overall sinus mucosal thickening on a sinus computed tomography (CT), as previously described²⁷ with additional detail provided in this article's Online Repository.

Measurement of pulmonary function

Medical charts were manually reviewed for documentation of pulmonary function tests for patients with asthma alone, CRSwNP + Asthma, or AERD. When documented, the percent-predicted FEV₁ was recorded and, if more than 1 test had been completed for a given patient, an average of the values was used. For multivariate analysis, asthma severity was classified into mild, moderate, or severe disease on the basis of a percent-predicted FEV₁ of 80% to 100%, 60% to 79%, or less than 59%, respectively.

Preoperative medication use

To compare preoperative medication use, we manually reviewed the surgical and anesthesia records for medications taken within 2 weeks before surgery for those patients who underwent sinus surgery at Northwestern Medicine with additional detail provided in this article's Online Repository.

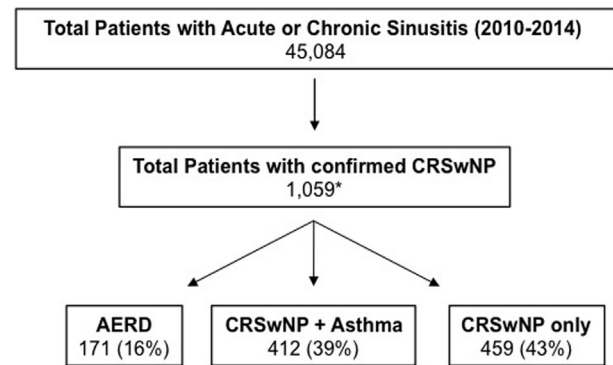
Confirmation of AERD

Eleven patients identified as having AERD in our EDW search underwent aspirin desensitization for medically indicated treatment of their disease.^{28,29} The diagnosis of AERD was confirmed if patients developed upper and/or lower respiratory tract reactions, a decrease in peak nasal inspiratory flow (PNIF), and/or a decline in lung function as measured by spirometry at any point during the procedure. Additional detail is provided in this article's Online Repository. The remaining 160 patients in our AERD cohort were found to historically fulfill all the criteria necessary for having AERD but have not yet undergone further confirmation of the diagnosis with an aspirin challenge and/or desensitization.

Statistical analysis

The goals of the analysis were to identify significant clinical or demographic differences between patients with AERD and patients with CRSwNP with or without asthma. All statistical calculations were performed using Graphpad Prism v6.0c. The chi-square test was used for comparisons among different patient groups regarding sex, atopy, corticosteroid dependency, and preoperative medication use. The Kruskal-Wallis test with Dunn's correction was used to compare means among different groups regarding age, sinus severity, number of sinus surgeries, and lung function.

Multivariable analysis was performed using logistic regression to model the outcome of AERD versus the other disease categories (CRSwNP, CRSwNP + Asthma, Asthma). Each demographic and



*17 patients were excluded from further analysis given a history of childhood asthma that was subsequently outgrown

FIGURE 1. Algorithm for identifying study cohorts.

disease-related predictor was first modeled individually against the outcome. Disease-related variables were then modeled one at a time controlling for significant demographic variables ($P < .05$). Preoperative medications were also modeled against the outcome of AERD versus CRSwNP + Asthma only. Logistic regression modeling was performed in SAS Enterprise Guide, v6.1 (SAS, Inc, Cary, NC).

RESULTS

Prevalence of AERD among patients with CRSwNP

From the original 45,084 patients identified in our EDW search with either acute or chronic rhinosinusitis, 1,059 fulfilled the criteria for having CRSwNP (Figure 1). Among this population, the prevalence of asthma was found to be 55%. Patients with both CRSwNP and asthma were significantly more likely to have reported having a respiratory reaction to a COX-1 inhibitor than a cutaneous, gastrointestinal, or hematologic reaction as documented in their medical record (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Among patients with CRSwNP, 171 (16%) had comorbid asthma as well as a documented respiratory reaction to at least 1 COX-1 inhibitor; 412 (39%) were found to have asthma but no evidence of COX-1 inhibitor intolerance (CRSwNP + Asthma); and 459 (43%) had only CRSwNP (Figure 1). Seventeen patients with CRSwNP had a physician diagnosis of childhood asthma that had since been outgrown and were excluded from further analysis.

Confirmation of AERD

Of the patients with AERD identified in our EDW study, 11 had undergone aspirin desensitization as medically indicated treatment of their disease. During this procedure, 9 patients (82%) developed a mix of upper and lower respiratory tract symptoms as well as a fall in PNIF and/or a decrease in percent-predicted FEV₁. Clinical symptoms typically developed after the administration of either 7.56 mg of ketorolac intranasally or 60 mg of aspirin orally. However, decreases in PNIF (see Figure E2, A, in this article's Online Repository at www.jaci-inpractice.org) and FEV₁ (Figure E2, B) were seen as early as 30 minutes after 5.04 mg of intranasal ketorolac in 1 patient. The presence of respiratory reactions during the aspirin desensitization confirmed the diagnosis of AERD.

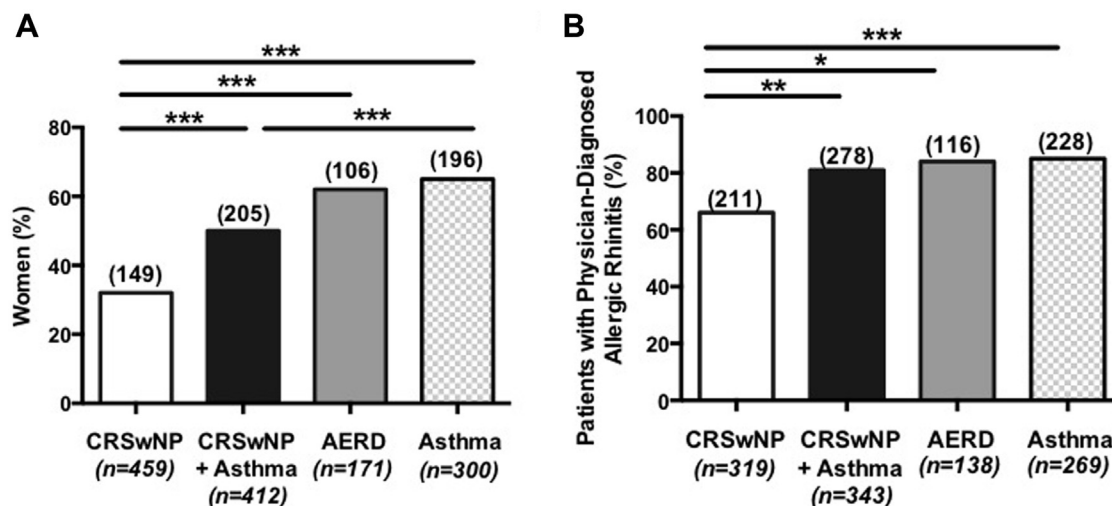


FIGURE 2. Frequency of women and atopy in each group. Significantly fewer women had CRSwNP than CRSwNP + Asthma, AERD, or asthma alone (A). Although the majority of all patients examined had physician-diagnosed allergic rhinitis, significantly fewer patients with CRSwNP had allergic rhinitis than did patients with CRSwNP + Asthma, AERD, or asthma alone (B). Columns represent the number of patients in each group, with the values over each column indicating the number of patients who were female (Figure 1, A) or who had physician-diagnosed allergic rhinitis (Figure 1, B). Statistical significance was determined by chi-square test, with * $P < .05$, ** $P < .01$, and *** $P < .001$.

Two of the 11 patients (18%) who underwent aspirin desensitization remained completely asymptomatic during the challenge with no decrease in either PNIF (Figure E2, C) or FEV₁ (Figure E2, D). Given the negative challenge, these patients would not be classified as having AERD. However, 1 of these patients noted improvement in clinical symptoms after long-term treatment with high-dose aspirin, suggesting they had AERD but may have undergone a “silent desensitization” as described by White et al.³⁰

Given these observations, it is likely that not all patients we have identified as having a clinical history consistent with AERD will have confirmed disease upon aspirin challenge and/or desensitization. As such, the prevalence of AERD in our CRSwNP cohort may be less than the 16% currently estimated. Previous work has suggested that as many as 14% of patients with a clinical history of AERD may in fact not have the disease.³¹ Using these estimates, the prevalence of AERD in our cohort would be lower at approximately 14%. However, it is also suggested that as many as 15% of patients with CRSwNP + Asthma are unknowingly intolerant of COX-1 inhibitors and have positive aspirin challenges and thus AERD.³¹ This would, in turn, raise the expected prevalence of AERD in our population. Although additional aspirin challenges are clearly warranted to further confirm or refute the diagnosis of AERD in our population, the remainder of the present study will focus on examining the clinical characteristics of patients with AERD, CRSwNP + Asthma, and CRSwNP alone as delineated solely by medical chart review.

Demographic characteristics

Although there was no significant difference in the mean age of patients with either CRSwNP alone (54 ± 15 years), CRSwNP + Asthma (52 ± 15 years), or AERD (54 ± 14 years), patients with asthma were younger than the other patients at the time of study (40 ± 15 years; $P < .001$). CRSwNP-only cases

had a smaller proportion of females (32%) than patients with CRSwNP + Asthma (50%, $P < .001$), AERD (62%, $P < .001$), or asthma (65%, $P < .001$) (Figure 2, A). There was a trend toward a higher percentage of women in the AERD group than in the CRSwNP + Asthma group ($P = .06$).

Allergic sensitization

Because both CRSwNP and asthma are associated with atopy, we investigated the frequency of allergic rhinitis in our cohort. The majority of all study patients with CRSwNP and/or asthma had allergic rhinitis, as documented by a treating allergist-immunologist, otolaryngologist, or pulmonologist (Figure 2, B). However, patients with CRSwNP only were significantly less likely to have physician-diagnosed allergic rhinitis (66%) than those with CRSwNP + Asthma (81%, $P < .01$), AERD (84%, $P < .05$), or asthma alone (85%, $P < .001$), suggesting that allergic rhinitis is more associated with asthma than with CRSwNP. We also found a similar trend, with fewer patients with CRSwNP (66%) having a positive skin prick test result to at least 1 aeroallergen compared with patients with CRSwNP + Asthma (78%), AERD (83%), or asthma alone (90%).

Clinical disease severity

The degree of sinonasal inflammation was determined by clinical radiologists' interpretation of overall sinus mucosal thickening on diagnostic sinus CT scans as previously reported.²⁷ Sixty-six percent of patients with AERD were classified as having severe sinus disease compared with only 23% or 10% of patients with CRSwNP + Asthma or CRSwNP only, respectively ($P < .001$, results not shown). When sinus disease severity was converted to a numeric scale ranging from 1 to 5 (1 indicating mild disease and 5 severe disease), patients with AERD, on average, had significantly higher scores (4.4) than did patients with CRSwNP + Asthma (3.2) or patients with CRSwNP (2.6) ($P < .001$; Figure 3, A). In addition, patients

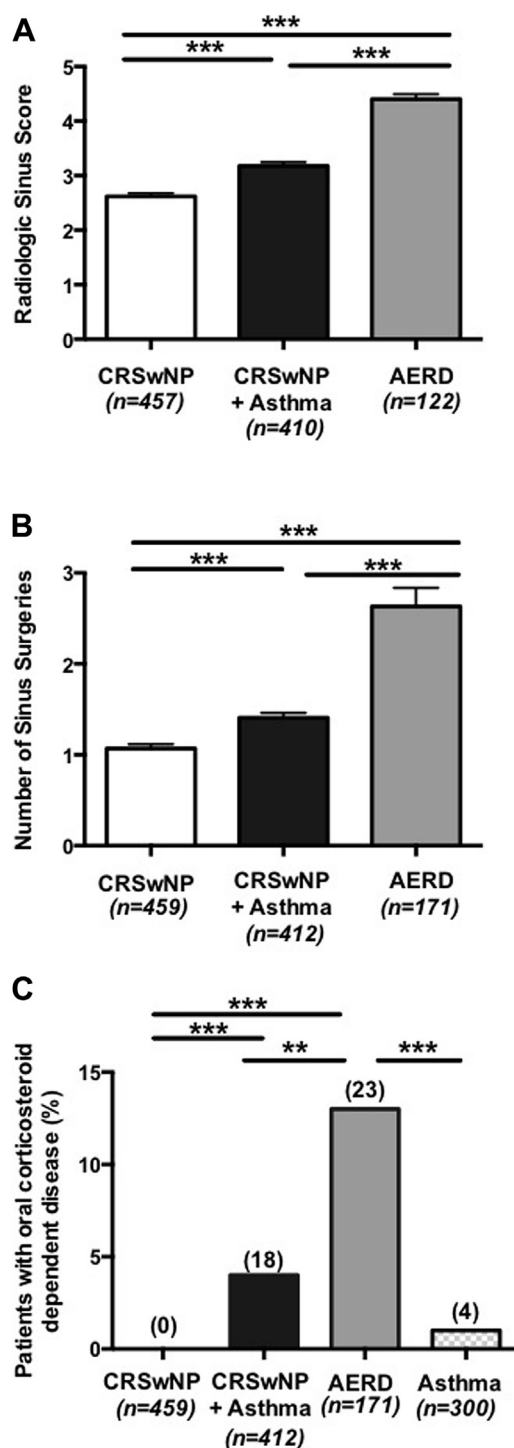


FIGURE 3. Sinus disease severity and dependence on oral corticosteroids. Patients with AERD, on average, had significantly more severe sinus disease (A), underwent more sinus surgeries (B), and were more likely to have oral corticosteroid-dependent disease (C) than did patients with CRSwNP or CRSwNP + Asthma. The number above each column indicates how many patients had oral corticosteroid-dependent disease in each condition (Figure 2, C). Statistical significance was determined by Kruskal-Wallis test with Dunn's correction (Figure 2, A and B) or by chi-square test (Figure 2, C) with $**P < .01$ and $***P < .001$.

with CRSwNP + Asthma had significantly more severe disease than did patients with CRSwNP alone ($P < .001$).

Patients with AERD also reported the highest number of sinus surgeries. Patients with AERD had undergone an average of 2.6 (range, 0-18) sinus surgeries compared with 1.4 surgeries for patients with CRSwNP + Asthma (range, 0-6; $P < .001$) and 1.1 surgeries for patients with CRSwNP (range, 0-9; $P < .001$; Figure 3, B). Patients with AERD were also significantly younger at the time of their first sinus surgery (40 ± 13 years) than those with CRSwNP + Asthma (42 ± 14 years) or CRSwNP alone (43 ± 14 years) ($P < .05$; Table I).

Patients with AERD also had significantly reduced lung function as determined by pulmonary function testing. The mean percent-predicted FEV₁ for patients with AERD was $80\% \pm 18\%$ compared with $84\% \pm 18\%$ in patients with CRSwNP + Asthma or $86\% \pm 17\%$ in patients with asthma ($P < .01$; Table II). Finally, 13% of patients with AERD were documented by their treating physician as having oral corticosteroid-dependent disease (Figure 3, C). This was significantly higher than what was reported for patients with CRSwNP + Asthma (4%, $P < .01$), asthma (1%, $P < .001$), or CRSwNP alone (0%, $P < .001$).

Presurgical medication use

We next used presurgical oral corticosteroid use as a surrogate marker for disease severity. Surgical information was available for 261 (57%) patients with CRSwNP, 247 (60%) with CRSwNP + Asthma, and 72 (42%) with AERD. At the time of sinus surgery, patients with AERD were significantly more likely to be taking oral corticosteroids than patients with either CRSwNP + Asthma ($P < .01$) or CRSwNP ($P < .001$) (Figure 4, A). These findings remained significant after excluding all patients who had been previously identified as having oral corticosteroid-dependent disease. In addition, patients with CRSwNP + Asthma were more likely to be taking oral corticosteroids before sinus surgery than patients with CRSwNP alone ($P < .001$; Figure 4, A).

In contrast, no significant difference was found in leukotriene antagonist (Figure 4, B), intranasal corticosteroid (Figure 4, C), or inhaled corticosteroid (Figure 4, D) use between patients with CRSwNP + Asthma and patients with AERD. Patients with CRSwNP + Asthma or patients with AERD were significantly more likely to report taking leukotriene antagonists ($P < .001$; Figure 4, B), intranasal corticosteroids ($P < .001$; Figure 4, C), or inhaled corticosteroids ($P < .001$; Figure 4, D) compared with patients with CRSwNP alone.

Multivariate analysis

Age at time of study and sex were significantly associated with AERD (data not shown) and retained in subsequent models. In contrast, race, ethnicity, and smoking status were not significantly associated with AERD.

After adjusting for age at time of study and sex (Table III), all disease-related predictors except for FEV₁ severity were significantly associated with AERD. Age at first sinus surgery showed decreased odds of AERD (odds ratio [OR] = 0.94), whereas the rest of the predictors showed increased odds of AERD compared with the other disease groups (OR > 1.0). For example, the odds of AERD were 6.88 times higher for those with oral corticosteroid dependency than for those without it.

TABLE I. Age at time of first sinus surgery

Group	Mean age (y)* $\pm$ SD
CRSwNP (n = 341)	43 $\pm$ 14
CRSwNP + Asthma (n = 347)	42 $\pm$ 14
AERD (n = 141)	40 $\pm$ 13

*Statistical significance determined by Kruskal-Wallis test ($P < .05$) with a post hoc Dunn's correction for multiple comparison significant between AERD and CRSwNP ($P < .05$).

TABLE II. Lung function

Group	FEV ₁ * % predicted $\pm$ SD
Asthma (n = 282)	86 $\pm$ 17
CRSwNP + Asthma (n = 267)	84 $\pm$ 18
AERD (n = 122)	80 $\pm$ 18

*Statistical significance determined by Kruskal-Wallis test ($P < .01$) with a post hoc Dunn's correction for multiple comparison significant between AERD and asthma ($P < .01$).

Significant associations were observed with the use of all 4 preoperative medication classes and AERD compared with CRSwNP + Asthma and CRSwNP combined. When assessing patients with AERD versus patients with CRSwNP + Asthma only, preoperative oral (OR = 2.24) and intranasal (OR = 1.73) corticosteroids remained significantly associated with AERD, although these associations were somewhat attenuated. Preoperative inhaled steroids and leukotrienes were no longer significantly associated with AERD in the comparisons with only patients with CRSwNP + Asthma.

DISCUSSION

This study has established one of the most extensive clinical cohorts of patients with CRSwNP to date. From this population, patients who had comorbid asthma with or without intolerance to COX-1 inhibitors were subsequently identified by manual chart review. This study is one of the first to determine the prevalence of AERD among patients with CRSwNP. In addition, it is one of the largest to directly compare patients with AERD with their closest controls (namely, patients with CRSwNP and asthma who tolerate COX-1 inhibitors) to identify unique clinical characteristics within the cohorts.

AERD in our study specifically refers to patients with CRSwNP and asthma who also developed respiratory reactions to COX-1 inhibitors. This is in contrast to other definitions where AERD was used to refer to patients with asthma and intolerance to COX-1 inhibitors but not necessarily chronic sinus disease or nasal polyps,^{13,15,32-35} or to patients who had nasal polyps and COX-1 inhibitor intolerances but not necessarily asthma.³⁶ Given the lack of universally accepted terminology and definitions, it is common for the same diagnosis (ie, AERD) to describe different clinical syndromes and for different diagnoses (ie, Samter's disease, AERD, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease) to describe the same clinical syndrome. These nuances can make it challenging to directly compare and interpret results across individual studies.

Although we chose the most stringent clinical definition of AERD, it remains unclear whether patients with only 2 of the 3 clinical features of AERD represent a distinct condition, or

rather, are part of a continuum of AERD. To address this, additional studies are needed to investigate and directly compare the underlying pathophysiologic mechanisms contributing to the clinical phenotype of these subgroups. In our cohort specifically, we found that most patients with a documented respiratory reaction to a COX-1 inhibitor had both CRSwNP and asthma, as opposed to having CRSwNP alone, asthma alone, or neither condition (Figure E1). Conversely, patients with both CRSwNP and asthma were significantly more likely to report having a respiratory reaction to a COX-1 inhibitor than cutaneous, gastrointestinal, or hematologic reactions.

The prevalence of AERD in our CRSwNP cohort was 16%. A recent meta-analysis reported that 9.7% of patients with nasal polyps and 8.7% with chronic sinus disease had AERD.³⁷ Although our estimate is higher than these reported values, it may be secondary to our exclusion of patients with CRS without nasal polyps and patients with nasal polyps who did not have evidence of chronic sinonasal inflammation by sinus CT scan or nasal endoscopy. In addition, there is potential for a referral bias given that our patient population is from a large tertiary care academic institution where the more severe phenotypes may be enriched. To address these concerns, future studies are needed to examine the prevalence of AERD among CRSwNP cases in the general population.

Of the 171 patients who met our clinical criteria for AERD, most were women (62%, Figure 2). These findings are supported by earlier work suggesting a female predominance in AERD.^{32,38} For example, of 300 patients with AERD referred to the Scripps Clinic for aspirin desensitizations over a 6-year period, 57% were women.³⁹ In addition, we found significantly more women to have AERD or CRSwNP + Asthma than CRSwNP alone. Although it cannot be excluded that women simply seek medical care more frequently than men, these findings could also suggest a potential association with asthma. Studies from the National Health Interview Survey found that 9.6% of women versus 5.1% of men in the general population reported having asthma in 2014. However, this observation cannot entirely explain why more women than men have CRSwNP + Asthma or AERD. This suggests that other factors, such as sex hormones, may play a role in driving the female predominance in AERD.

The unified airway hypothesis suggests that disease in upper and lower airways is related. Our study suggests that the presence of asthma may impact the severity of upper respiratory tract disease. We found that patients with CRSwNP + Asthma had significantly more severe radiological evidence of sinonasal inflammation and had undergone more sinus surgeries than patients with CRSwNP alone. This is supported by a previous study in which patients with CRS with asthma had more severe sinonasal inflammation and were more likely to have nasal polyps than those patients with CRS without asthma.¹¹ In addition, a separate study found a significant positive association between the level of asthma severity and both the degree of sinonasal inflammation and the likelihood of having nasal polyps.⁴⁰ Future studies will be needed to discern whether this is simply an association of more severe disease or whether disease at one site worsens the related disease in the other.

In further support of the unified airway hypothesis, we found a significant difference in percent-predicted FEV₁ among patients with AERD, CRSwNP + Asthma, and asthma alone, with the lowest values observed in the AERD cohort. There was also a trend for patients with CRSwNP + Asthma to have a lower

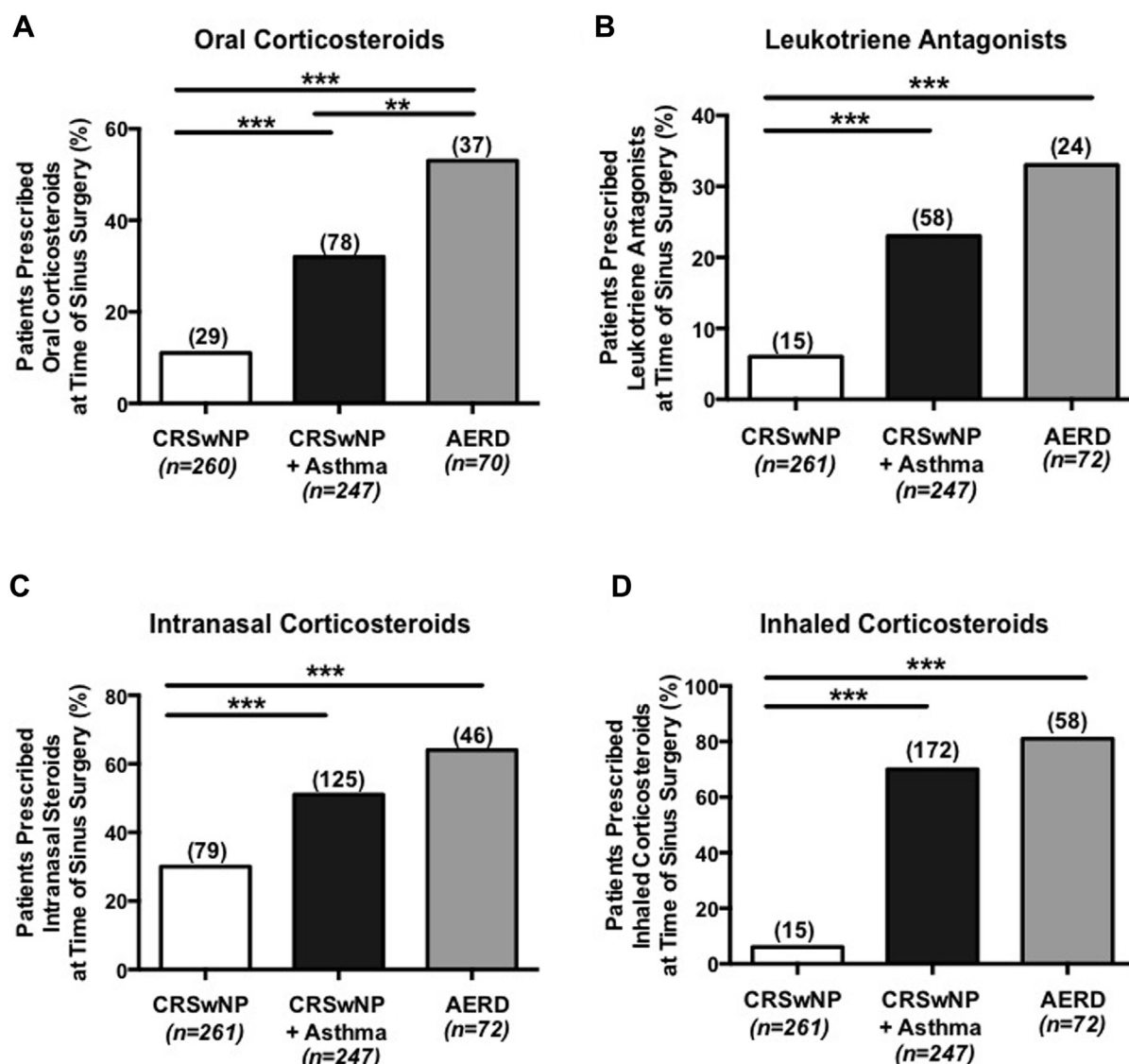


FIGURE 4. Preoperative medication use. When compared with patients with CRSwNP or patients with CRSwNP + Asthma, patients with AERD were significantly more likely to be prescribed oral corticosteroids within 2 weeks of sinus surgery (A). There was no difference in prescribed leukotriene antagonists (B), intranasal corticosteroids (C), and inhaled corticosteroids (D) within 2 weeks of sinus surgery between patients with AERD and patients with CRSwNP + Asthma. The number over each column represents how many patients were taking the medication. Statistical significance was determined by chi-square test with $**P < .01$ and $***P < .001$.

percent-predicted FEV_1 than patients with only asthma. However, it should be noted that not all patients in this study had pulmonary function test results documented in their medical records. In addition, the level of asthma control likely varied within the cohorts, given that pulmonary function tests were available only at certain time points within the natural course of a patient's disease. Despite these limitations, our results support previous observations by Mascia et al⁴¹ who found patients with AERD to have a significantly decreased percent-predicted FEV_1 compared with non-aspirin-sensitive asthma.

Patients with CRSwNP + Asthma were significantly more likely to have oral corticosteroid-dependent disease compared with patients with either condition alone ($P < .01$). This finding is similar to an association observed between increased asthma severity and the presence of sinusitis.⁴² At the time of sinus

surgery, patients with both CRSwNP and asthma were significantly more likely to report taking leukotriene modifiers, intranasal corticosteroids, inhaled corticosteroids, and oral corticosteroids than patients with CRSwNP alone. Although this may reflect the medical practice within our tertiary care institution, it also suggests that patients with CRSwNP and asthma have more severe overall disease that requires adjunct treatments.

Interestingly, even in the absence of COX-1 inhibitor use, patients with AERD had more severe upper and lower respiratory tract disease than did patients with CRSwNP + Asthma. Previous studies have suggested that patients with AERD are more likely to have recurrent sinonasal disease following sinus surgery.⁴³⁻⁴⁵ We found patients with AERD to have enhanced sinonasal inflammation on sinus CT scan, to undergo repeated sinus surgeries, and be more likely to have oral

TABLE III. Adjusted associations* between AERD and selected disease-related factors

Variable	OR (95% CI)
Age at first sinus surgery†	0.94 (0.92-0.97)‡
Allergic rhinitis§	1.72 (1.05-2.80)‡
Sinus severity score†	2.70 (2.18-3.33)‡
Number of sinus surgeries†	1.73 (1.53-1.95)‡
Oral corticosteroid dependence§	6.88 (3.68-12.87)‡
Preoperative medication use†	
Oral corticosteroids	3.70 (2.18-6.26)‡
Intranasal corticosteroids	2.56 (1.52-4.30)‡
Inhaled corticosteroids	6.57 (3.54-12.20)‡
Leukotriene receptor antagonists	2.57 (1.46-4.51)‡
Preoperative medication use	
Oral corticosteroids	2.24 (1.29-3.88)‡
Intranasal corticosteroids	1.73 (1.00-3.00)‡
Inhaled corticosteroids	1.74 (0.90-3.34)
Leukotriene receptor antagonists	1.52 (0.85-2.72)
FEV ₁ severity¶	
Moderate vs mild	1.37 (0.88-2.14)
Severe vs mild	1.69 (0.90-3.17)

*Associations are adjusted for sex and age at time of study.

†AERD compared with CRSwNP and CRSwNP + Asthma cohorts.

‡Association is significant.

§AERD compared with CRSwNP, CRSwNP + Asthma, and Asthma-only cohorts.

||AERD compared with CRSwNP + Asthma cohort.

¶AERD compared with CRSwNP + Asthma and Asthma-only cohorts.

corticosteroid-dependent disease than patients with CRSwNP + Asthma. In addition, there was a trend toward significantly reduced lung function in patients with AERD versus patients with CRSwNP + Asthma. This suggests that patients with AERD have a different clinical profile than do patients with CRSwNP + Asthma, even in the absence of COX-1 inhibitor use.

The clinical characteristics of our AERD cohort were generally similar to what was observed at the Scripps Clinic.³⁹ Notably, at the time of aspirin desensitization, Berges-Gimeno et al³⁹ reported that 76% and 80% of patients with AERD were taking nasal corticosteroids and inhaled corticosteroids, respectively. This is compared to 64% and 81% of patients with AERD using nasal or inhaled corticosteroids, respectively, at the time of sinus surgery in the present study. Other similarities between the 2 cohorts were the number of patients with corticosteroid-dependent disease (13% in our study vs 22% at Scripps) and the number of patients who had undergone sinus surgery (86% vs 94%).³⁹

In our study, we found that most patients in all subgroups had a diagnosis of allergic rhinitis listed in their medical record by a treating physician in association with positive allergy testing. A strong association between allergic rhinitis and asthma is well established.⁴⁶⁻⁴⁸ However, the relationship between allergic rhinitis and chronic sinus disease is less clear. Furthermore, the presence of allergic sensitization does not necessarily imply that a patient will be symptomatic. Attributing nasal symptoms as secondary to allergic rhinitis versus CRS can be difficult, especially when only reviewing patient medical records, and additional work is needed to investigate a possible relationship between allergic rhinitis and CRS. To date, studies have suggested that as many as 51% to 86% of patients with CRSwNP

have positive skin prick test results, but there are conflicting reports as to whether allergic sensitization is associated with more severe sinonasal disease.^{9,11,49-51}

In one of the first reports by Samter and Beers,¹³ only 5% of patients with AERD had sensitivities to “seasonal and/or environmental inhalants.” More recently, European studies reported positive skin prick testing to at least 1 aeroallergen in 50% of patients with AERD.^{33,34} Importantly, within these cohorts, not all patients with AERD had nasal polyps.^{33,34} In contrast, 66% and 83%, respectively, of patients from the Scripps study and our study had documented positive skin prick test results to at least 1 environmental allergen.³⁹ It is possible that the increased prevalence of allergic sensitization in the United States compared with Europe is reflective of an additive effect of having nasal polyps.

Findings from the Severe Asthma Research Program suggest that patients with asthma with the highest prevalence of sinus disease (clusters 3 and 5) are less atopic than patients with asthma without sinus disease (64%-66% vs 77%-85%).⁴² However, in these studies, only half the patients reported previous sinus surgery and the status of aspirin intolerance is unclear. In a separate analysis, patients with severe asthma who were the most likely to undergo nasal polypectomy (cluster 5) had lower numbers of allergen-induced skin reactions.¹² Although most patients with AERD would fit in this cluster, not all patients with severe asthma in this cluster have AERD. As a result, additional studies are needed to further investigate any potential associations between allergic sensitization and AERD.

One of the major limitations of our study is that the diagnosis of AERD was made by clinical history alone. The current criterion standard for confirming AERD is an aspirin challenge. Studies have suggested that as many as 14% of patients with a clinical history consistent with AERD (ie, having asthma, CRSwNP, and a respiratory reaction following COX-1 inhibitor use) in fact do not have a reaction during an aspirin challenge, thus disproving the diagnosis of AERD.³¹ In addition, as many as 15% of patients with CRSwNP and asthma who were previously unaware that they had AERD will have a positive clinical aspirin challenge. To address these limitations, we have begun to perform aspirin challenges to confirm the diagnosis in our cohort.

Our patient cohort represents a large tertiary care population where patients may be referred because of having more significant or refractory disease. As a result, our findings may not necessarily reflect the clinical characteristics of all patients in a primary care setting. However, the use of medical record data from patients treated in a tertiary care setting may be less vulnerable to case misclassification because the patients are diagnosed by physicians specializing in these disease areas.

The identification of patients with AERD within an electronic medical record system remains hampered by the lack of a unique *International Classification of Diseases, Ninth Revision* diagnosis code. As a result, patients were identified only following an allergist-immunologists' exhaustive manual review of their individual medical records. Furthermore, the diagnosis of AERD relied on a respiratory reaction to a COX-1 inhibitor being (1) known by the patient; (2) addressed by the physician at a clinical visit; and (3) documented correctly in the medical record system. The absence of proper medical record documentation does not guarantee the absence of disease and thus, it is very likely that additional patients with AERD exist within

Northwestern Medicine who were not detected by our approach. It is the hope that new implementation of a specific *International Classification of Diseases, Tenth Revision* code for AERD will greatly enhance the ability to identify patients with this disease in the future. Moreover, increased clinical awareness of AERD would also assist in better understanding the clinical and pathological features of this disease.

Finally, all data in this retrospective study were obtained by computer algorithm and then confirmed by manual chart review. By design, identified patients could not be contacted to validate or clarify any information listed in their medical records. This restriction prevented any collection of prospective data. For example, we excluded patients with an unclear reaction to COX-1 inhibitors because we could not contact them to clarify the nature of this previous reaction. Furthermore, it was not possible to perform aspirin challenges, with the exception of the 11 patients with AERD who underwent an aspirin desensitization as part of their clinical care, in this retrospective study to validate aspirin sensitivity. In addition, to assess the degree of sinonasal inflammation, we had to rely on past sinus CT reports because we could not use a validated visual analog scale score to measure disease severity.

In summary, CRSwNP and AERD are clinically important diseases characterized by the presence of chronic sinonasal inflammation and nasal polyps. Although, by definition, all patients with AERD have CRSwNP, not all patients with CRSwNP have AERD. We determined the prevalence of AERD to be 16% among patients with CRSwNP, suggesting that AERD is a disease physicians will likely encounter in practice. Furthermore, our findings suggest that although patients with AERD have CRSwNP and asthma, the clinical course of their disease is not the same as that of patients who have CRSwNP and asthma but are tolerant to COX-1 inhibitors. Further research is needed to investigate whether these clinical differences are due solely to the underlying dysregulation of arachidonic acid metabolism or reflect other yet to be discovered mechanisms.

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METHODS

Identification of subjects with CRSwNP

To identify cases, we conducted an automated search of the Northwestern University EDW, a large repository that contains both outpatient and inpatient health record data for adult patients seen within Northwestern Medicine. To ensure that a patient's full health record was available electronically (instead of in physical paper charts), records only from patients seen on or after January 1, 2010, were queried. This study concluded on December 31, 2014.

Patients were selected if they met any of the following criteria: (1) had at least 1 *International Classification of Diseases, Ninth Revision (ICD-9)* code for acute sinusitis (461.x); (2) had at least 1 *ICD-9* code for chronic sinusitis (473.x); (3) had at least 1 *ICD-9* code for nasal polyps (471.x); or (4) had at least 1 Current Procedural Terminology (CPT) code associated with surgery for chronic sinusitis or nasal polyps (30110, 30115, 31254, 31255, 31256, 31267, 31276, 31287, 31288, 31296, 31297). From this query, 45,084 patients were identified.

Within this cohort, we next aimed to identify patients with AERD. However, there is no *ICD-9* code specifically for AERD or Samter's triad. As a result, a more rigorous approach was used to first identify patients with CRSwNP and then determine, from this subset, how many patients also had comorbid asthma as well as developed respiratory reactions to COX-1 inhibitors.

The medical records of all patients identified with an *ICD-9* code for nasal polyps were manually reviewed. The diagnosis of CRSwNP was established using the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guidelines if there was documentation by an allergist or otolaryngologist of the patient having at least 1 of the following clinical symptoms persisting for greater than 12 weeks: anterior and/or posterior rhinorrhea, nasal congestion, facial pressure/pain, or hyposmia.^{E1} In addition, objective evidence of sinonasal mucosal inflammation in patients with CRSwNP was confirmed upon reviewing the Northwestern radiologists' or otolaryngologists' interpretation of the patient's sinus CT scan. Alternatively, nasal polyps were confirmed if their presence was noted on direct observation by nasal endoscopy.

The medical records of patients with CRSwNP were subsequently manually reviewed to determine asthma status. Asthma was confirmed if the diagnosis was listed in the patient's office encounter note by a treating pulmonologist, allergist-immunologist, or otolaryngologist. Any patient who had a documented childhood history of asthma that was either completely asymptomatic as an adult or was considered outgrown by either an allergist-immunologist or a pulmonologist was excluded from further analysis.

Finally, patients with CRSwNP and asthma were diagnosed as having AERD if (1) there was documented evidence of upper or lower respiratory tract symptoms developing with exposure to COX-1 inhibitors; or (2) if a reaction to a COX-1 inhibitor was listed as "AERD." COX-1 inhibitors could be specifically named in the medical record (eg, Acular, Advil, Aleve, aspirin, diclofenac, diflusal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, Motrin, naproxen, Naprosyn, nimesulide, piroxicam, sulindac, tolmentin, and Toradol) or listed as a general class of drugs (eg, nonsteroidal anti-inflammatory drugs and salicylates). Information regarding COX-1 inhibitor

intolerances was obtained by manually reviewing both the allergy section of the patient's medical record as well as individual notes from encounters in allergy-immunology, otolaryngology, or pulmonary clinics.

Identification of subjects with asthma alone

In this query, 300 patients were randomly selected who had an *ICD-9* code of asthma (493.x) as diagnosed by a treating allergist-immunologist or pulmonologist at Northwestern Medicine between January 1, 2010, and December 31, 2014. Patients were excluded from this cohort if they were previously identified in our EDW search or if they were diagnosed with any of the following: acute sinusitis (461.x), chronic sinusitis (473.x), cystic fibrosis (277.x) or chronic obstructive pulmonary disease (490.x, 491.x, 492.x, and 496.x).

Identification of subjects with allergic rhinitis

Allergic rhinitis was established if the diagnosis was documented in the medical record by a treating allergist-immunologist, otolaryngologist, or pulmonologist.

Determination of sinonasal disease severity

Briefly, clinical radiologists characterized a patient's overall sinus mucosal thickening on sinus CT scan as being mild, mild-moderate, moderate, moderate-severe, or severe. These disease severities were then numerically scored as 1, 2, 3, 4, and 5, respectively. Sinus CT scans were not available for 2 patients with CRSwNP, 2 with CRSwNP + Asthma, and 49 with AERD because most of these scans were performed at outside institutions and thus not read by Northwestern Medicine radiologists. Such patients were excluded from this analysis. The total number of sinus surgeries each patient had undergone and the age of the patient at the time of their first sinus surgery were determined by manual review of the patient's surgical and clinical records.

Preoperative medication use

We manually reviewed the surgical and anesthesia records for those patients who underwent sinus surgery at Northwestern Medicine. Patients were included in this analysis if they had information regarding medication use within the 2 weeks before surgery. Medications commonly used to treat CRSwNP and asthma were evaluated including oral corticosteroids (eg, prednisone), leukotriene antagonists (eg, montelukast), intranasal corticosteroids (eg, fluticasone propionate, mometasone furoate, and triamcinolone acetonide), and inhaled corticosteroids with and without long-acting beta-agonists (eg, pulmicort, flovent, and flovent-salmeterol). If a patient's surgical information was not available, they were excluded from this analysis. Also, because patients with asthma alone did not undergo sinus surgery (by definition), they were also excluded from this analysis.

Confirmation of AERD

The aspirin desensitization protocol involved the use of intranasal ketorolac and oral aspirin administered in graded doses over a 2-day period as previously described.^{E2,E3} As part of this process, the diagnosis of AERD was confirmed if patients developed upper and/or lower respiratory tract reactions, a decrease in PNIF, and/or a decline in lung function as measured by spirometry at any point during the procedure.

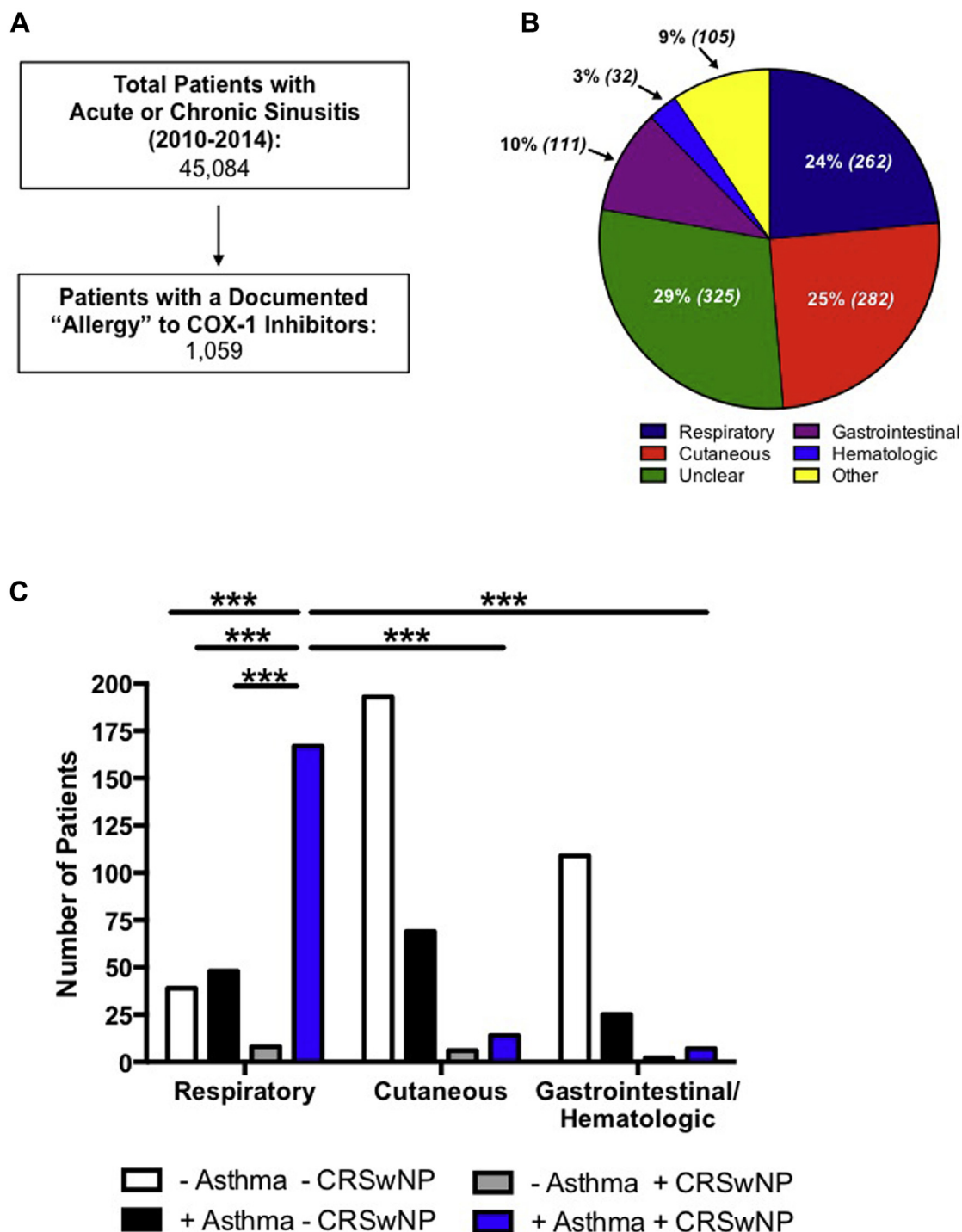


FIGURE E1. Classification of reactions to COX-1 inhibitors. Among patients identified as having acute or chronic sinusitis, 1117 were also found by automated search to have documentation of an adverse reaction to a COX-1 inhibitor listed in the allergy section of their medical record (A). On manual review of these patients, the type of reaction to the COX-1 inhibitor could be classified as being (1) respiratory (eg, nasal congestion, wheezing, difficulty breathing, and anaphylaxis); (2) cutaneous (eg, skin rash, pruritus, urticaria, and/or angioedema); (3) unclear (eg, no description was provided); (4) gastrointestinal (eg, stomach upset); (5) hematologic (eg, increased bruising); or (6) other (eg, none of the above symptoms) (B). Patients with asthma and CRSwNP (blue bars) were statistically more likely to have a respiratory reaction to aspirin than patients with CRSwNP alone (gray bars), asthma alone (black bars), or neither CRSwNP nor asthma (white bars) (C). Patients with CRSwNP + Asthma were also significantly more likely to have a respiratory reaction than a cutaneous or gastrointestinal/hematologic reaction to COX-1 inhibitors (Figure E1, C). Statistical significance was determined by chi-square test with *** $P < .001$.

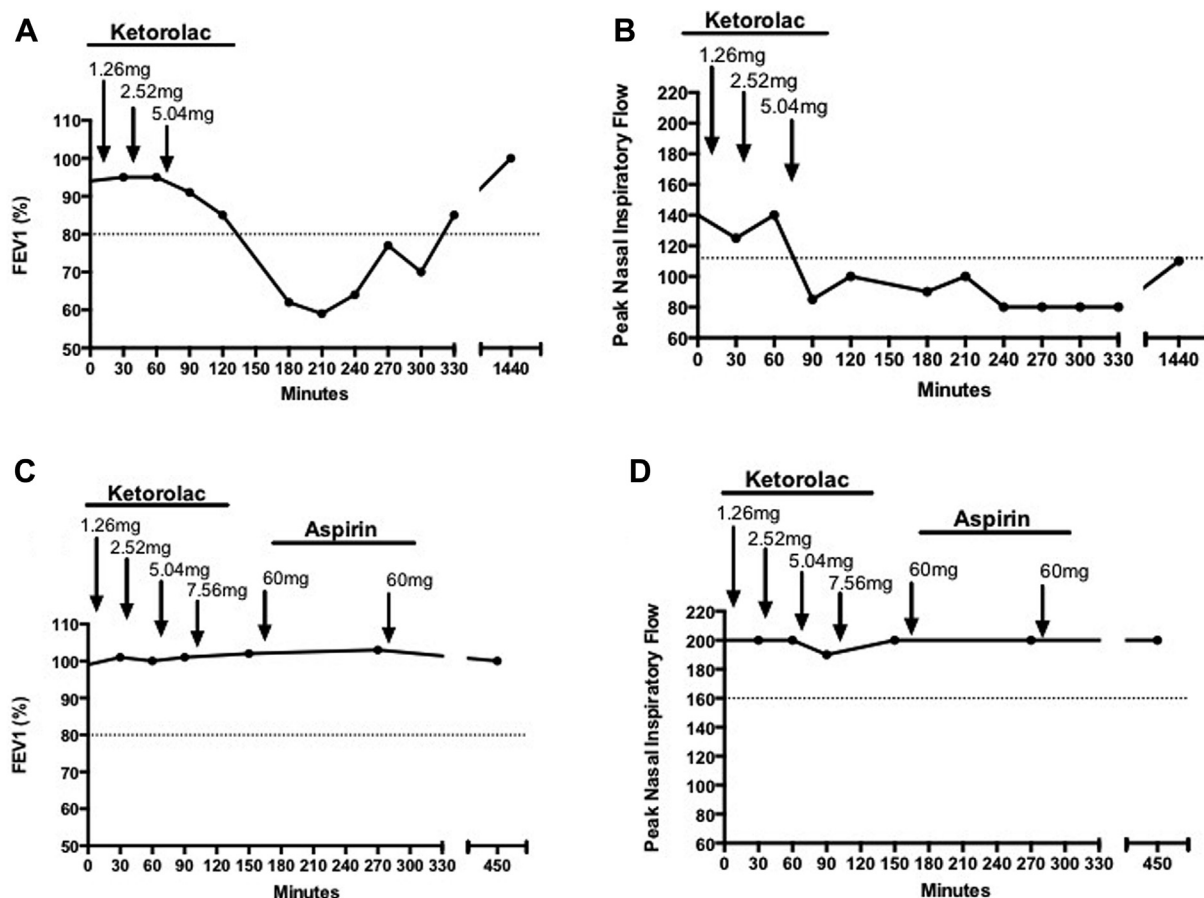


FIGURE E2. Representative patients who underwent an intranasal ketorolac/oral aspirin challenge to confirm the diagnosis of AERD. During an aspirin desensitization for medically indicated treatment of their disease, patient 1 developed upper and lower respiratory symptoms as well as a more than 15% reduction in FEV₁ (A) and a more than 20% decline in PNIF (B) following 5.04 mg of intranasal ketorolac. In contrast, patient 2 remained asymptomatic throughout the entire challenge with no significant decline in either FEV₁ (C) or PNIF (D).

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