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The association of premorbid diseases with chronic rhinosinusitis with and without polyps

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Abstract

Purpose of review—This article reviews recent insights regarding the epidemiology of adult chronic rhinosinusitis (CRS) with particular attention to its association with other premorbid conditions. Identifying premorbid disease associations establishes potential risk factors for developing CRS and helps corroborate current postulates of the various pathophysiologic mechanisms involved with the development and persistence of paranasal sinus inflammation.

Recent findings—Recent findings demonstrate that the diagnosis of CRS is associated with a higher premorbid prevalence of upper airway diseases, lower airway diseases, gastroesophageal reflux disease, diseases of epithelial tissues, autoimmune disorders, and psychiatric conditions. While some of these conditions have long been associated with CRS, improvements in study design and future studies in the general population will more accurately estimate the relative strengths of associations, clinical relevance and temporal relationship of these various conditions in relation to the development of CRS.

Summary—The predisposing patterns of premorbid illnesses may provide valuable information regarding the underlying causes of CRS and allow for both therapeutic and preventive interventions. There remains conflicting evidence within the literature regarding the association of CRS with some medical conditions, signifying the need for continued research on the subject. Limitations of current studies include small sample sizes, lack of prospective longitudinal or interventional studies that help establish causality, and variable criteria for diagnosis of CRS in the outpatient setting.

Keywords

Sinusitis; comorbidities; risk factors; epidemiology; premorbid conditions

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Introduction

Chronic rhinosinusitis (CRS) is a common inflammatory disorder of the nasal passages and paranasal sinuses with chronicity defined by a symptom duration of 12 or more weeks.(1, 2) The definition of CRS encompasses two clinically distinguishable phenotypes: chronic rhinosinusitis without nasal polyposis (CRSsNP) and chronic rhinosinusitis with nasal polyposis (CRSwNP). While CRSsNP remains a pathobiologically heterogeneous condition, CRSwNP possesses a significant predilection for T-helper 2 (Th2) responses and tissue eosinophilia.(3, 4) Current prevalence figures estimate that both forms of CRS affect about 13% of the population in the United States(5) and 10.9% of the population in Europe.(6) CRS is strongly correlated with decreased health utility, emotional distress, and decreased physical and social functioning.(7, 8) In addition to negatively impacting the quality of life, CRS also takes a significant toll on health-resource utilization and expenditures, accounting for 18 to 22 million office visits annually and approximately \$6 billion in healthcare costs. (9–11)

Current conceptualizations of the pathogenesis of CRS have evolved over the past 30 years. (12) While in a minority of CRS cases, specific genetic disorders, such as Kartagener's syndrome, cystic fibrosis, primary immunodeficiencies, Wegener's granulomatosis, and sarcoidosis, are identified as the underlying basis for systemic inflammation that simultaneously affects the paranasal sinuses, the systemic implications and etiology of CRS in most patients remains uncertain.(13, 14) Historically, CRSsNP was considered a consequence of bacterial infection similar to acute rhinosinusitis, whereas CRSwNP was viewed as a noninfectious disorder linked to atopy. Other proposed causes for the persistent mucosal inflammation found in both forms of CRS have included anatomical obstruction of the osteomeatal complex, impaired mucociliary clearance, osteitis, acquired infectious pathogens, and inhaled allergens and irritants. Further evidence also suggests that host-mediated mechanisms within the sinonasal epithelium in CRS may play an important role in the dysregulation of both the innate and adaptive immune responses.(1, 15, 16)

Given the significant prevalence, costs and lack of representative mechanistic animal models of CRS, epidemiologic investigations into the temporal relationship of CRS with other diseases provide a powerful means to test various hypotheses and assess the relative importance of these various host and environmental factors. In particular, establishing premorbid conditions associated with CRS onset provides valuable insights into the common underlying pathogenic mechanisms and facilitates studies evaluating whether early intervention for premorbid conditions may prevent the onset of disease.

The limitations of current studies of premorbid disease in CRS patients include small sample sizes, lack of prospective longitudinal or interventional studies that help establish causality, an excessive focus on tertiary care populations and variable criteria for diagnosis of CRS in the outpatient setting. Tan *et al.* recently published the findings of the first non-specialty care-based, population-representative, case-control study examining the premorbid conditions of patients with CRS. (17) Briefly, the study team used the electronic health records (EHR) of 446,480 primary care patients within the Geisinger Health System (GHS)-to compare rates of various premorbid medical conditions among patients with an incident

(ie. no prior diagnosis) ICD-9 diagnosis of CRS to that of age, gender, and visit-frequency matched control patients who did not develop CRS. Unlike previous studies, the longitudinal data in the EHR made it possible to evaluate the temporal relationship between CRS and other conditions. This study was also able to capture the full spectrum of CRS, while most previous longitudinal studies have been limited to specialty care populations with more severe disease and have not distinguished between incident and prevalent CRS.

This review summarizes the GHS study findings in light of limited literature to date on associations of CRS with pre-morbid disease. Given the lack of data on premorbid conditions, we have included findings from studies of co-morbid associations where relevant. The sections below specifically discuss associations with diseases that have a suspected pathophysiological link to CRS, including diseases of the upper and lower airway, gastroesophageal reflux disease, epithelial conditions, autoimmune diseases, psychiatric disorders, and heart and vascular diseases.

Disorders of the upper airway: association by proximity

The anatomical proximity of the sinonasal cavity to the nasopharynx and oropharynx suggests a close association between CRS and various inflammatory states of all areas of the upper airway. Indeed, the GHS study found strong associations between CRS and inflammatory conditions affecting the sinonasal cavity, middle ear, and pharynx. While clinically suspected though never formally evaluated, patients diagnosed with CRSsNP and CRSwNP were found to have a higher prevalence of prior episodes of acute rhinosinusitis as compared to controls. Since CRS transitions through a period of acute symptoms, the association with acute airway illnesses was indeed strongest immediately before the diagnosis, but increased rates of acute and chronic airway illnesses were also detected 7 to 24 months prior to the actual CRS diagnosis. Similarly, otitis media and adenotonsillitis were both modestly but significantly associated with the subsequent diagnosis of CRSsNP, although there was no statistical significance for CRSwNP. These findings provide strong support that all regions of the upper airway, including the middle ear and Waldeyer's ring, share an environmental milieu with common pathogens, innate immunity, and mechanisms of inflammation.(18)

In the GHS study, allergic rhinitis (AR) was specifically found to have a large and significant association with the subsequent diagnosis of both forms of CRS. While there are physiologic responses in the paranasal sinuses following nasal allergen challenge (19, 20) and similarities between the immunohistologic characteristics of CRS, particularly CRSwNP, and classic atopic diseases (eosinophilic infiltrates of affected tissues, increased Th2 inflammatory markers such as IL-5, and IL-13), elevated IgE and atopic sensitization is not universal in CRS.(21, 22) Furthermore, given the symptomatic overlap between AR and CRS, some degree of misclassification can be expected and may partially explain the association. The prevalence of atopic sensitization among CRS subjects in tertiary care has been variably reported between 30–80% (vs 30–55% in the general population(23, 24)) but significant differences are likely to exist in the threshold for atopic testing, the means of determining atopy and the composition of the aeroallergen panel used to test patients in these various retrospective studies. In a previously published study, Tan and colleagues had

previously compared CRS subjects who had failed medical therapy and were undergoing surgery to controls with symptoms of chronic rhinitis being evaluated for atopy.(25) They found high rates of sensitization to one or more aeroallergens in all three populations (72–85%) but CRSwNP patients had higher rates of multiple sensitization. There were no specific allergens that were strongly associated with either CRS subtype. While numerous studies have found an association between allergic rhinitis and CRS (Table 1)(6, 26), studies that have examined the effect of atopy within CRS populations also do not find a correlation with clinical symptom or radiographic severity, radiographic correlation or need for surgical intervention.(27, 28) Thus, while a history of atopic sensitization is likely to be more common among patients with CRS, its longitudinal effect on CRS severity and treatment response rates remains unclear.

One inhaled environmental non-allergic exposure viewed as a risk factor for a variety of upper airway disorders, including CRS, is tobacco exposure. Tobacco exposure, as defined by active cigarette smoking or secondhand smoke (SHS) exposure, has been found to adversely increase in the incidence of CRS (Table 1). The Global Allergy and Asthma European Network determined that there is a strong association between CRS and active tobacco use (OR: 1.9, 95% CI: 1.8–2.1), and a positive, but smaller, susceptibility in former smokers (OR: 1.3, 95% CI: 1.2–1.4).(29) Similarly, in a separate study, SHS exposures at home, work, public places, and private social functions similarly independently increase the risk of CRS in a dose-dependent manner.(30) Extensive research on the pathophysiology of tobacco smoke in CRS suggests that smoke decreases the mucociliary clearance of sinonasal mucosa by altering ionic transport mechanisms along epithelial cells, impairing ciliogenesis, and suppressing sinonasal innate immunity.(31)

Diseases of the lower airway: link to the unified airway

In addition to the strong association of CRS with premorbid upper airway conditions, the GHS study also showed a pattern of episodic and chronic lower airway illnesses preceding the diagnosis of both CRS subtypes. Incident CRS was most strongly associated with asthma, however, a number of airway conditions less traditionally associated with CRS, including bronchitis, pneumonia, and obstructive sleep apnea, were also significantly more common in patients who developed CRS. These findings support to the notion of the unified airway and further suggest that acute episodic respiratory diseases can modify host susceptibility to CRS, perhaps similarly to the relationship between rhinovirus and respiratory syncytial virus infections and subsequent asthma development.(32, 33) Although much of that data comes from studies in asthmatic children, James et al (33) have proposed that the pathogenesis of asthma is related to a defective host immune response that enhances latent viral and bacterial colonization of the lower airway. There is evidence to suggest deficient epithelial cell function, mucus overproduction, decreased interferon responses, and impaired alveolar macrophage function are potential mechanisms that allow select pathogens to flourish within the unified airway.

Of the diseases of the lower airway, asthma has typically been the most strongly associated with co-morbid CRS, with a stronger association found in CRSwNP patients (Table 2). Asthma has traditionally been regarded as a comorbidity of CRS, given the strength of

positive association between asthma and CRS in both genders and across all ages. In a population-based study examining the prevalence of asthma in European adults, Jarvis et al (6) found an overall adjusted OR of 3.5 (95% CI: 3.2–3.8) when comparing subjects with CRS to those without. This figure increased to 11.9 (95% CI: 10.6–13.2) when the prevalence of among those with both asthma and AR. Other studies have shown 70–88% of asthmatic patients report sinonasal symptoms, with a significant concordance between the frequency and severity of CRS and the severity of coexistent asthma.(37, 38) Furthermore, there is an even stronger relationship between asthma and CRSwNP, as concurrent asthma has been observed to be the most significant factor in the presence of nasal polyposis in CRS patients.(28, 39, 40) While these studies did not specifically look at the temporal relationship between asthma and CRS, the findings are consistent with the associations between a diagnosis of asthma prior to incident CRS, as found in the GHS study.

Historically, CRSwNP, asthma, and aspirin sensitivity form a well-established association known as aspirin-exacerbated respiratory disease or Samter's triad. The onset of this disorder is specifically during adulthood, when urticaria, angioedema, and anaphylaxis may additionally manifest. Arising following exposure to aspirin, Samter's triad presumably results from the overproduction of cysteinyl leukotrienes and prostaglandin D₂, which are proinflammatory mediators of eosinophilic inflammation, and the downregulation of anti-inflammatory prostaglandin E₂.(14, 41) Batra et al recently conducted a tertiary care study of patients undergoing revisions surgery for CRS that highlights the strong association of aspirin sensitivity and asthma to refractory CRS, especially CRSwNP.(10) Asthma and aspirin sensitivity were more prevalent in CRSwNP patients at rates of 68.5% (OR: 7.5) and 28.3% (OR: 78.6), respectively, while 27.6% of CRSwNP patients demonstrated both asthma and aspirin sensitivity.

Gastroesophageal reflux disease: how does it affect the upper airway?

Gastroesophageal reflux disease (GERD) is suspected to play an active role in the development and maintenance of various diseases of the upper and lower airway, including chronic cough,(42) asthma,(43) and otitis media with effusion, especially in young children.(44) The proposed pathophysiology involved with these associations centers around the retrograde flow of gastric contents or its aerosolized form into various sites in the airway, resulting in direct mucosal injury with subsequent inflammation. In the GHS study, pre-morbid GERD showed modest but highly significant associations with both forms of CRS (Table 2). DelGaudio and colleagues reported significant associations in a tertiary care population with refractory CRS, finding that patients with persistent CRS after endoscopic sinus surgery (ESS) had more reflux at the nasopharynx, upper esophageal sphincter, and distal esophagus than controls. (34) Separately, the European Community Respiratory Health Study (ECRHS), a multinational longitudinal study, has suggested that GERD, particularly the nocturnal subtype, is strongly associated with the development of lower respiratory tract diseases, such as asthma, but has not specifically examined its effect on rhinosinusitis.(45)

Despite the established association between GERD and CRS (42–44), current literature lacks evidence to support direct causation. Only the GHS study looked at the temporal

relationship between GERD and asthma. In addition, various studies have failed to consistently show the presence of pH changes or pepsinogen within the nasopharynx or nasal cavity to stimulate the inflammatory responses of CRS.(35, 46) Future research should evaluate the association of GERD with eosinophilic esophagitis, which has histologic, and possibly etiologic, parallels to CRS.

Associations with epithelial conditions outside the airway: potential evidence to the barrier defect

The GHS study was also the first in the literature to show a modest but significant association of CRS with various infectious and inflammatory conditions at epithelial sites outside the airway, in particular, atopic dermatitis, conjunctivitis, skin and soft tissue infections, and urinary tract infections were more common in patients with CRSsNP. While underpowered to examine the associations with rare conditions, the GHS study also demonstrated a weak but non-significant association between inflammatory bowel disease (IBD) and the eventual development of CRS. Consistent with these results, Chandra et al reported a significantly higher prevalence of CRSwNP in patients with atopic dermatitis and IBD, as compared to a reference group of patients with hypertension. Book and colleagues also studied the associations between IBD and CRS, using patient reported symptoms to define CRS, rather than ICD-9 codes from an EHR as used in the GHS study and Chandra et al's study.(36) Book's team reported that CRS symptoms were prevalent in approximately 50% of IBD patients.(47) Although additional studies are needed to better clarify and characterize the relative strength of association between CRS and these epithelial conditions, these potentially premorbid associations highlights the impaired host epithelial barrier as the unifying pathophysiologic mechanism behind these disorders at epithelial sites within and beyond the aerodigestive airway. Thus, the epithelial integrity of the sinonasal mucosa, skin, and gastrointestinal lining may be affected by variations in the expression patterns of epithelial barrier proteins that separate the host from its external environment.(48)

Inflammatory and autoimmune diseases: associations limited by rarity

Recent findings show that local immune responses in CRSwNP seem to generate autoreactive class switched antibodies.(49, 50) Various case series in the literature have demonstrated conflicting data regarding possible associations of CRS with autoimmune disorders.(51) In a retrospective case-control study, Chandra et al (36) found that the prevalence of CRS in patients with multiple sclerosis, psoriasis, lupus, rheumatoid arthritis, and ankylosing spondylitis did not differ significantly from control patients with hypertension. However, the GHS study revealed potentially strong associations between CRS and premorbid autoimmune conditions, including systemic lupus erythematosus, but these associations were not statistically significant using the strict ($P < 0.0005$) threshold used to determine significance. Overall, the relative infrequency of autoimmune disorders suggests that larger epidemiologic studies are needed to more carefully examine these associations.

Psychiatric conditions: Effects on perceived symptom reporting

Prior studies applying the self-reported hospital anxiety and depression score (HADS) to tertiary care populations (6) have suggested that psychiatric comorbidities, primarily anxiety and depression, are prevalent in CRS patients: 25.9% of patients who seek evaluation for CRS reportedly have high levels of anxiety, while 14.7% of these patients also report high levels of depression. In evaluating the role of anxiety and depression as potential premorbid risk factors, the GHS study found a strong and significant association between anxiety, but not depression, and the subsequent diagnosis of CRS. Separating the individual contributions of CRS symptoms and comorbid psychiatric effects can be difficult due to the overlapping effects imparted by both diseases on quality of life. Since the diagnosis of CRS is based upon both subjective reporting on sinonasal symptoms and objective measures focused on radiographic and endoscopic evidence of mucosal inflammation, the coexistence of anxiety may increase somatosensory amplification, thus increasing rates of CRS diagnosis and consequent treatment in anxious patients.(6, 52)

Associations with heart and vascular disease

The GHS study was the first study to look at associations between CRS and premorbid heart and vascular disease. None of the conditions evaluated (hypertension, heart failure) nor risk factors for these conditions (diabetes, obesity) were associated with incident CRS. Recently a few population-based case-control studies published using a national insurance database in Taiwan have demonstrated that patients with CRS are at a higher risk for cerebrovascular diseases (53), and myocardial infarctions (54, 55), post-CRS diagnosis. In these studies, CRS patients were more likely to have a diagnosis of ischemic stroke during a 5-year follow-up period (OR: 1.3 95% CI: 1.2–1.5) and myocardial infarction during a 3-year follow-up period (OR: 1.8; 95% CI: 1.4–2.4) when compared to a control group consisting of patients matched on sex, age, and urbanization level. Interestingly, in these studies, the authors found a highly significant baseline increase in the prevalence of cerebrovascular risk factors such as hypertension, obesity, diabetes mellitus and tobacco use among CRS patients compared with controls. Prior to these Taiwanese studies, the published literature including the GHS study, have not found strong associations between CRS and baseline hypertension or diabetes. This suggests that either an intrinsic race-specific genetic difference, the increased power of the Taiwanese studies, or the selection of a particularly healthy control population may account for these differences. Nonetheless, epidemiological studies provide a powerful means to ascertain the longitudinal post-morbid effects of a CRS diagnosis and additional longitudinal studies are needed to confirm whether there is a temporal relationship between CRS and heart and vascular diseases.

Other variables: insights in studying CRS epidemiology

Besides determining significant associations between CRS and premorbid medical conditions, the GHS study also provides valuable epidemiologic data that may continue to elucidate the pathophysiologic mechanism of CRS in the general population. The GHS study, for example, demonstrated the peak incidence of CRS among adults was between ages 45 and 54 years. Age-specific effect in CRS have been investigated by Cho et al (56),

who demonstrated an age related impairment in the epithelial barrier function, as measured by the expression of S100 protein levels. Conversely, eosinophilic inflammation appears to wane with age in the natural history of CRS. In the GHS study, we also found that sex also had an effect of CRS subtype with more females developing CRSsNP, while males were more likely to exhibit the CRSwNP phenotype. This tendency of CRS subtypes to favor a specific gender provides a basis for future research to determine possible hormone-specific effects on the pathogenesis and clinical manifestation of CRS.

Conclusions

The association of premorbid medical conditions with the subsequent diagnosis of adult CRS serves an important role in identifying potential at-risk patients that may allow for the development of future therapeutic and preventive interventions for CRS patients. The identification of pneumonias, tobacco exposure, and GERD as possible risk factors for the development of CRS, for example, provides strong support that the mucosal surfaces of the upper and lower airways share common pathogens and mechanisms of inflammation and innate immunity. Epidemiologic studies also provide quantitative evidence for the strength with which conditions long associated with CRS, such as asthma, affect CRS risk. Improvements in study design and prospective longitudinal studies involving the general population will be required in order to use epidemiologic studies to ascertain disease causality.

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Key points

- Chronic and episodic upper airway disorders, lower airway disorders, GERD, conditions of epithelial tissues, autoimmune and inflammatory diseases, and psychiatric disorders have recently been associated with an eventual diagnosis of CRS.
- There are only a precious few general population based epidemiologic studies regarding CRS and these studies may better represent CRS in the real world.
- Of the various conditions, asthma, which may present with or without aspirin sensitivity, has the strongest associations with a subsequent diagnosis of both CRSsNP and CRSwNP, particularly CRSwNP.
- The predisposing patterns of associated illnesses may provide valuable information regarding the underlying causes of CRS and allow for both therapeutic and preventive interventions.

General population studies

Figure 1.

Diagram illustrating the importance of carrying out general population-based studies of chronic sinusitis. In this model, the extensive literature from tertiary care-based CRS populations may capture the full spectrum of disease resulting in a skewed perspective of disease.

Table 1

Representative studies highlighting the associations of CRS with corresponding premorbid and comorbid conditions of the upper airway

Condition/Study (Ref)	Design	Criteria for CRS diagnosis	Criteria for comorbidity diagnosis	Relevant results OR (95%CI) if available	Comments
<i>Allergic rhinitis (AR)</i>					
Tan et al, 2013 (17)	Case-control retrospective	Provider coded ICD-9	Provider coded ICD-9	aOR(95%CI) for AR CRSsNP vs control: 2.4(2.2–2.5); CRSsNP vs control: 2.6(2.2–3.1)	<ul style="list-style-type: none"> Based on a US primary care population (n=446,480) Premorbid association with incident CRS
Batra et al, 2013 (10)	Cross-sectional retrospective	Symptoms and objective measures (guidelines)	Skin-prick or in vitro testing	aOR(95%CI) for AR CRSsNP vs CRSsNP: 3.6(2.0–6.5)	<ul style="list-style-type: none"> US tertiary care population undergoing revision sinus surgery (n=225) Comorbid association with CRS
Jarvis et al, 2012 (6)	Cross-sectional prospective	Symptoms and history	Self reported symptoms	aOR(95%CI) for AR CRS vs non CRS: 5.7(5.3–6.2)	<ul style="list-style-type: none"> European general population based on survey responses (n=53,185) Demonstrated comorbid association with prevalent CRS
Min et al, 1996 (26)	Cross-sectional prospective	Symptoms and physical examination performed by otolaryngologists	Patient-reported symptoms	aOR(95%CI) for AR CRSvsnon-CRS: 10.73(5.22–22.06)	<ul style="list-style-type: none"> Korean general population (n=9,069) Demonstrated comorbid association with prevalent CRS
<i>Tobacco exposure</i>					
Tan et al, 2013 (17)	Case-control retrospective	Provider coded ICD-9	Provider coded ICD-9	aOR(95%CI) for tobacco CRSsNP vs control: 1.3(1.1–1.6); CRSsNP vs control: 1.2(0.8–1.9)	<ul style="list-style-type: none"> Based on a US primary care population (n=446,480) Lacked statistical significance in demonstrating premorbid association with incident CRS
Hastan et al, 2011 (27)	Cross-sectional prospective	Subject-reported symptoms	Subject response	aOR(95%CI) for tobacco CRS vs non-CRS in current smokers: 1.9(1.8–2.1) former smokers: 1.3(1.2–1.4)	<ul style="list-style-type: none"> European general population based on survey responses (n=57,128)

Condition/Study (Ref)	Design	Criteria for CRS diagnosis	Criteria for comorbidity diagnosis	Relevant results OR (95% CI) if available	Comments
Jarvis et al, 2012 (6)	Cross-sectional prospective	Patient-reported symptoms	Subject response	aOR (95% CI) for tobacco CRS vs non-CRS for current smokers: 1.0(0.9–1.2); former smokers: 1.2(1.1–1.3)	<ul style="list-style-type: none">• Demonstrated comorbid association with prevalent CRS• European general population based on survey responses (n=53,185)• Lacked statistical significance in demonstrating association with prevalent CRS
Tammemagi et al, 2010 (28)	Case-control retrospective	ICD-9 with confirmation by CT or nasal endoscopy	Patient response	OR (95% CI) for tobacco CRS vs non-CRS: Secondhand smoke: 2.2(1.5–3.2)	<ul style="list-style-type: none">• CRS patients from a specially clinic and controls from primary care (n=612)• Demonstrated <i>premorbid</i> association with incident CRS• Workplace exposure had the highest aOR and there was a dose response relationship between SHS exposure and CRS

Table 2

Representative studies highlighting the associations of CRS with corresponding premorbid and comorbid conditions outside the upper airway

Condition/Study (Ref)	Design	Criteria for CRS diagnosis	Criteria for comorbidity diagnosis	Relevant results OR (95%CI) if available	Comments
Asthma					
Tan et al, 2013 (17)	Case-control retrospective	Provider coded ICD-9	Provider coded ICD-9	aOR (95% CI) for asthma CRSsNP vs control: 1.7(1.6–1.9) CRSwNP vs control: 2.8(2.3–3.5)	<ul style="list-style-type: none"> Based on a US primary care population (n=446,480) Premorbid association with incident CRS
Batra et al, 2013 (10)	Retrospective cross-section	Symptoms and objective measures of inflammation	Clinical evaluation by allergist or pulmonologist	aOR for asthma CRSwNP vs CRSsNP: 7.5(4.1–13.8)	<ul style="list-style-type: none"> US tertiary care population consisting of patients requiring revision sinus surgery from specialty clinic (n=225) Demonstrated comorbid association with prevalent CRS
Jarvis et al, 2012 (6)	Cross-sectional prospective	Patient-reported symptoms	Patient-reported symptoms	aOR for asthma CRSvsnon-CRS: 2.71(2.30–3.20) for asthma AND AR CRS vs non-CRS 11.9 (10.6–13.2)	<ul style="list-style-type: none"> European general population based on survey responses (n=53,185) Demonstrated comorbid association with prevalent CRS
Kim et al, 2011(26)	Cross-sectional prospective	Symptoms and physical examination performed by clinicians	Symptoms and physical examination performed by clinicians	aOR(95%CI) for asthma CRSvsnon-CRS: 1.9(0.8–4.6)	<ul style="list-style-type: none"> Korean general population (n=4,098) Findings did not reach statistical significance
GERD					
Tan et al, 2013 (17)	Case-control retrospective	Provider coded ICD-9	Provider coded ICD-9	aOR(95%CI) for GERD CRSsNP vs control: 1.7(1.6–1.8); CRSwNP vs control: 1.5(1.2–1.8)	<ul style="list-style-type: none"> Based on a US primary care population (n=446,480) Demonstrated significant premorbid association with incident CRSsNP
DeGaudio, 2005 (34)	Case-control prospective	Clinical history of prior sinus surgery with persistence of symptoms and objective findings on endoscopy	24-hour pH measurement via probe in nasopharynx, upper esophageal sphincter and distal esophagus	Prevalence of GERD was 66% in refractory CRS vs 31 % in control. There was also a statistically significant increase in prevalence in the nasopharynx	<ul style="list-style-type: none"> US tertiary care population consisting of patients with refractory CRS despite sinus surgery (n=38), patients with CRS relieved with sinus

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aOR = adjusted odds ratio; 95%CI = 95% confidence interval