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Risk Factors For Chronic Rhinosinusitis

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Abstract

Purpose of review—To review the recent literature on risk factors for chronic rhinosinusitis (CRS) with an emphasis on genetic, comorbid diseases and environmental factors associated with CRS. Through identifying potential risk factors for CRS, we glean insights into the underlying pathogenic mechanisms and essential for developing effective therapeutic strategies.

Recent findings—Recent findings demonstrate that genetics, comorbid medical conditions including airway diseases, gastroesophageal reflux disease, inflammatory and autoimmune diseases and various demographic and environmental factors are associated with having a CRS diagnosis. Limitations of current studies include, variable application of disease definitions, lack of prospective longitudinal studies and a disproportionate focus on tertiary care populations.

Summary—CRS has a broad spectrum of associations ranging from genetics to comorbid diseases and environmental factors. These predisposing factors provide valuable information for possible designing therapeutic and preventive interventions. However, to better understand whether these associations cause CRS, further studies are needed to independently replicate findings, establish temporal relationships between exposure and disease onset, evaluate the influence of exposure dose on disease severity, and to understand the biological effects of these risk factors in the context of CRS.

Keywords

Sinusitis; Comorbidity; Risk factors; Epidemiology; Genetics; Environment

Introduction

Chronic rhinosinusitis (CRS) is defined as symptomatic inflammation of the sinonasal mucosa that persists for at least 12 weeks is one of the most common chronic diseases of adults in the United States.[1–3] CRS is typically classified clinically into two distinguishable phenotypes: chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP). CRS is estimated to affect about 13% of the population in the United States[4] and 10.9% of the population in Europe with an incidence of 1.13 per 100 person-years.[5, 6**] Patients with CRS suffer from significantly

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impaired quality of life including decreased health utility, emotional distress, and decreased physical and social activity with disease-specific expenditures totaling approximately \$6 billion annually.[7–11]

Although the pathogenesis of CRS has been under active investigations, the etiology of CRS still remains controversial.[12] CRSsNP has traditionally been considered a consequence of bacterial infection similar to acute rhinosinusitis, whereas CRSwNP is most frequently characterized by Type 2 inflammation in Western populations. Other potential risk factors for both forms of CRS have included anatomical obstruction of the osteomeatal complex, impaired mucociliary clearance, osteitis, microbes, biofilms, superantigen effects, immune dysfunctions, impaired epithelial defense, genetic factors, and environmental exposures such as inhaled allergens and irritants (Fig. 1).[1, 13–15]

Given the significant health and economic impact, and lack of widely accepted representative animal models to study CRS mechanistically, understanding risk factors for CRS might provide insights into the underlying pathogenic mechanisms and may facilitate preventive interventions that mitigate risk factors to reduce progression to CRS. This review will briefly summarize the recent literature with an emphasis on genetic factors, comorbid conditions and environmental factors associated with adult CRS.

Genetics associated with CRS

While specific monogenic disorders including cystic fibrosis, primary immunodeficiencies and primary ciliary dyskinesia (Kartagener's syndrome) are associated with a high prevalence of CRS, their contribution to overall prevalence is low.[16, 17] Recently, Hsu *et al.* performed a comprehensive and current review of the literature examining the genetics of CRS- in this section we will briefly summarize her major findings and highlight pertinent emerging literature published in the interim.[18**] As pointed out in her excellent review, interpretation of genetic studies in CRS has been limited by the resolution to which CRS patients were phenotyped, over-representation of CRS patients undergoing sinus surgery, sparse replication studies, differences in study design, and inadequate accounting for linkage disequilibrium and multiple testing. Nonetheless, genes found to significantly associate with CRS can broadly be categorized into genes involved with ion channels (eg, *CFTR*); genes encoding human leukocyte antigens (eg, *HLA-A*, *-B*, *-C*, *-DR* and *-DQ*); genes involved in innate immunity (eg, *CD14*, *IRAK4*, *LFT*, *MET*, *NOS1*, *NOS1AP*, *NOS2A*, *SERPINA1* and *TLR2*); genes involved in Type 2 inflammation (eg, *IL1RL1*, *IL4*, *IL13* and *IL33*); genes involved in inflammation (eg, *IDO1*, *IL1A*, *IL1B*, *IL1R2*, *IL1RN*, *IL6*, *IL22RA1*, *LTA*, *TNF* and *TNFAIP3*); genes involved in tissue remodeling (eg, *MMP9*, *POSTN* and *TGFB1*); genes involved in arachidonic acid metabolism (eg, *LTC4S*, *PTGDR* and *PTGS2*), and other genes significantly associated with CRS (eg, *ADRB2*, *AOAH*, *CACNA11*, *DCBLD2*, *EMID2*, *GSTT1*, *KIAA1456*, *LAMA2*, *LAMB1*, *MSRA*, *MUSK*, *NAV3*, *PARS2*, *PTGS2*, *RYBP*, *TP73* and *TRIP12*). In Table 1 [19–38], we highlight genes, which showed association with specific phenotype of CRS or high odds ratio in paper from Hsu *et al.* In most of these studies, CRSwNP patients served as cases and candidate gene approaches were used although several studies demonstrate that genes including *CFTR*, *IL1RL1* and *AOAH* associate with CRSsNP.[18**–38] Until recently, outside of *CFTR*, there were no

replication studies validating these prior findings and no mechanistic studies demonstrating their biological relevance.

Recently, Henmyr *et al.* conducted a study of single nucleotide polymorphisms (SNP) associations of 613 patients with CRS compared against a publically available, though racially unmatched, control population comprised of 1588 participants.[39*] They found significant ($P < .05$) associations between genetic variations in only 7 genes (eg, *PARS2*, *TGFB1*, *NOS1*, *NOS1AP*, *IL22RA1*, *DCBLD2* and *ALOX5AP*) of the 53 SNPs previously associated with CRS status.[39*] Of these, only the association between the rs2873551 SNP in *PARS2* gene was significant after a Bonferroni correction. *PARS2* is a mitochondrial prolyl t-RNA synthase for which limited research exists- further validation of these genetic association studies and research on the function of *PARS2* gene may shed light on reasons for its association with CRS. In analysis comparing CRSwNP against the CRSsNP patient populations, the authors also found the rs4504543 SNP in the acyloxyacyl hydrolase (*AOAH*) gene with the CRSwNP phenotype ($P = .022$). This SNP had previously been associated with CRS in a pooling-based genomewide association study (pGWAS) and replicated in a Chinese population with CRS.[36, 40]

Another emerging line of research suggests that polymorphisms in the bitter taste receptor T2R38 gene (*TAS2R38* gene) may also be associated with CRS status. In human sinonasal epithelial cells, microbial secretions activate the T2R38 receptor that regulates calcium-flux dependent NO production, stimulates mucociliary clearance and increases direct antibacterial effects. The activity of these innate responses is dependent on three common polymorphisms and the polymorphisms segregate together to form two common haplotypes of the *TAS2R38* gene.[41] The functional PAV haplotype combines with the non-functional AVI haplotype to generate three genotypes- PAV/PAV, PAV/AVI and AVI/AVI with the AVI/AVI genotype showing significantly impaired pseudomonas aeruginosa killing *in vitro* cultured epithelial cells. More recently, Adappa *et al.* examined the relative frequency of the AVI/AVI genotype and PAV/PAV genotypes in medically recalcitrant CRS patients compared to a geographically matched control population and found a significantly higher rate of AVI/AVI genotype patients among the medically recalcitrant CRS group ($P = .0383$) suggesting that the PAV/PAV genotype may decrease CRS risk.[42] Separately, Mfunu Endam *et al.* used a pGWAS and demonstrated SNPs associated with the *TAS2R38* gene were found at a higher frequency in the CRS population compared to controls although statistics and odds ratios were not reported.[43] In other lines of research, Purkey *et al.* examined the association between selected potassium channels and CRS status in a study comparing 828 children with CRS against 5083 controls and found that two epithelial potassium channels *KCNMA1* and *KCNQ5* were associated with CRS status in Caucasian and African American children respectively.[44] This line of research, together with the *TAS2R38* findings, and known associations with *CFTR* suggest that genes regulating ion flux in epithelial cells may confer significant genetic predisposition to CRS.

Comorbid diseases and conditions associated with CRS

In addition to genes specifically associated with CRS, it has been recognized that CRS is associated with specific comorbid medical conditions that directly affect the airway. Other

studies also suggest gastroesophageal reflux disease (GERD) and autoimmune/inflammatory diseases, and various demographic factors may similarly be associated with having CRS. These factors have been recently reviewed by Lam *et al.* in a recently published review article but are further summarized in our discussion and in Table 2.[5, 6**, 45**, 46, 47**, 48]

Airway diseases

Tan *et al.* recently published the findings of a nonspecialty care-based, population representative, case-control study using the electronic health records of the Geisinger Health System (referred to subsequently as the GHS study).[6**] They compared the premorbid conditions of patients during a period 0–24 months prior to a new diagnosis of CRS with those of a control group matched on age, sex and incident encounter.[6**] This study was able to reveal patterns of care and diagnosis prior to receiving a CRS diagnosis and contrasts from prior studies that have used specialty care populations with more treatment refractory severe disease, or have used only assessments without information regarding the temporal relationships of diagnosis. In this study, allergic rhinitis (AR) was specifically found to have a significant association with CRS [[adjusted odds ratio (aOR)= 2.4 and 2.6 for CRSsNP and CRSwNP respectively]. Although high (30–80%) rates of atopic sensitization among CRS patients have long been reported, few studies have compared these results against those of the general population even though rates of atopic sensitization in the general population have been reported as high as 40–55%.[49, 50] Furthermore, there are significant differences in the threshold for atopic testing among the various published studies of atopy amongst CRS patients. In our own studies, we found higher rates of multiple sensitization among tested patients with CRSwNP compared with a control population of patients with rhinitis symptoms.[51] Other larger population-based studies have found strong associations between AR and comorbid CRS although the timing of the AR diagnosis relative to CRS onset was not elucidated (Table 2).[5, 46] In the study by Kim *et al.*, the aOR of having CRS among patients with moderate-severe persistent AR was 8.2 when compared to mild intermittent AR. One limitation of epidemiologic studies of AR and CRS is that the symptoms of these two conditions overlap substantially and may be difficult to differentiate using a questionnaire. Despite these associations, other studies do not find that AR status affects management of CRS, need for surgical intervention or correlations with clinical symptom or radiographic severity.[52–54] Thus, while a history of atopic sensitization is more common among patients with CRS, its effect on CRS severity and treatment response rates remains unclear.

Similar to AR, asthma is strongly associated with CRS status, especially CRSwNP (Table 2). In the GHS study, the aOR of having an asthma diagnosis preceding the incident CRSwNP diagnosis was 2.8 and 1.7 for CRSsNP compared to control patients without an incident CRS diagnosis and was further increased to 4.4 and 2.5 respectively in the 6-months prior to the CRS diagnosis. In the population-based Global Allergy and Asthma European Network (GA²LEN) study of European adults, Jarvis *et al.* revealed an overall aOR of 3.5 (95% CI: 3.2–3.8) when comparing subjects with CRS to those without. This association increased further to 11.9 (95% CI: 10.6–13.2) among those adults with both asthma and AR.[5] Chung *et al.*, using Taiwan's Longitudinal Health Insurance Database

2000 (LHID2000), recently reported that of the 38 chronic conditions evaluated, asthma (aOR=3.1, 95% CI: 2.8–3.4) had the strongest with CRS when compared to control patients without CRS.[47*] However, unlike AR, studies do demonstrate that asthma severity may correlate with radiographic CRS severity and that the frequency and severity of CRS affects the severity of coexistent asthma.[55, 56] In some patients, CRSwNP, asthma and aspirin sensitivity form a well-established association known as aspirin-exacerbated respiratory disease (AERD) or Samter's triad. Following exposure to aspirin, patients with AERD presumably overproduce cysteinyl leukotrienes and prostaglandin D₂ that are mediators of eosinophilic inflammation and downregulate anti-inflammatory prostaglandin E₂. [17, 57]

In addition to asthma and AR, the GHS study also revealed a pattern of episodic and chronic lower airway illnesses preceding the diagnosis of CRS and supported to the hypothesis of the unified airway. Interestingly, premorbid bronchitis and pneumonia were significantly more common in patients who developed CRS. These findings suggest that acute episodic respiratory diseases may modify host susceptibility to CRS, perhaps similarly to the relationship between rhinovirus (RV) and respiratory syncytial virus infections and subsequent asthma development.[58, 59] These findings have also been supported by the more recently published study utilizing the insurance claims-based LHID2000 dataset in which "chronic pulmonary disease" was the second most strongly associated condition, after asthma, with Otolaryngologist diagnosed CRS (aOR = 3.0, 95% CI: 2.8–3.3).[47*]

Gastroesophageal reflux disease and other Gastrointestinal diseases

GERD is known to play some roles in various diseases of the upper and lower airway diseases such as chronic cough,[60] asthma[56] and otitis media with effusion, especially in young children.[61] There is some evidence to suggest an association between GERD and CRS.[48, 61–64] For example, the GHS study showed modest, but significant, relationship between GERD and CRS. The European Community Respiratory Health Study (ECRHS), a multinational longitudinal study, has similarly 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.[65] Others have suggested that omeprazole-responsiveness of sinusitis symptoms was indicative of a role for GERD in CRS pathogenesis.[66] However, intriguing research from the eosinophilic esophagitis literature suggests that omeprazole may have anti-inflammatory independent of its effects on suppressing acid production in gastric parietal cells.[67] It should be noted that eosinophilic esophagitis shares histologic, and immunopathologic, parallels to CRSwNP.

Inflammatory and autoimmune diseases

Other premorbid diseases associations with CRS include inflammatory and autoimmune diseases.[47*, 68–70] In the GHS study, the association between lupus and CRS had an aOR of 3.6 although this was not statistically significant at the stringent $P < .0005$ level used in the study. These associations are remarkable given recent findings that local immune responses in CRSwNP seem to generate autoantibodies, particularly against nuclear and epithelial antigens.[71, 72] In a more recently published paper using the LHID2000 database

from Taiwan, the investigators found significant comorbid associations between a rheumatoid arthritis diagnosis (aOR=1.85, 95% CI: 1.63–2.1) and CRS although the association between lupus and CRS was not statistically significant due to the relative rarity of lupus in the Taiwanese population.

Other comorbidities and demographic factors

Comorbid psychiatric conditions like anxiety and depression may increase rates of CRS diagnosis and health care utilization associated with CRS.[6**, 47*, 73, 74] Another condition strongly associated with CRS includes headache disorders like migraine potentially due to the overlapping symptoms and symptom vocabulary of chronic migraine and CRS.[47*, 75] In both the LHID2000 study and the GHS study, the strength of co/pre-morbid associations between CRS and headache diagnoses was moderate with aOR between 2.0 and 2.3. However, other lines of research suggest that while migraine affects CRS risk, it does not affect symptomatic improvement following treatment for CRS.[76]

Besides comorbid disease, epidemiologic studies demonstrate underlying demographic factors that are associated with CRS. These studies demonstrated that the peak incidence of CRS among adults was between ages 45 and 54 years [6**] while others subsequently demonstrate that peak prevalence is between 50–59[77]. Sex also had an effect of CRS phenotype with more females developing CRSsNP, while males were more likely to exhibit the CRSwNP. The age of onset and gender predisposition for CRS phenotypes may provide a basis for future research to determine possible hormone or aging-specific effects on the pathogenesis of CRS.

Environmental factors associated with CRS

Environmental factors are known to have significant effects in the pathogenesis of various airway diseases as best illustrated in studies on asthma, tobacco exposure and hypersensitivity pneumonitis. Since airway diseases are unified by the responses of airway epithelial cells and exposure to inhaled pollutants, allergens, irritants and toxins, it is tempting to speculate that many of the environmental exposures linked to lower airway disease will be of relevance to CRS (Table 3).

Tobacco exposure

Tobacco exposure is one of the best studied risk factors for various airway diseases, including CRS. There is some evidence that active cigarette smoking is more prevalent among patients with CRS.[78, 79**, 80]. The GA²LEN determined that there is a strong association between CRS and active tobacco use (aOR=1.9, 95% CI: 1.8–2.1), with a significant, but smaller, association of CRS with former smokers (aOR=1.3, 95% CI: 1.2–1.4).[78] In the subset of GA²LEN patients from Denmark, Thilsing *et al.* revealed that smoking status (non-, former-, or current smoker) significantly affected the CRS prevalence ($P = .000$) while current smoking associated with an increased CRS prevalence in women [relative risk (RR)=2.5], as well as men (RR=1.9), compared to nonsmokers.[79] Separately, analysis of the third National Health and Nutrition Examination Survey (NHANES III) study found more modest associations between self-reported sinusitis and active smokers.

Even at the highest exposure to more than 40 cigarettes per day, the adjusted RR for CRS was only ~1.20.[81] Neither of these studies, however, specifically separated associations for CRSsNP and CRSwNP. The few studies examining the relationship between second hand smoke exposure or environmental tobacco smoke (ETS) and adult CRS have produced conflicting results, while studies of CRS in children have demonstrated a consistent association between ETS and CRS among children who have had sinus surgery.[80–83] Studies examining the pathophysiologic effects of tobacco smoke on sinonasal mucosa suggest the reported associations are biologically plausible given findings that smoke decreases the mucociliary clearance of sinonasal mucosa by altering ionic transport mechanisms, impairs ciliogenesis, and suppresses innate immunity through alterations in toll-like receptors (TLRs), effector proteins (eg, β -defensins) and complement components.[84, 85]

Outdoor and indoor air quality

While patients and the lay media frequently ascribe sinusitis to air quality, there are surprisingly few previous studies that examine the relationship between air pollution and sinusitis and fewer yet that use the commonly accepted diagnostic criteria for CRS. Min *et al.*, in the first epidemiologic survey to determine CRS prevalence in South Korea, found no difference between rural and urban areas with regard to the prevalence of CRS.[86] Wolf analyzed the addresses of 1435 patients who sought treatment for CRS in a tertiary care hospital in Cologne, Germany and correlated this against outdoor air quality measures that were collected through a program monitoring air quality in the Rhine and Ruhr area with 1km² resolution.[87] It was found that when air pollution levels were correlated against CRS patient rates, no correlation was found, but if analysis was done only in the districts with above average air pollution levels, a weak (adjusted R²=0.3), but significant, positive correlation was found between air pollution levels and CRS case rates.[87] The author acknowledged that only SO₂, NO₂ and total suspended particulate matter were analyzed, only a convenience sample of patients was used, no information on individual outdoor exposure was collected, and there was no attempt to correlate air pollution levels with disease severity. Another study by Bhattacharyya correlated national rates of self-reported sinusitis in the United States with average national ambient SO₂, NO₂, CO and particulate matter and found significant, but weak, correlations in the prevalence of sinusitis with all air pollution parameters despite the lack of geographic resolution.[88] Asian sand dust (ASD), originating in the arid deserts of Mongolia and China brings large amounts of windborne soil particles to countries in the Asia-Pacific area has been associated with inducing respiratory illness in recent years.[89] ASD and spreads over large areas of several countries, especially Korea, Japan and China. To our knowledge, while no direct studies have examined the effects of ASD exposure and CRS status but Yeo *et al.* showed that ASD directly increased RV replication and aggravated RV-induced inflammation in human nasal epithelial cells by enhancing IFN- γ , IL-1 β , IL-6, and IL-8 secretion providing a possible mechanism by which dust exposure, nasal microbiology and the immunologic barrier may be intertwined.[90]

In addition to outdoor air pollution, the effects of indoor air pollutions on respiratory disease can be substantial- in fact, studies suggest that indoor pollutant levels are substantially

higher than outdoor pollutant levels and further, do not intercorrelate. Studies in asthma suggest that indoor endotoxin; allergen exposure to mouse, cockroach, pets, dust mite and mold; as well as indoor pollutants such as particulate matter and NO₂ levels have been significantly effects on asthma morbidity.[91] Similarly, some volatile organic compounds (eg, formaldehyde, benzene, toluene and chlorobenzene) which are irritants and indoor sources (eg, solvents, floor adhesive, paint, cleaning products, furnishings, polishes and room fresheners) effects on development of asthma.[92, 93] To our knowledge, there has been only one study focused on indoor environments and nasal polyps. Kim and Hanley reported an association between the use of woodstoves as a principal source of heat and nasal polyposis.[94] No study has examined the association between indoor pollutants and CRS without polyps, outside of occupational exposure studies.

Airborne particles and vapors in the occupational environment may play an important role in CRS risk, although studies of these exposures have used definitions that make it difficult to differentiate between CRS and conditions with similar symptoms, such as occupational rhinitis.[95] Thisling *et al.*, using the symptom-based definition of CRS, found that working in a blue collar job significantly increased the CRS prevalence in women but conversely, adjusted risk was significantly lower among male blue collar compared to male white collar workers.[79] Additionally, workplace exposure to “gases, fumes, dust, or smoke” increased the crude risk of CRS, although adjusted RR did not reach statistical significance.[79] Further analysis of 14 specific exposures found that only working with “fish or shellfish” was significantly associated with CRS status.[79] Other lines of work examining occupational rhinitis have also found significant associations between low-molecular weight agent exposure, persulfate salts, latex and animal exposure and rhinosinusitis symptoms in specific occupations. However, none of these studies utilized the symptomatic and duration dependent definition of CRS, without requiring objective evidence of inflammation, and thus, extrapolating these findings to CRS is difficult. [96–100]

Conclusions

Risk factors associated with CRS include genetic and comorbid medical as well as environmental factors. From these insights, we glean insights into the pathophysiology of CRS and can conceptualize studies of novel therapeutic and preventive strategies to reduce the burden of CRS. However, most current study designs establish associations but causality and dose-response cannot yet be established. Improvements in study design, particularly interventional studies or longitudinal cohort studies, and biological validation studies may provide estimates of magnitude these risk factors have on disease severity and prevalence.

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Key points

- CRS is associated with a range of genetic factors, comorbid medical conditions and environmental factors.
- Identification of risk factors for CRS may provide valuable information regarding the underlying pathogenic mechanisms and developing effective therapeutic strategies and preventive interventions for CRS patients.
- As most of current studies of risk factors for CRS include small samples sizes drawn from tertiary care studies and lack of prospective longitudinal studies, general population-based epidemiologic studies are needed for better representation of risk factors for CRS.

Figure 1.
Risk factors for the development of CRS

Table 1

Genes significantly associated with CRS in prior studies

Study [Ref]	Gene	Chromosome	Location	Variation Surveyed	CRS Phenotype	Relevant Results OR (P value)	Involved Function
Pinto <i>et al.</i> 2008 [19]	<i>CFTR</i>	7q31	7q31	Multiple SNPs	CRSsNP	NA (.0023)	Chloride ion transport
Raman <i>et al.</i> 2002 [20]	<i>CFTR</i>	7q31	7q31	Multiple SNPs	CRS	3.5 (<.05)	Chloride ion transport
Keles <i>et al.</i> 2008 [21]	<i>HLA-C</i>	6p21	6p21	Multiple SNPs	CRSsNP	NA (<.05)	Encoding human leukocyte antigens
Takeuchi <i>et al.</i> 1999 [22]	<i>HLA-B</i>	6p21	6p21	Multiple SNPs (HLA-B*54)	CRS	3.23 (<.037)	Encoding human leukocyte antigens
Luxenberger <i>et al.</i> 2000 [23]	<i>HLA-A</i>	6p21	6p21	Multiple SNPs (HLA-A*74)	CRSsNP	71.3 (<.003)	Encoding human leukocyte antigens
Zhai <i>et al.</i> 2007 [24]	<i>HLA-DR</i>	6p21	6p21	HLA-DR*16	CRSsNP	8.9 (.03)	Encoding human leukocyte antigens
Schubert <i>et al.</i> 2004 [25]	<i>HLA-DQ</i>	6p21	6p21	HLA-DQB1*03	CRSsNP	4.25 (.001)	Encoding human leukocyte antigens
Monar-Gabor <i>et al.</i> 2000 [26]	<i>HLA-DR</i>	6p21	6p21	HLA-DR*7	CRSsNP	2.55 (<.05)	Encoding human leukocyte antigens
Fajardo-Dolci <i>et al.</i> 2006 [27]	<i>HLA-DQ</i>	6p21	6p21	HLA-DQA1*0201	CRSsNP	6.79 (.0027)	Encoding human leukocyte antigens
Pascual <i>et al.</i> 2008 [28]	<i>NOS2A</i>	17q11-q12	17q11-q12	Promoter VNTR	CRSsNP	14.39 (.001)	Innate immunity
Yazdani <i>et al.</i> 2012 [29]	<i>CD14</i>	5q31	5q31	rs2569190	CRSsNP	1.88 (.04)	Innate immunity
Erbek <i>et al.</i> 2007 [30]	<i>IL1A</i>	2q14	2q14	rs17561	CRSsNP	2.743 (<.001)	Inflammation
Batikhan <i>et al.</i> 2010 [31]	<i>TNF</i>	6q21	6q21	rs1800629	CRSsNP	3.68 (.016)	Inflammation
Zhang <i>et al.</i> 2011 [32]	<i>NOS1</i>	12q24	12q24	Multiple SNPs	CRS	Varied (.0023-.0129)	Innate immunity
Zhang <i>et al.</i> 2011 [32]	<i>NOS1AP</i>	1q23	1q23	rs4657164	CRS	1.67(.0178)	Innate immunity
Zielinska-Blizniewska <i>et al.</i> 2012 [33]	<i>POSTN</i>	13q13	13q13	-33C>G	CRSsNP	4.56 (<.001)	Tissue remodeling
Kim <i>et al.</i> 2007 [34]	<i>TGFB1</i>	19q13	19q13	rs1800469	CRSsNP	NA (.012)	Tissue remodeling
Benito <i>et al.</i> 2012 [35]	<i>PTGDR</i>	14q22	14q22	Diplotype	CRSsNP	2.44 (.043)	Arachidonic acid metabolism
Zhang <i>et al.</i> 2012 [36]	<i>AOAH</i>	7q14-p12	7q14-p12	rs4504543	CRSsNP	0.03 (<.0001)	Others
Ozcan <i>et al.</i> 2010 [37]	<i>GSTT1</i>	22q11	22q11	Homozygous deletion	CRSsNP	2.03 (.05)	Others
Bosse <i>et al.</i> 2009 [38]	<i>PARS2</i>	1p32	1p32	Rs2873551	CRS	0.49(.000026)	Others

CRS, chronic rhinosinusitis; OR, odds ratio; CRSsNP, chronic rhinosinusitis without nasal polyp; NA, not applicable; CRSwNP, chronic rhinosinusitis with nasal polyp

Table 2

Summary of selected studies on comorbid diseases associations with CRS status

Study [Ref]	Design	Criteria for CRS Diagnosis	Criteria for Comorbidity Diagnosis	Relevant Results aOR (95%CI)	Comments
Airway disease: Allergic Rhinitis					
Jarvis <i>et al.</i> 2012 [5]	Cross-sectional Prospective	Patient-reported symptoms	Patient-reported symptoms	CRS vs non-CRS: 5.7 (5.3–6.2)	European general population based on survey responses (n=53,185)
Tan <i>et al.</i> 2013 [6**]	Case-control Retrospective	ICD-9	ICD-9	CRSSNP vs control: 2.4 (1.6–1.9)* CRSwNP vs control: 2.8(2.3–3.5)*	Based on a US primary care population (n=446,480)
Kim <i>et al.</i> 2011 [46]	Cross-sectional Prospective	Symptoms and physical examination performed by clinicians	Patient-reported symptoms	CRS vs non-CRS: AR: 1.4 (0.9–2.2) Intermittent/moderate-severe AR: 1.6 (0.9–3.0) Persistent/mild AR: 2.6 (1.3–5.0)* Persistent/moderate-severe AR: 8.2 (4.7–14.4)*	Korean general population (n=4,098)
Airway disease: Asthma					
Jarvis <i>et al.</i> 2012 [5]	Cross-sectional Prospective	Patient-reported symptoms	Patient-reported symptoms	CRS vs non-CRS Asthma: 2.7 (2.3–3.2) Asthma & AR: 11.9 (10.6–13.2)	European general population based on survey responses (n=53,185)
Tan <i>et al.</i> 2013 [6**]	Case-control Retrospective	ICD-9	ICD-9	CRSSNP vs control: 1.7 (1.6–1.9)* CRSwNP vs control: 2.8 (2.3–3.5)*	Based on a US primary care population (n=446,480)
Kim <i>et al.</i> 2011 [46]	Cross-sectional Prospective	Symptoms and physical examination performed by clinicians	Patient-reported symptoms	CRS vs non-CRS: 1.9(0.8–4.6)	Korean general population (n=4,098)
Chung <i>et al.</i> 2014 [47*]	Cross-sectional Prospective	ICD-9 Diagnosed by certified otolaryngologist	Elixhauser Comorbidity Index	CRS vs non-CRS: 3.1(2.8–3.4)*	Taiwan's Longitudinal Health Insurance Database 2000 (LHID2000) (n=5,734)
GERD and other Gastrointestinal diseases					
Tan <i>et al.</i> 2013 [6**]	Case-control Retrospective	ICD-9	ICD-9	GERD CRSSNP vs control: 1.7 (1.6–1.8)* CRSwNP vs control: 1.5 (1.2–1.8)*	Based on a US primary care population (n=446,480)
Chung <i>et al.</i> 2014 [47*]	Cross-sectional Prospective	ICD-9 Diagnosed by certified otolaryngologist	Elixhauser Comorbidity Index	CRS vs non-CRS: Peptic ulcer: 1.9 (1.7–2.0)* Liver disease: 1.4 (1.3–1.6)*	Taiwan's Longitudinal Health Insurance Database 2000 (LHID2000) (n=5,734)

Study [Ref]	Design	Criteria for CRS Diagnosis	Criteria for Comorbidity Diagnosis	Relevant Results aOR (95%CI)	Comments
Wong <i>et al.</i> 2004 [48]	Cross-sectional Prospective	Symptoms and evaluation by rhinologist	24-hour pH measurement via probe in nasopharynx and hypopharynx	Of included CRS patients, 32.4% were diagnosed with GERD. Only 0.2% had reflux episodes recorded in the nasopharynx.	Australian tertiary care population consisting of patients with CRS (n=40)
Inflammatory and autoimmune disease					
Tan <i>et al.</i> 2013 [6**]	Case-control Retrospective	ICD-9	ICD-9	Rheumatoid arthritis CRSsNP vs control: 1.5 (1.1–2.0) CRSwNP vs control: 1.0 (0.5–2.2) Systemic lupus erythematosus CRSsNP vs control: 2.2 (1.1–4.3) CRSwNP vs control: 3.6 (1.0–12.8)	Based on a US primary care population (n=446,480)
Chung <i>et al.</i> 2014 [47*]	Cross-sectional prospective	ICD-9 Diagnosed by certified otolaryngologist	Elixhauser Comorbidity Index	CRS vs non-CRS: Rheumatoid arthritis 1.9 (1.6–2.1)* Systemic lupus erythematosus 1.5 (0.9–2.7) Ankylosing spondylitis 1.4 (1.1–1.8)*	Taiwan's Longitudinal Health Insurance Database 2000 (LHID2000) (n=5,734)
Psychiatric and neurologic disease					
Tan <i>et al.</i> 2013 [6**]	Case-control Retrospective	ICD-9	ICD-9	Anxiety CRSsNP vs control: 1.7 (1.5–2.0)* CRSwNP vs control: 1.7 (1.2–2.4) Depression CRSsNP vs control: 1.3 (1.1–1.5) CRSwNP vs control: 1.1 (0.8–1.6) Headache CRSsNP vs control: 1.8 (1.7–2.0)* CRSwNP vs control: 2.1 (1.7–2.6)	Based on a US primary care population (n=446,480)
Chung <i>et al.</i> 2014 [47*]	Cross-sectional Prospective	ICD-9 Diagnosed by certified otolaryngologist	Elixhauser Comorbidity Index	CRS vs non-CRS: Depression 2.0 (1.7–2.2)* Psychosis 1.4 (1.2–1.7)* Headaches 1.7 (1.6–1.8)* Migraines 2.3 (2.0–2.6)* Parkinson's disease 1.7 (1.3–2.3)*	Taiwan's Longitudinal Health Insurance Database 2000 (LHID2000) (n=5,734)

CRS, chronic rhinosinusitis; aOR, adjusted odds ratio; 95% CI, 95% confidence interval; CRSsNP, chronic rhinosinusitis without nasal polyp; CRSwNP, chronic rhinosinusitis with nasal polyp; AR, allergic rhinitis

* statistically significant

Table 3

Environmental factors significantly associated with CRS in prior studies

Study [Ref]	Design	Criteria for CRS Diagnosis	Criteria for Environmental Factors Exposure Confirmation	Relevant Results aOR (95%CI)	Comments
Tobacco					
Jarvis <i>et al.</i> 2012 [5]	Cross-sectional prospective	Patient-reported symptoms	Patient response	CRS vs non-CRS Current smoker: 1.0 (0.9–1.2) Former smoker: 1.2 (1.1–1.3)	European general population based on survey responses (n=53,185)
Tan <i>et al.</i> 2013 [6**]	Case-control Retrospective	ICD-9	ICD-9	CRSsNP vs control: 1.3 (1.1–1.6) CRSsNP vs control: 1.2 (0.8–1.9)	Based on a US primary care population (n=446,480)
Chen <i>et al.</i> 2003 [77]	Cross-sectional Prospective	Patient-reported symptoms	Patient response	CRS vs non-CRS <i>In male with allergy, without allergy</i> Current smoker: 0.8 (0.5–1.3), 1.7 (1.1–2.4) Former smoker: 0.7 (0.4–1.1), 1.0 (0.6–1.5) <i>In female with allergy, without allergy</i> Current smoker: 1.7 (1.2–2.4), 1.4 (1.0–2.0) Former smoker: 1.2 (0.9–1.6), 1.2 (0.9–1.7)	Canadian second cycle of National Population Health Survey (NPHS) (n=73,364)
Hastan <i>et al.</i> 2011 [78]	Cross-sectional Prospective	Patient-reported symptoms	Patient response	CRS vs non-CRS Current smoker: 1.7 (1.6–1.9)* Former smoker: 1.2 (1.0–1.3)	European general population based on survey responses (n=57,128)
Thilising <i>et al.</i> 2012 [79**]	Cross-sectional Prospective	Patient-reported symptoms	Patient response	CRS vs non-CRS (aRR, 95% CI) <i>In male</i> Current smoker: 1.9 (1.3–2.8)* Former smoker: 1.1 (0.7–1.8) <i>In female</i> Current smoker: 2.5 (1.7–3.7)* Former smoker: 1.6 (1.0–2.6)*	Part of a trans-European GA ² LEN (Global Asthma and Allergy European Network)-based study, Danish population (n=4,554)
Tammenaigi <i>et al.</i> 2010 [80]	Case-control retrospective	ICD-9 with confirmation by CT or nasal endoscopy	Patient response	CRS vs non-CRS: SHS 2.2 (1.5–3.2)*	CRS patients from a specialty clinic and controls from primary care (n=612)
Lieu <i>et al.</i> 2000 [81]	Cross-sectional prospective	Patient-reported symptoms	Patient response	CRS vs non-CRS (aRR, 95%CI) Current smoker: 1.2 (1.1–1.4) Former smoker: 1.1 (0.9–1.3)	National Health And Nutritional Examination Survey (NHANES III) (n=20,050)
Air Pollution					
Min <i>et al.</i> 1996 [86]	Cross-sectional prospective	Symptoms and physical examination performed by clinicians	Patient response	CRS vs non-CRS Rural 0.7 (0.4–1.1)	Korean general population based on survey responses (n=9,069)

Study [Ref]	Design	Criteria for CRS Diagnosis	Criteria for Environmental Factors Exposure Confirmation	Relevant Results aOR (95%CI)	Comments
Wolf 2002 [87]	Case-control retrospective	Diagnosed by otolaryngologist	Air quality measurement	In total, no correlation between air pollution levels and CRS rates. In the districts with above average air pollution levels, positive correlation between air pollution levels and CRS rates (adjusted $R^2=0.3$)	Tertiary care hospital in Cologne, Germany (n=1,435)
Occupational factors					
Thilising <i>et al.</i> 2012 [79**]	Cross-sectional prospective	Patient-reported symptoms	Patient response	CRS vs non-CRS (aRR, 95% CI) <i>High molecular weight agents</i> 0.9 (0.6–1.4) <i>Animal dander</i> 1.9 (1.0–3.6) <i>Fish or shellfish</i> 2.07 (1.4–3.0) <i>* Latex</i> 1.1 (0.7–1.7) <i>Pharmaceutical products</i> 0.5 (0.1–2.0) <i>Low molecular weight agents</i> 1.3 (0.9–1.9) <i>Highly reactive chemicals</i> 1.4 (1.0–2.2) <i>Isocyanides</i> 3.1 (0.9–10.7) <i>Reactive cleaning disinfectants</i> 1.3 (0.8–2.2) <i>Metal and metal fumes</i> 0.9 (0.4–1.8) <i>Mixed environments</i> 0.9 (0.4–1.7) <i>Agriculture</i> 0.9 (0.4–2.0)	Part of a trans-European GA ² LEN (Global Asthma and Allergy European Network)-based study, Danish population (n=4,554)

CRS, chronic rhinosinusitis; aOR, adjusted odds ratio; 95% CI, 95% confidence interval; CRSsNP, chronic rhinosinusitis without nasal polyp; CRSwNP, chronic rhinosinusitis without nasal polyp; aRR, adjusted risk ratios; 95%CL, 95% confidence limits; SHS: second hand smoke

* statistically significant