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Occupational and environmental risk factors for chronic rhinosinusitis: a systematic review

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Abstract

Background—Chronic rhinosinusitis (CRS) is a prevalent and disabling paranasal sinus disease, with a likely multi-factorial etiology potentially including hazardous occupational and environmental exposures. We completed a systematic review of the occupational and environmental literature to evaluate the quality of evidence of the role that hazardous exposures might play in CRS.

Methods—We searched PubMed for studies of CRS and following exposure categories: occupation, employment, work, industry, air pollution, agriculture, farming, environment, chemicals, roadways, disaster, or traffic. We abstracted information from the final set of articles across six primary domains: study design; population; exposures evaluated; exposure assessment; CRS definition; and results.

Results—We identified 41 articles from 1080 manuscripts: 37 occupational risk papers, 1 environmental risk paper, and 3 papers studying both categories of exposures. None of the 41 studies used a CRS definition consistent with current diagnostic guidelines. Exposure assessment was generally dependent on self-report or binary measurements of exposure based on industry of employment. Only grain, dairy and swine operations among farmers were evaluated by more than one study using a common approach to defining CRS, but employment in these settings was not

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consistently associated with CRS. The multiple other exposures did not meet quality standards for reporting associations or were not evaluated by more than one study.

Conclusion—The current state of the literature allows us to make very few conclusions about the role of hazardous occupational or environmental exposures in CRS, leaving a critical knowledge gap regarding potentially modifiable risk factors for disease onset and progression.

Keywords

sinusitis; epidemiology; environmental health; occupational health; farming

Chronic rhinosinusitis (CRS) is a prevalent and disabling condition of the paranasal sinuses. It affects approximately 31 million people in the United States and accounts for an estimated \$8.6 billion in direct health care expenditures.¹ CRS is reported to have a more negative impact on quality of life than other chronic conditions, such as congestive heart failure, chronic obstructive pulmonary disease (COPD), and chronic back pain.^{2–4} The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) defines the clinical definition of CRS using both subjective symptoms and objective evidence by endoscopy or sinus CT scan.⁵ Without objective evidence of inflammation, it is challenging to distinguish CRS from conditions with overlapping symptoms, such as allergic rhinitis or migraine. Furthermore, it is difficult to use symptoms alone to differentiate between CRS subtypes, such as CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSSNP).⁶

The requirement for expensive, invasive, or ionizing radiation-exposed tests for diagnosis has created a barrier to epidemiological research, as large-scale studies including sinus CT or endoscopy are generally not feasible. Subsequently, most CRS studies have been conducted in tertiary care settings, where objective evidence is readily available on only the most severe cases. However, this approach is not suitable for occupational and environmental epidemiology studies, which should be population-based, and include the full spectrum of disease.

While little is known about the natural history of CRS, its variation, and the factors that explain that variation, evidence suggests that CRS is a chronic relapsing and remitting condition, beginning with the transition from acute rhinosinusitis (ARS) or rhinitis to CRS.⁶ Once CRS is established, it can transition between different disease states, including exacerbated CRS and difficult-to-treat CRS.^{5,6} Environmental exposures are among the proposed causes of transition from acute sinus disease to CRS and among the suggested triggers for symptom exacerbation of CRS, as the nasal and paranasal mucosa is the first interface with inhaled toxins, toxicants, and pollutants.^{7,8} Furthermore, some of the proposed pathways to CRS, including inflammatory dysregulation, epithelial barrier dysfunction, and impaired innate immunity can be triggered by several of the traditional hazardous exposures encountered in the workplace or the general environment, including toxic or irritant chemicals, secondhand smoke (SHS), and particulates.^{8–11} Several of these exposures are also known to cause occupational asthma or to exacerbate pre-existing asthma, a disease thought to have some overlapping pathophysiology with CRS.^{12–15} While there have been systematic reviews of the association between SHS and CRS, there have been no prior efforts to summarize and understand the complex literature concerning the

broader set of possibly important etiologies for CRS or its progression that are amenable to preventive intervention.^{8,16}

We completed a systematic review of the occupational and environmental epidemiology literature to evaluate the quality of evidence about the role that hazardous exposures may play in the onset of CRS, the differentiation into the two important CRS phenotypes (i.e., with or without nasal polyps), and the transition to CRS exacerbation or difficult-to-treat stage of CRS as defined by EPOS.⁵ Identification of the specific phenotype and disease stage under study is useful, as prior authors have argued that when CRS is considered as a single entity, consistent genetic and environmental risk factors have not been consistently identified.¹⁷

METHODS

Search strategy

We performed a systematic literature search to identify all relevant studies of the associations between occupational and environmental exposures and CRS. We searched PubMed of the U.S. National Library of Medicine with no limits on search period and limited the language to English. We searched for all possible combinations of terms for our outcomes and exposures of interest, linked by “and.” We used the following terms for our outcome: “chronic rhinosinusitis,” “rhinosinusitis,” “sinusitis” or “nasal polyp.” For exposures we searched on the following: “occupation,” “employment,” “work,” “industry,” “air pollution,” “agriculture,” “farming,” “farm,” “environment,” “chemicals,” “roadways,” “disaster,” or “traffic.” In addition to the articles captured by the search criteria, we manually reviewed the references in these publications for additional publications not previously identified. Although SHS is considered an environmental exposure, we excluded this exposure from our review because of two recent literature reviews of SHS and CRS.^{8,16}

We first screened the articles for relevance by the title and abstract (Figure 1). We included articles if sinusitis and either an occupational or environmental exposure were mentioned in the title or abstract. We excluded publications that described a case report or case series or that were ecological in design. If the abstract did not provide sufficient details to conclude relevance to the review, we evaluated the full article. Next, we reviewed the full text of articles that met the initial eligibility criteria. If after reviewing the full article we determined that studies did not explicitly evaluate CRS, but studied another outcome (e.g., acute respiratory illness) we excluded the article. When eligibility of the article remained unclear after review, we contacted corresponding authors by e-mail for clarification. A single member of the study team identified the initial set of eligible articles using this selection criteria and two additional members of the team confirmed eligibility of the articles.

Data extraction

We abstracted information from the final set of articles across six primary domains: study design (case-control, cohort, cross-sectional); study population (location, sample size, characteristics); exposures evaluated (environmental, occupational); exposure assessment and parameterization (e.g., exposure measurements vs. surrogates); CRS definition and stage

in natural history (e.g., onset, exacerbation, difficult-to-treat); and results (associations of exposures with outcomes). All the disease stages and epidemiologic parameters under study were standard and previously defined in the literature.⁵ We also recorded the country in which the study was conducted, the time period of the study, and how confounding was addressed in analysis. Two authors abstracted the data elements independently and a third author adjudicated differences in the two abstractions.

We categorized the CRS outcome as CRS onset (incident disease), prevalent CRS, CRS exacerbation, or difficult-to-treat CRS, indicating the phenotype (e.g. CRSwNP, CRSsNP) when specified. We categorized the definitions used to determine CRS status into probable CRS, possible CRS, and least likely to be CRS. We classified a CRS definition as “probable” if the study used one of the following criteria to determine a CRS diagnosis: objective evidence of disease (sinus CT, nasal endoscopy, X-ray); diagnosis by an otolaryngologist (ENT) physician; or history of endoscopic sinus surgery (ESS) for treatment of sinusitis. We classified a CRS definition as “possible” if the study used one of the following to define CRS: the EPOS CRS epidemiologic definition (i.e., compatible symptoms without objective test);⁵ diagnosis from a physician (physician specialty not specified) based on a physical exam; or self-report of a physician diagnosis. CRS definitions that did not meet criteria for probable or possible CRS were classified as “least likely.”

Statistical analysis

As we found that there was very little between-study consistency in CRS definition, stage in natural history, exposure characterization, or associations evaluated, we did not perform any meta-analysis of reported associations across studies. We did not address publication bias using funnel plot as there were not enough studies with common methods to warrant the evaluation of publication bias.

RESULTS

Study characteristics

We identified 41 studies that met the final inclusion criteria. Of these studies, 37 articles evaluated only occupational risk factors, 1 only environmental, and 3 included both types of exposures (Table 1). Thirty-seven of these studies were of prevalent CRS. These papers did not specify whether the outcome was difficult-to-treat CRS or included the full spectrum of disease. There were no studies on CRS exacerbation. Of the three studies of disease onset, only one used a definition meeting probable CRS criteria.^{9,18,19} The most common study design identified, described in 19 of the papers, used a cross-sectional design that used a least likely CRS definition based on self-reported symptoms and measured exposure using an exposure surrogate of plant or job location. Only grain, dairy and swine operations among farmers were evaluated by more than one study using a possible or probable CRS definition. Self-reported hazardous work exposure was evaluated by 6 studies; however, each of the 6 studies assessed different exposures.^{9,20–24}

Studies were published between 1964 and 2012 and were performed in 14 different countries. Half of the occupational risk studies (n=20) were conducted in Croatia or the

former Yugoslavia and one study team, led by Zuskin and colleagues, conducted 19 of the 20 studies. Only 8 of the studies were primarily designed to study CRS. The remaining studies were designed to study respiratory or general health. All these studies were done on adults. No study used a CRS definition consistent with the EPOS clinical criteria. Thilsing et al. performed a population based study using a questionnaire containing the EPOS CRS symptom elements. This epidemiologic definition requires that two of four cardinal symptoms required for diagnosis of CRS be present for at least 12 weeks, but does not require objective evidence of inflammation.²⁴

Approaches to CRS definition

There was heterogeneity in the definitions used for CRS across papers. Of the 41 papers, 11 met the probable CRS criteria, 8 met the possible criteria, and 22 met the least likely CRS criteria (Tables 2 and 4). Approximately 64% of the studies (N = 7/11) that met criteria for a CRS probable definition explicitly mention that they required objective evidence of inflammation via a CT or nasal endoscopy. Among the studies that met criteria for a CRS possible definition, four used a physician diagnosis and three used self-report of a physician diagnosis. The 22 papers we categorized as least likely CRS all depended on self-report of symptoms. In many cases the self-reported symptoms evaluated were not consistent with the EPOS definition for CRS. A number of studies classified individuals as CRS cases based on headache or facial pain symptoms, which in the absence of other nasal symptoms does not constitute CRS.²⁵ While the EPOS definition for CRS requires sinus symptoms for at least three months, many studies did not specify duration of symptoms.⁵

With few exceptions, the definitions used for CRS did not distinguish between phenotypes (CRSwNP and CRSsNP). Only 6 of the 41 studies focused on CRSwNP.^{20,21,23,26–28} All 6 studies required an ENT diagnosis and 4 of the 6 studies also required objective evidence from an endoscopy to confirm the presence of nasal polyps. There were no studies that attempted to exclusively identify CRSsNP cases. The studies rarely distinguished among stages of disease. One study focused on difficult-to-treat CRS cases, defining these patients as having ENT confirmed CRS undergoing ESS who had persistent symptoms despite appropriate treatment.^{5,22} Three studies looked at onset of CRS, but two of the three studies used self-report of past and current symptoms to define onset of CRS.^{18,19} Tammemagi et al., in a study of air pollution and work exposure, used a definition for onset that met the possible CRS definition criteria, using medical record data to confirm the absence of CRS history and a combination of medical record data and CT or endoscopy to confirm case status.⁹

Approaches to exposure characterization

All of the studies identified used a surrogate measure (e.g., job role, job title, employer) or self-reported measure to assess exposure. The majority of the occupational studies (30 of 37) relied on employment at a facility (e.g., manufacturing plant) where the exposure of interest was suspected to be present. In nearly half of the occupational studies (17 of 40), workplace airborne exposure measurements were used to confirm the presence of the contaminant of interest. However, air quality and questionnaire data like duration of employment were rarely used to categorize exposure (e.g., high, medium, low) or create quantitative exposure

gradients; rather, most studies used binary exposure groups (e.g., yes vs. no employed in industry) (Tables 3 and 5). Two studies used geographic information systems (GIS)-based approaches to ambient exposure characterization, generally by calculating the distance of residence to the source of environmental pollution like intensive hog farming, industries and dust-producing activities.^{20,29} The remaining studies used self-report to assess exposure (e.g., job roles, industry, exposures in home). Thilsing et al. used an asthma-specific job exposure matrix to create yes/no exposure variables for the different exposure categories like high molecular weight (HMW) chemicals, low molecular weight (LMW) chemicals, and mixed environment jobs, and Hox et al. used a similar classification.^{22,24}

Study design and sample selection

There were 33 cross-sectional, 5 cohort, and 3 case-control studies with different approaches to confounding (Tables 3 and 5). Multivariate analysis, stratification, and modeling were used to address a range of confounders, most commonly age, gender, and smoking status. The cross-sectional studies generally included only a one-time assessment of symptoms and none of the cross-sectional studies confirmed the absence or presence of CRS prior to exposure. Four of the 5 cohort studies selected cohorts based on employment in the industry of interest while one followed a cohort of patients with CRSwNP. For the case control studies and the CRSwNP cohort study, cases were generally recruited from tertiary referral populations or from among patients with a history of ESS.

Reported associations

A meta-analysis could not be performed, so here we summarize associations with exposures that were studied using probable or possible CRS definitions and for which exposure characterization was similar in at least one other study (Tables 3 and 5). We could not assign levels of evidence across the body of studies using standard approaches because there were no exposures for which similar approaches to exposure and outcome assessment were reported on more than once.³⁰ Instead, we graded the level of evidence at the individual study level using the Oxford Centre for Evidence-based Medicine – Levels of Evidence scoring system.³⁰ This system assigns levels of evidence from 1a (strongest) to 5 (weakest) based on the design of the study. Most of the studies we identified used a cross-sectional study design (80.5%), an approach that does not allow for causal inference and is not graded by the Oxford system. Of the eight remaining studies, five were cohort studies, categorized as level 2b, and the three were case-control studies, categorized as level 3b. Farmers were evaluated in three studies.^{27,28,31} However, one study did not mention the kind of farming that was done, so only two studies with clear and similar exposure descriptions were available for review.^{27,28} Both studies were occupation-based cross-sectional studies that compared farmers to working non-farmers and used an ENT diagnosis and endoscopy to confirm prevalent CRSwNP. Neither study found an association between dairy or swine farming and CRSwNP; associations with grain farming were inconsistent, with Holstrom et al. reporting an association and Ahmen et al. reporting no association. In other studies, there were multiple other evaluated exposures but none that were reported on by more than one study.

DISCUSSION

We conducted, to our knowledge, the first systematic review of the relationship between hazardous occupational and environmental exposures and CRS. Our focus on these occupational and environmental exposures was a departure from previous literature that used the term “environmental exposure” in a very loose sense, to include, for example, personal tobacco use, viruses, and bacteria, as triggers for disease onset or exacerbation. While we identified 41 studies on occupational and environmental hazardous exposures, the literature to date is insufficient to draw conclusions about the relationship between the exposures studied and CRS. Most of the studies used a cross-sectional design, which does not allow causal inferences. With the exception of exposures related to farming, no exposures were studied more than one time using a definition for CRS based on more than self-reported symptoms. Due to poorly ascertained exposures and outcomes; an inability to assess between-study findings because of a lack of similar, separate studies of exposures and outcomes; and the use of research methods vulnerable to bias, the role of hazardous occupational and environmental exposures in the onset, natural history, and phenotypic expression (i.e., with and without nasal polyps) of CRS has been, to date, insufficiently characterized. This is a missed opportunity as these are likely important and numerous potentially modifiable risk factors for CRS.

In general, it is challenging to make conclusions about occupational and environmental risk factors for CRS due to a number of limitations in the current literature. The majority of the studies we identified used self-reported symptoms to classify cases without documenting objective evidence of inflammation. This approach to disease definition is vulnerable to misclassification. In addition, we found that multiple studies used non-standard approaches to symptom characterization, such as those that required only facial pain to identify CRS cases, potentially mislabeling conditions with facial pain symptoms, such as migraine, as CRS. Studies have revealed poor correlation between symptoms and radiologic findings, reporting that only 20 to 36% of patients with symptoms of CRS have objective evidence of inflammation on sinus CT scan.^{32,33} This suggests that studies that relied on symptoms only likely included only a small minority of patients who actually had CRS according to current definitions. Alternatively, the majority of studies that required CT or endoscopy to confirm case status ascertained cases from tertiary care clinics, jeopardizing both internal and external validity because of the inclusion of only the most severe subset of individuals. A less costly and invasive method like a questionnaire based methodology that does not involve ionizing radiation to identify CRS in large-scale population studies is needed. This would greatly assist future efforts to evaluate the environmental epidemiology of CRS.

Studies most often used surrogate measures of exposure, including job task or role, job title, or employment in the industrial setting of interest. These methods of exposure assessment, particularly the self-reported measures, are subject to dependent measurement error and exposure misclassification. Very few studies attempted to evaluate exposure temporality, intensity, duration, and none evaluated latency. No studies attempted to rank study subjects along a continuous exposure gradient with quantitative measurements, thus not allowing evaluation of exposure-effect relations for disease risk or severity. No studies used internal dose measurements (e.g., cotinine for tobacco, chemical metabolites).

The majority of occupational exposure studies were cross-sectional studies conducted on individuals currently employed in the industry. This type of sample selection is vulnerable to healthy worker bias, a well-documented source of selection bias that occurs because healthier individuals are more likely to be selected for the workforce and remain in the workforce,³⁴ as well as survivor bias, as individuals who might have developed symptoms after workplace exposures would consider leaving to seek employment in settings that did not cause illness. Generally, both of these sources of bias tend to result in associations closer to the null. While the majority of studies used a comparison group that was also in the workforce, the healthy worker effect can differ across occupations, and results could be biased in either direction depending on how the health of employees differs between industries.

Given the prevalence of CRS and the high degree of burden of the disease, there has been a disproportionately small amount of research dedicated to understanding this condition. The majority of the studies we identified were designed to study general health or respiratory health, rather than CRS (80%). As a result, few of the studies were attentive to the complexity of the condition, including its distinct phenotypes and different disease stages. Nearly all of the studies in our review failed to distinguish between phenotypes, collapsing them into a single outcome of sinusitis. While there is considerable symptom overlap between CRSwNP and CRSsNP, there are differences in respective inflammatory profiles, treatment outcomes, and potentially, etiology.^{5,35,36} Regarding symptom exacerbations, while there are known relationships between occupational and environmental hazards and asthma and COPD, we did not find any studies of the role these exposures play in CRS exacerbations.^{37,38} Similarly, just as early life exposures may be protective for asthma, no studies have explored the role of early life exposures in CRS.^{39,40} Finally, studies have generally focused on prevalent symptoms consistent with, but not specific for, CRS. The current literature thus offers few insights into the role of the workplace or general environment in disease onset, disease severity, or the transition from a less severe stage to a more difficult-to-treat stage of disease.

CONCLUSION

It is biologically plausible that environmental and occupational hazardous exposures could increase the risk of incident CRS, play a role in critical transition points in the natural history of the disease, affect the medical control of the disease, and influence the two primary types of disease expression, specifically CRSwNP and CRSsNP. However, the current scientific literature has not rigorously evaluated any of these issues. This leaves a critical knowledge gap regarding potentially modifiable risk factors for disease onset, progression, and subtypes.

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Abbreviations

CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
CT	computerized tomography
ENT	ear, nose, throat
EPOS	European position paper on rhinosinusitis and nasal polyps
ESS	endoscopic sinus surgery
FESS	functional endoscopic sinus surgery
FDNY	Fire Department of New York
GIS	geographic information systems
HMW	high-molecular weight
ICD-9	International Classification of Diseases, Ninth Revision
ISCO	International Standard Classification of Occupations
JEM	job exposure matrix
LMW	low molecular weight
NR	not reported
NS	not significant
OR	odds ratio
RR	relative risk
SES	socioeconomic status
TWA	time weighted average
TWH	temperature-wind-humidity
WTC	World Trade Center

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Figure 1.
Flow diagram of study selection process

Table 1

Summary of included studies on CRS and environmental and occupational risk factors through May 2014

Study characteristic	Frequency
Risk factors studied^a	
Occupational	40
Environmental	4
Study design	
Cross-sectional	33
Case-control	3
Cohort	5
Sample size across studies	
Mean $\pm$ standard deviation	3551.5 $\pm$ 11317.8
Median	216
Range	48–59563
Continents where studies were conducted	
Africa	1
Asia	4
Europe ^b	29
North America	7
CRS definition (see methods)	
Probable CRS	11
Possible CRS	8
Least likely CRS	22
CRS Phenotypes	
CRSwNP	6
CRSSNP	0
CRS unspecified	35
CRS natural history framework (stage of disease)	
Onset	

Study characteristic	Frequency
Probable CRS	1
Least likely CRS	2
Exacerbation	0
Difficult-to-treat	
Probable CRS	1
Prevalent (stage not specified)	37
Number of studies that specifically report duration of symptoms	
Probable CRS ^c	0
Possible CRS	5
Least likely CRS	13
Summary of the studies	
Cross-sectional, least likely CRS, exposure surrogate of plant or job location and self-reported symptoms	19
Cross-sectional, at least possible CRS, exposure surrogate of job title	11
Any design, any CRS category, self-reported occupational exposure or job title	7
Cross-sectional, at least possible CRS, geographic proximity to exposure like industrial facilities or hog farms using geographic information systems	2
Case-control, probable CRS, self-reported exposure to woodstove or air pollution	2

^a Studies can be counted more than once;

^b 20 of the 29 European studies were conducted in Yugoslavia/Croatia;

^c 9 studies had an ENT diagnosis as the CRS criteria but did not mention duration, but it could be assumed that duration was considered in the diagnosis

CRS: chronic rhinosinusitis; CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps

Table 2

Characteristics of Included OCCUPATIONAL Studies

First author, Year Country Quality ranking ^a	Study Design	Population	Data period	Sample size	Exposure	CRS definition	CRS natural history studied
Alman, 2001 ²⁸ Sweden PROBABLE CRS	Industry-based cross-sectional	Exposed: dairy, swine, and grain farmers Control: non-farmers	1998	Exposed: n=66 Control: n=19	Plant antigens: grain; animal dander: swine and cow	ENT diagnosed; endoscopy	Unspecified- prevalent CRSwNP
Casson, 1998 ⁴¹ Italy PROBABLE CRS	Industry-based cross-sectional	Exposed: fishermen Control: male employees of the Local Health Authority	NR	Exposed: n=139 Control: n=136	Fishing profession: fat soluble and persistent toxic contaminants, nitrous oxides and mineral oil spray, and adverse weather conditions	ENT diagnosed by local exam	Unspecified- prevalent CRS
Collins, 2002 ²³ England PROBABLE CRS	Cross-sectional	CRSwNP patients	1991–1995; 1997	Retrospective group: n=900 Prospective group: n=120	Dust and chemicals	ENT diagnosed	Unspecified- prevalent CRSwNP
Elbatawi, 1964 ⁴² Egypt PROBABLE CRS	Industry-based cross-sectional	Exposed: workers in dusty card rooms in a cotton textile plant Control: unexposed workers from the same plant	NR	Exposed: n=119 Control: n=84	Cotton dust inhalation	Physician exam; X ray	Unspecified- prevalent CRS
Holmstrom, 2008 ²⁷ Sweden PROBABLE CRS	Industry-based cross-sectional	Exposed: dairy, swine, and grain farmers Control: office workers	NR	Exposed: n=53 Control: n=15	Plant antigens: grain; animal dander: swine and cow	ENT diagnosed; endoscopy	Unspecified- prevalent CRSwNP
Hox, 2012 ²² Belgium PROBABLE CRS	Case-control	Case: FESS patients for recurrent ARS and CRS Control: vocal cord surgery patients	2004–2008	Case n=890 Control n=182	Bleach, inorganic dust, paints, cement, thinner, ammonia, white spirit, fuel gas, acetone	ENT diagnosis	Difficult-to-treat
Klingmann, 2007 ⁴³ Germany PROBABLE CRS	Cohort	Injured divers	2002–2005	n=306	Barotrauma: diving accidents	ENT diagnosis; sinus CT scan	Unspecified- prevalent CRS
Rugina, 2002 ²⁶ France PROBABLE CRS	Cohort	Bilateral CRSwNP patients	1991–1996	n=221	Air pollutants	ENT diagnosed; endoscopy and CT	Unspecified- prevalent CRSwNP
Bener, 1998 ⁴⁴ United Arab Emirates POSSIBLE CRS	Industry-based cross-sectional	Exposed: garage mechanics Control: taxi drivers	NR	Exposed n=158 Controls n=165	Motor vehicle exhaust emission	Physician diagnosis	Unspecified- prevalent CRS
Bener, 1999 ³¹ United Arab Emirates POSSIBLE CRS	Industry-based cross-sectional	Exposed: male farmers exposed to pesticides Control: male workers, not in farming or agriculture	1997	Exposed: n=98 Control: n=98	Pesticides: organophosphates and carbamate	Physician diagnosis	Unspecified- prevalent CRS
Koh, 2009 ⁴⁵ Korea POSSIBLE CRS	Cross-sectional	Civilian, non-institutionalized Korean adults aged 20–59 years	1998, 2001, 2005	1998: n=20829 2001: n=20468 2005: n=18266	Gas, fumes, plant antigens	Self-reported physician diagnosis	Unspecified- prevalent CRS

First author, Year Country Quality ranking ^a	Study Design	Population	Data period	Sample size	Exposure	CRS definition	CRS natural history studied
Thilising, 2012 ²⁴ Denmark POSSIBLE CRS	Cross-sectional	Danish residents: aged 20–75 years	2008	Men: n= 1200 Women: n=1331	Gases, fumes, dust, or smoke	EPOS epidemiologic definition	Unspecified- prevalent CRS
Webber, 2011 ⁴⁶ US POSSIBLE CRS	Cohort	World Trade Center (WTC) collapse responders	2007–2009	n=10943	Caustic dust and toxic pollutants	Self-reported physician diagnoses	Unspecified- prevalent CRS
Zuskin, 1993 ⁴⁷ Croatia POSSIBLE CRS	Industry-based cross-sectional	Exposed: male glass blowers Control: clerical office workers	NR	Exposed: n=80 Control: n=80	Barotrauma: glass blowers	Physician diagnosis	Unspecified- prevalent CRS
Zuskin, 1993 ⁴⁸ Croatia POSSIBLE CRS	Industry-based cross-sectional	Exposed: mustard and pickling workers Control: fruit juice bottling factory workers	NR	Exposed: n=117 Control: n=65	Plant antigen: mustard seeds; vinegar, salt, various spices, natural flavoring, and turmeric	Physician diagnosis	Unspecified- prevalent CRS
Al-Neaimi, 2001 ⁴⁹ United Arab Emirates LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: cement factory workers Control: Retail salesmen	NR	Exposed: n=67 Control: n=134	Cement dust	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Herbert, 2006 ¹⁹ US LEAST LIKELY CRS	Cohort	WTC collapse responders	2002–2004	n=9442	Caustic dust and toxic pollutants	Self-reported symptoms	Onset
Mustajbegovic, 2001 ⁵⁰ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: fulltime male firefighters Control: male food product packers	NR	Exposed n=128 Control n=88	Caustic dust and toxic pollutants	Sinus pressure > 3 months AND/OR nasal discharge ^b	Unspecified- prevalent CRS
Webber, 2009 ¹⁸ US LEAST LIKELY CRS	Cohort	WTC collapse responders	2001–2004	n= 10378	Caustic dust and toxic pollutants	Self-reported symptoms	Onset
Wilson, 1973 ⁵¹ US LEAST LIKELY CRS	Cross-sectional	Exposed: civilian, non-institutional adults	1970	Households: n= 42,000	Not specified (blue vs. white collar occupation)	Self-reported sinusitis	Unspecified- prevalent CRS
Zuskin, 1979 ⁵² Yugoslavia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: processors of roasted and green coffee Control: soft drink workers	NR	Exposed: n=103 Control: n=103	Plant antigens: green and roasted coffee	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Zuskin, 1984 ⁵³ Yugoslavia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: female tea factory workers Control: soft drink workers	NR	Exposed: n=100 Control: n=84	Plant antigens: dog-rose, sage, and chamomile, Indian, and gruzyan teas	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Zuskin, 1988 ⁵⁴ Yugoslavia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: female spice factory workers Control: female fruit juice bottling workers	NR	Exposed: n=92 Control: n=104	Plant antigens: spices including hot paprika, sweet paprika, black pepper, parsley, garlic, onion, ginger, parsnip, turmeric, salt, and dextrose	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Zuskin, 1988 ⁵⁵ Yugoslavia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: furriers Control: fruit juice bottling workers	NR	Exposed: n=40 Control: n=31	Animal fur: marten, domestic fox, polar fox, mink, Chinese lamb, domestic lamb, and Chinese calf	Chronic sinusitis symptoms	Unspecified- prevalent CRS

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First author, Year Country Quality ranking ^a	Study Design	Population	Data period	Sample size	Exposure	CRS definition	CRS natural history studied
Zuskin, 1988 ⁵⁶ Yugoslavia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: soybean workers Control: nonalcoholic beverage packers	1982	Exposed: n=27 Control: n=21	Plant antigens: soy	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Zuskin, 1990 ⁵⁷ Yugoslavia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: hemp factory workers Controls: packers in the food industry with no exposure to noxious dusts or fumes	NR	Exposed: n=111 Control: n=79	Textiles: hemp used in the manufacturing of rope, fire hose, rugs, and clothing	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Zuskin, 1991 ⁵⁸ Yugoslavia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: male soybean workers Control: transport workers not exposed to industrial dust or fumes	NR	Exposed: n=19 Control: n= 31	Plant antigens: soy	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Zuskin, 1994 ⁵⁹ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: confectionary workers Control: factory transport workers	NR	Exposed: n=288 Control: n=96	Plant antigens: nuts, almonds, cocoa, cacao, chocolate, butter, honey, aromatic oil, fruits, flour, sugar, starch, talc, egg powder, and yeast; ethyl alcohol and food colorings	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Zuskin, 1995 ⁶⁰ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: wool textile workers Controls: delivery workers in plastic material plant	NR	Exposed: n=216 Control: n=130	Textiles: wool	Sinus pressure > 3 months AND/OR nasal discharge ^b	Unspecified- prevalent CRS
Zuskin, 1996 ⁶¹ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: female dried fruits and teas processors Controls: female transport workers	NR	Exposed: n=54 Control: n=40	Plant antigens: fruits and teas including pineapple, orange, lemon, apple, peach, sage, dog rose, and chamomile	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Zuskin, 1998 ⁶² Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: male paper-recycling workers Control: food products packers	NR	Exposed: n=101 Control: n=87	Paper dust, talc, chlorine gas, sulfur dioxide (SO ₂), chlorine dioxide, ammonia, and caustic soda	Sinus pressure > 3 months AND/OR nasal discharge ^b	Unspecified- prevalent CRS
Zuskin, 1998 ⁶³ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: synthetic fiber textile factory workers Control: unexposed workers from various industries	1995	Exposed: n=400 Control: n= 238	Textiles: polyester	Sinus pressure > 3 months AND/OR nasal discharge ^b	Unspecified- prevalent CRS
Zuskin, 1998 ⁶⁴ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: female cocoa and flour workers Control: female confectionary packers	NR	Exposed: n=93 Control: n=65	Plant antigens: cocoa and flour	Chronic sinusitis symptoms	Unspecified- prevalent CRS
Zuskin, 2000 ⁶⁵ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: male mail carriers Control: food industry packers	1997	Exposed n=136 Control n=87	SO ₂ and black smoke	Sinus pressure > 3 months AND/OR nasal discharge ^b	Unspecified- prevalent CRS
Zuskin, 2000 ⁶⁶ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: female workers exposed to the following: <div><div>1</div>Coffee</div> <div><div>2</div>Tea</div> <div><div>3</div>Spices</div>	NR	Exposed: n=764 Control: n=387	Plant antigens: green and roasted coffee, tea, spices, dried fruits, cocoa, and flour	Chronic sinusitis symptoms	Unspecified- prevalent CRS

First author, Year Country Quality ranking ^a	Study Design	Population	Data period	Sample size	Exposure	CRS definition	CRS natural history studied
		<div>4 Confectionary</div> <div>5 Dried fruits</div> <div>6 Cocoa</div> <div>7 Flour</div> <div>Control: female unexposed workers</div>					
Zuskin, 2004 ⁶⁷ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: pharmaceutical manufacturers Control: employees at a food packing plant	NR	Exposed: n=198 Control n=113	Pharmaceutical products: mainly antibiotics including Sumamed, Amoxyl, Klavocin, Ceporex, Novocet, and sulfonamides	Sinus pressure > 3 months AND/OR nasal discharge ^b	Unspecified- prevalent CRS
Zuskin, 2009 ⁶⁸ Croatia LEAST LIKELY CRS	Industry-based cross-sectional	Exposed: male wind instrument musicians Control: male string instrument musicians	NR	Exposed: n=99 Control: n=41	Barotrauma: wind musicians	Sinus pressure > 3 months AND/OR nasal discharge ^b	Unspecified- prevalent CRS

^a CRS probable: objective evidence of disease (by sinus CT scan, nasal endoscopy, X-ray); diagnosis by an ENT physician; or history of endoscopic sinus surgery for treatment of sinusitis. CRS possible: EPOS CRS epidemiologic definition; diagnosis from a physician (ENT status not specified) based on a physical exam; or self-report of a physician diagnosis. Least likely CRS: CRS definitions that did not meet criteria for probable or possible CRS.

^b Definition confirmed by the author, Dr. Mustajbegovic by email on 4/1/2014 as “headache/facial pain or pressure of a dull, constant, or aching sort over the affected sinuses which lasts longer than three months. May be accompanied by thick nasal discharge that is usually green in color and may contain pus (purulent) and/or blood”

ARS: acute rhinosinusitis; CRS: chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyps; CT: computed tomography; ENT: Ear Nose Throat; EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps; FESS: functional endoscopic sinus surgery; NR: not reported; SO₂: sulfur dioxide; WTC: World Trade Center

Table 3

Exposure assessment, approach to confounding, exposure parameterization, and primary associations reported for eligible OCCUPATIONAL studies

First author, Year Quality ranking ^a	Exposure assessment	Approach to Confounding	Exposure Parameterization	Primary Association
Ahman, 2001 ²⁸ PROBABLE CRS	Mailed survey regarding the farm and work conditions	Not reported (NR)	Yes/no 1 Dairy farmer 2 Swine farmer 3 Grain farmer	Prevalence, % of farmers with polyps: Dairy farmer: 4 Swine farmers: 10 Grain farmers: 14 Control: 0 All comparisons vs. controls not significant (NS)
Casson, 1998 ⁴¹ PROBABLE CRS	Selected from deep sea fishing cooperatives. Survey: work duration, job, fishing in coastal/distant waters	Adjusted for cigarettes/day and chronic laryngitis	Yes/no: Job as a deck hand vs. employee of Local Health Authority (control) Yes/no: Job fishing in high sea vs. control	Corresponding adjusted prevalence ratio (95% CI) of CRS: 1 17.8 (1.55–2.03) ^b 2 15.5 (1.16–218)
Collins, 2002 ²³ PROBABLE CRS	Postal survey regarding occupational dust and chemical exposure : detailed report of occupational and recreational exposures and dates of exposure	NR	Yes/no: occupational exposure to dusts and chemicals	Prevalence, % (n) of occupational exposure: Retrospective group: 44.5 (400/900) Prospective group: 44.2 (53/120) ^c
Elbatawi, 1964 ⁴² PROBABLE CRS	Work in dusty card-rooms in cotton textile plant. Card-room air analysis using an electrostatic sampler to determine dust levels	Duration of work	Yes/no: work in dusty cardroom in cotton textile plant	Prevalence of chronic bacterial sinusitis: Exposed: 32.7% (39/119) vs. control: 14.3% (12/84) (p<0.01)
Holmstrom, 2008 ²⁷ PROBABLE CRS	Questionnaire regarding farm work tasks and TWA dust values over a working day	Matched on sex and age	Yes/no 1 Milk farmer 2 Swine farmer 3 Grain farmer	Prevalence, % (n) of nasal polyps: Dairy farmer: 5 (1/20) (NS) Swine farmer: 7 (1/15) (NS) Grain farmer: 33 (6/18) (<0.05) Control: 0 (0/15)
Hox, 2012 ²² PROBABLE CRS	Mailed survey: occupational/recreational exposures, duration of exposures, type of agents. Reviewed and scored by occupational medicine physicians	Adjusted for asthma, current smoking state, presence of nasal polyps, and atopy	Yes/no to exposure to at least one of the following: HMW agents, LMW sensitizers, irritants	OR (95% CI) for occupational exposure yes vs. no: 2.45 (1.14–5.29) among patients with at least 1 FESS compared to those with no FESS
Klingmann, 2007 ⁴³ PROBABLE CRS	Self-report to ENT: date of accident, number of dives, diving certification, history of acute diving accidents or follow up treatment, assessment of fitness to dive	NR	Average dives	Chronic sinusitis cases (33) had an average of 320 dives compared to 265 dives for those without chronic sinusitis (p < 0.05)
Rugina, 2002 ²⁶ PROBABLE CRS	In-person survey: self-report exposure at work	NR	Yes/no: pollution at work Urban population vs. rural area residence	No significant difference in natural history of NP by pollution at work or area of residence

First author, Year Quality ranking ^d	Exposure assessment	Approach to Confounding	Exposure Parameterization	Primary Association
Bener, 1998 ⁴⁴ POSSIBLE CRS	Garage work : job title/job location	Matched on age, sex, nationality, working hours, and duration of job	Yes/no: garage worker	Prevalence ratio of sinusitis: 1.33 (1.06–1.68) (p<0.03)
Bener, 1999 ³¹ POSSIBLE CRS	Farming : job title/job location	Matched on age, sex, and nationality. Stratified by IgE level >180 IU/ml	Yes/no: farmer	OR (95% CI) for sinusitis: 2.53 (0.99–6.47)
Koh, 2009 ⁴⁵ POSSIBLE CRS	Interviewer-administered survey: occupational classification by: Korean Standard Classification of Occupations	Adjusted for age; stratified by sex	Yes/no <ol style="list-style-type: none"> 1 Unemployed 2 Homemakers 3 Elementary occupations 4 Plant or machine operators and assemblers 5 Craft and related trades workers 6 Skilled agricultural, forestry, and fishery workers 7 Sales workers 8 Service workers 9 Technicians and associated professionals 10 Professionals 	Prevalence ratio (95% CI) of exposed compared to clerical workers: (only significant associations listed) Elementary occupations: 1.68 (1.02–2.77) males (1998 wave) 3.07 (1.13–8.32) males (2001 wave) Plant/machine operators and assemblers: 2.88 (1.13–7.34) males (2001 wave) 1.76 (1.02–3.05) males (2005 wave) Unemployed: 1.81 (1.05–3.14) males (2005 wave) 2.07 (1.08–3.96) females (2005 wave) Craft and related trades workers: 1.73 (1.03–2.92) males (2005 wave)
Thilising, 2012 ²⁴ POSSIBLE CRS	Mailed survey. ISCO codes occupational exposure assessment and an asthma-specific JEM	Adjusted for smoking status, asthma, and nasal allergy. Stratified by sex	<ol style="list-style-type: none"> 1 Blue vs. white collar 2 Yes/no: job exposure to gases, fumes, dust or smoke 3 Yes/no: left or changed job due to respiratory symptoms 4 HMW job vs. low risk jobs 5 LMW job vs. low risk jobs 6 Mixed environment job vs. low risk jobs 	Corresponding adjusted prevalence ratio (95% CI) for CRS: <ol style="list-style-type: none"> 1 RR 1.15 (0.87–1.52) 2 RR 1.35 (1.01–1.80) 3 RR 1.36 (0.88–2.10) 4 RR 0.92 (0.58–1.44) 5 RR 1.29 (0.87–1.90) 6 RR 0.85 (0.43–1.65)
Webber, 2011 ⁴⁶ POSSIBLE CRS	Fire Department of New York (FDNY) survey on world trade center (WTC) collapse responders : occupation, duty status, arrival group, and duration of exposure	NR	Exposure categories based on arrival at the WTC site: <ol style="list-style-type: none"> 1 Group 1: morning of 9/11 2 Group 2: afternoon of 9/11 	Prevalence (%) of sinusitis: <ol style="list-style-type: none"> 1 Group 1: 11.6 2 Group 2: 10.0 3 Group 3: 9.6

First author, Year Quality ranking ^a	Exposure assessment	Approach to Confounding	Exposure Parameterization	Primary Association
			<p>3 Group 3: day 2 (9/12)</p> <p>4 Group 4: days 3–14</p>	<p>4 Group 4: 6.0</p>
Zuskin, 1993 ⁴⁷ POSSIBLE CRS	Physician administered survey: duration of employment in the glass-blowing industry	Stratified by duration in industry	Yes/no: glass blower	Prevalence, % (n) of chronic sinusitis: Exposed: 28.8 (43/80) vs. control: 3.8 (3/80) (p<0.001)
Zuskin, 1993 ⁴⁸ POSSIBLE CRS	Occupational survey on the pickling and mustard producing factory workers	Stratified by duration in industry	<p>Yes/no</p> <p>1 Pickling</p> <p>2 Packing</p> <p>3 Mustard</p>	<p>Prevalence, % (n) of sinusitis among exposed vs. control</p> <p>Pickling: 33.3 (12/36)</p> <p>Packing: 18.9 (7/37)</p> <p>Mustard: 22.7 (10/44)</p> <p>Controls: 1.5 (1/65)</p> <p>All comparisons vs. controls p<0.01</p> <p>Pickling workers exposed more than 1 year (45.5%) vs. 1 year or less (14.2%) p <0.01</p>
Al-Neaimi, 2001 ⁴⁹ LEAST LIKELY CRS	Interviewer-administered survey: use of personal protection equipment; work setting in cement factory ; work role	Matched on age, nationality, and socioeconomic status (SES)	Yes/no: cement worker	Prevalence, % (n) of sinusitis: Exposed: 26.9 (18/67) vs. unexposed: 11.2 (15/134) (p<0.05)
Herbert, 2006 ¹⁹ LEAST LIKELY CRS	Interviewer-administered survey: job role at job site of WTC collapse responders	NR	<p>Exposure categories by arrival date for work at WTC site</p> <p>1 9/11/01 in dust cloud</p> <p>2 9/11/01 not in dust cloud</p> <p>3 9/12/01–9/13/01</p> <p>4 9/14/01–9/30/01</p> <p>5 On or after 10/1/01</p>	<p>Prevalence (crude), % (n) of new or worsened sinus related symptoms by exposure category:</p> <p>Group 1: 41.9 (785)</p> <p>Group 2: 36.9 (712)</p> <p>Group 3: 36.6 (1,020)</p> <p>Group 4: 37.0 (783)</p> <p>Group 5: 30.1 (200)</p> <p>(trend test p<0.001)</p>
Mustajbegovic, 2001 ⁵⁰ LEAST LIKELY CRS	Survey: occupational history of firefighters	Stratified by smoking habit	Yes/no: firefighter	Prevalence, % (n) of sinusitis: Exposed: 32.8 (42/128) vs. control: 2.3 (2/88) (p<0.01)
Webber, 2009 ¹⁸ LEAST LIKELY CRS	Self-administered survey: arrival time, duration of work on WTC site from September 2001 to July 2002	NR	<p>FDNY-WTC exposure intensity index, based on arrival at the WTC site:</p> <p>1 Group 1: morning of 9/11/01</p> <p>2 Group 2: afternoon of 9/11/01</p> <p>3 Group 3: day 2 (9/12/01)</p> <p>4 Group 4: days 3–14 mostly</p>	<p>OR (95% CI) for persistent rhinosinusitis among earliest arriving workers compared with all others: 1.3 (1.1–1.6).</p> <p>Test for trend by arrival group: p<0.0001</p>

First author, Year Quality ranking ^d	Exposure assessment	Approach to Confounding	Exposure Parameterization	Primary Association
Wilson, 1973 ⁵¹ LEAST LIKELY CRS	Health Interview Survey: job title self-report stratified blue/white collar occupation	NR	Blue vs. white collar	Sinusitis prevalence (%): Blue collar: 12.9% White collar: 14.8%
Zuskin, 1979 ⁵² LEAST LIKELY CRS	Occupational survey of coffee workers . Casella personal samplers (2-stage, stationary samplers with membrane filter preceded by horizontal elutriator for respirable fraction) were used to measure airborne dust as an 8hr time weighted average (TWA)	Stratified by sex. Matched on age, height, and smoking.	Yes/no: 1 Work with roasted coffee 2 Work with green coffee	Prevalence, (%) of sinusitis: Exposed roasted coffee females: 25.2 vs. control: 3.9 (p<0.01) Exposed green coffee females: 22.5 vs. control: 3.2 (p<0.05) Exposed roasted coffee males: 23.8 vs. control: 9.5 (NS)
Zuskin, 1984 ⁵³ LEAST LIKELY CRS	Occupational survey of tea workers . Casella personal samplers (2-stage, stationary samplers with membrane filter preceded by horizontal elutriator for respirable fraction) were used to measure airborne dust as an 8hr TWA	NR	Yes/no 1 Dog-rose 2 Gruzayan 3 Sage 4 Indian 5 Chamomile	Prevalence, (%) of sinusitis in tea workers and controls: Dog-rose: 30.0 (p<0.05) Gruzayan: 10.7 Sage: 15.0 Indian: 6.3 Chamomile: 11.5 Controls: 4.7
Zuskin, 1988 ⁵⁴ LEAST LIKELY CRS	Occupational survey of spice factory workers . Casella personal samplers (2-stage, stationary samplers with membrane filter preceded by horizontal elutriator for respirable fraction) were used to measure airborne dust as an 8hr TWA	Matched on sex, age, and smoking	Yes/no: spice factory worker	Prevalence, % of sinusitis: Exposed: 27.2 vs. control: 2.9 (p<0.01)
Zuskin, 1988 ⁵⁵ LEAST LIKELY CRS	Survey of furriers . Dust samples collected from the air of the workplaces. Sampling performed using a membrane filter. Respirable fur fibers counted by phase-contrast optical microscopy. Dust particles were determined by counting respirable fraction and nonrespirable fraction	Matched on sex, age, smoking	Yes/no: furrier	Prevalence, % (n) of chronic sinusitis: Exposed: 30.0 (12/40) vs. control: 3.2 (1/31) (p<0.01)
Zuskin, 1988 ⁵⁶ LEAST LIKELY CRS	Occupational survey of soybean workers . Casella personal samplers (2-stage, stationary samplers with membrane filter preceded by horizontal elutriator for respirable fraction) were used to measure airborne dust as an 8hr TWA	Matched on town, sex, and age	Yes/no: employed in processing soy bean	Prevalence, % (n) of sinusitis: Exposed: 14.8 (4/27) vs. control: 9.8 (2/21) (NS)
Zuskin, 1990 ⁵⁷ LEAST LIKELY CRS	Occupational survey of hemp workers . Casella personal samplers (2-stage, stationary samplers with membrane filter preceded by horizontal elutriator for respirable fraction) were used to	Stratified for sex and site	Yes/no: hemp worker	Prevalence, % (n) of sinusitis: Females Mill A: 26.1 (12/46) vs. controls 6.1 (3/49) (p<0.01)

First author, Year Quality ranking ^d	Exposure assessment	Approach to Confounding	Exposure Parameterization	Primary Association
	measure airborne dust as an 8hr TWA. 2 stage. Agar plates were used to measure bacterial flora in the work areas measure airborne dust as an 8hr TWA. 2 stage. Agar plates were used to measure bacterial flora in the work areas measure airborne dust as an 8hr TWA. 2 stage. Agar plates were used to measure bacterial flora in the work areas			Mill B: 50 (19/38) vs. controls 6.1 (3/49) (p<0.01) Males Mill A: 33.3 (9/27) vs. controls: 6.7 (2/30) (p<0.01)
Zuskin, 1991 ⁵⁸ LEAST LIKELY CRS	Occupational survey of soybean workers . Casella personal samplers (2-stage, stationary samplers with membrane filter preceded by horizontal elutriator for respirable fraction) were used to measure airborne dust as an 8hr TWA	Matched on sex, age, and smoking habit	Yes/no: employed in processing soy bean	Prevalence, % (n) of sinusitis: Exposed: 10.5 (2/19) vs. control: 6.5 (2/31) (NS)
Zuskin, 1994 ⁵⁹ LEAST LIKELY CRS	Occupational survey of confectionery workers . Airborne dust samples in the mill were collected with Hexhlet horizontal 2 stage samplers during the 8 hr. work shift. 20 dust samples were collected in the areas where workers were examined	Stratified by sex and exposure group	Yes/no: 1 Exposed to aerosols of flour, sugar, starch, talc, and egg powder 2 Exposed to the vapors of ethyl alcohol in preparing candied fruits 3 Processing of nuts, almonds, cacao and chocolate 4 Processed butter, honey, aromatic oil, yeast, and different food colorings 5 Packed the confectionery products in a cold room	Prevalence, % (n) of sinusitis by sex: Exposed women: 23.6 (61/259) vs. control women: 1.5 (1/65) (p<0.001) Exposed men: 24.1 (7/29) vs. control men: 0 (0/31) (p<0.001) Prevalence, % (n) of sinusitis by group/sex: 1 Women: 24.4 (19/78) 1 Men: 24.1 (7/29) 2 Women: 26.3 (5/19) 3 Women: 31.6 (7/22) 4 Women: 22.4 (13/67) 5 Women: 20.5 (15/73) Control women: 1.5 (1/65) Control men: 0 (0/31) All comparisons vs. controls p<0.01
Zuskin, 1995 ⁶⁰ LEAST LIKELY CRS	Occupational survey of wool textile workers . Airborne dust in mill was sampled with Hexhlet horizontal 2-stage samplers as 8-hr TWA (n=25 samples) in opening, carding, and spinning and weaving areas. At least 3 measurements were made at each location	Stratified by sex and smoking status	Yes/no: wool textile worker	Prevalence, % (n) of sinusitis: Exposed female: 43 (68/158) vs. controls: 3.4 (3/87) (p<0.01) Exposed male: 62.1 (36/58) vs. controls: 2.3 (1/43) (p<0.01)
Zuskin, 1996 ⁶¹ LEAST LIKELY CRS	Occupational survey of dried fruits and teas processing workers . Casella personal samplers (2-stage, stationary samplers with membrane filter preceded by horizontal elutriator for respirable fraction) were used to measure airborne dust as an 8hr TWA. A total of 12 dust samples were collected	Stratified by result of skin prick test	Yes/no: employed in processing of dried fruits/teas	Prevalence, % (n) of sinusitis: Exposed: 14.8 (8/54) vs. control: 0 (0/40) (NS)
Zuskin, 1998 ⁶²	Occupational survey of paper-recycling workers . Dust concentrations were	Stratified by skin prick test	Yes/no: employed in the paper recycling industry	Prevalence, % (n) of sinusitis:

First author, Year Quality ranking ^d	Exposure assessment	Approach to Confounding	Exposure Parameterization	Primary Association
LEAST LIKELY CRS	measured by 2-stage Hexhlet apparatus as 8-hr TWA in two areas of the plant on five separate days			Exposed: 31.7 (32/101) vs. controls 2.3 (2/87) (p<0.01)
Zuskin, 1998 ⁶³ LEAST LIKELY CRS	Occupational survey of synthetic textile workers . Airborne dust in 2 textile synthetic fiber mills was sampled with Hexhlet horizontal 2-stage samplers as 8-hr TWA (n=23 samples). At least three measurements were made at each location	Stratified by sex, age, smoking status and duration of employment	Yes/no: employed in a synthetic textile plant	Prevalence, % (n) of sinusitis in females: Textile workers: 21.4 (66/308) vs. controls: 0.6 (1/160) (p<0.01) All other strata NS.
Zuskin, 1998 ⁶⁴ LEAST LIKELY CRS	Occupational survey of cocoa and flour processing workers . Dust concentrations were measured by a 2-stage Hexhlet apparatus as 8 hr TWA. 5 samples of dust were collected in the cocoa processing areas and six samples were collected in the flour processing area	NR	Yes/no: 1 Cocoa worker 2 Flour worker	Prevalence, % (n) of sinusitis: Cocoa: 20 (8/40) Flour: 16.9 (9/53) Control: 1.5 (1/65) Both comparisons vs. controls (p<0.01)
Zuskin, 2000 ⁶⁵ LEAST LIKELY CRS	Occupational history survey of mail carriers . Exposures of workers determined by analysis of atmospheric parameters over last 10 years using the temperature-wind-humidity (TWH) index and a review of sulfur dioxide and black smoke during past 10 years	Matched on sex, age, duration of job and smoking habits. Stratified by smoking	Yes/no: mail carrier	Prevalence, % (n) of sinusitis: Exposed: 38.9 (53/136) vs. control: 2.3 (2/87) (p<0.01)
Zuskin, 2000 ⁶⁶ LEAST LIKELY CRS	Occupational survey of food processing industrial workers . Dust concentrations were measured by 2-stage Hexhlet apparatus as 8-hr TWA. At least 10 samples were collected for each industry	Matched on age, sex and smoking	Yes/no: 1 Coffee 2 Tea 3 Spices 4 Confectionary 5 Dried fruits 6 Cocoa 7 Flour	Prevalence, % of sinusitis by groups: 1 Coffee: 25 2 Tea: 13 3 Spices: 27.2 4 Confectionary: 23.6 5 Dried fruits: 14.8 6 Cocoa: 20 7 Flour: 16.9 Controls: 0
Zuskin, 2004 ⁶⁷ LEAST LIKELY CRS	Physician administered survey. Employment at pharmaceutical manufacturer plant	Stratified by sex	Yes/no: pharmaceuticals processor	Prevalence, % (n) of sinusitis: Females: exposed: 33.7 (55/163) vs. controls 0 (0/92) (p<0.01) Males: exposed: 20 (7/35) vs. controls 0 (0/21) (p<0.01)
Zuskin, 2009 ⁶⁸ LEAST LIKELY CRS	Detailed occupational history survey of wind instrument musicians : working	Matched on sex. Stratified by smoking habit	1 Yes/no: wind instrument musician	Prevalence, % (n) of chronic sinusitis: Exposed, smoker: 27.8 (10/36) Exposed, nonsmoker: 19.0 (12/63)

First author, Year Quality ranking ^a	Exposure assessment	Approach to Confounding	Exposure Parameterization	Primary Association
	environment, playing technique, and length of time they have played environment, playing technique, and length of time they have played	of time they have played of time they have played	2 Duration of employment	Control, smoker: 7.1 (1/14) Control, nonsmoker: 0 (0/27) p<0.01 prevalence of sinusitis in exposed compared to controls. Sinusitis symptoms in relation to length of employment among exposed OR: 1.011 (0.912–1.125)

^aCRS probable: objective evidence of disease (by sinus CT scan, nasal endoscopy, X-ray); diagnosis by an ENT physician; or history of endoscopic sinus surgery for treatment of sinusitis. CRS possible: EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) CRS epidemiologic definition; diagnosis from a physician (ENT status not specified) based on a physical exam; or self-report of a physician diagnosis. Least likely CRS: CRS definitions that did not meet criteria for probable or possible CRS.

^bThe upper limit of confidence interval seems to be an error because its value is lower than the prevalence ratio itself. This is likely to be 203.

^cManuscript notes this percent to be 53%

CI: confidence interval; CRS: chronic rhinosinusitis; ENT: Ear Nose Throat; FDNY: Fire Department of New York; FESS: functional endoscopic sinus surgery; HMW: high-molecular weight; ISCO: International Standard Classification of Occupations; JEM: job exposure matrix; LMW: low-molecular weight; NP: nasal polyps; NR: not reported; NS: not significant; OR: Odds ratio; RR: relative risk; SES: socioeconomic status; TWA: time weighted average; TWH: temperature-wind-humidity; WTC: World Trade Center

Table 4

Characteristics of Included ENVIRONMENTAL Studies

First author, Year Country Quality ranking ^a	Study Design	Population	Data period	Sample size	Exposure	CRS definition	CRS natural history studied
Alexiou, 2011 ^{20b} Greece PROBABLE CRS	Cross-sectional	Case: CRSwNP patients admitted to otolaryngology department Control: orthopedic trauma patients	2007–2009	Case: n=100 Control: n=102	Dust, fumes, formaldehyde, chrome, nickel, arsenic, irritants, colors, solvents, and other volatile organic compounds	ENT diagnosis	Unspecified- prevalent CRSwNP
Kim, 2002 ^{21b} Canada PROBABLE CRS	Matched case-control	Case: CRSwNP diagnosis Control: CRSsNP diagnosis	1998 and 2001	Case: n=55 Control: n=55	Woodstove, indoor tobacco smoke, pets, and occupational exposures to noxious inhalant compounds	ENT diagnosis; endoscopy	Unspecified- prevalent CRSwNP
Tammemagi, 2010 ^{9b} US PROBABLE CRS	Matched case-control	Case: Nonsmoking incident CRS patients Control: Nonsmoking patients	2000–2004	Case: n=306 Control: n=306	Chemicals or respiratory irritants	ICD-9; CT or nasal endoscopy	Onset
Villeneuve, 2009 ²⁹ Canada POSSIBLE CRS	Cross-sectional	Adults from rural communities in Ottawa	2005–2006	Adults: n= 723	Animal dander; swine; smoking	Self-reported physician diagnosis	Unspecified- prevalent CRS

^a CRS probable: objective evidence of disease (by sinus CT scan, nasal endoscopy, X-ray); diagnosis by an ear, nose and throat (ENT) physician; or history of endoscopic sinus surgery for treatment of sinusitis. CRS possible: EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) CRS epidemiologic definition; diagnosis from a physician (ENT status not specified) based on a physical exam; or self-report of a physician diagnosis. Least likely CRS: CRS definitions that did not meet criteria for probable or possible CRS.

^b Study has both occupational and environmental data

CRS: chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyps; CRSsNP: chronic rhinosinusitis without nasal polyps; CT: computed tomography; ENT: Ear Nose Throat; ICD-9: International Classification of Diseases, Ninth Revision

Table 5

Exposure assessment, approach to confounding, exposure parameterization, and primary associations reported for eligible ENVIRONMENTAL studies

First author, Year Quality ranking ^a	Exposure assessment	Approach to Confounding	Exposure Parameterization	Primary Association
Alexiou, 2011 ^{20b} PROBABLE CRS	Interviewer-administered survey: 3 independent experts classified environmental exposure as none, not certain, and evident based on participant-reported past/current address; distance of homes from pollutant activities (e.g., industry, traffic); use of wood stove in home. Same procedure was followed for occupational exposure	Adjusted for sex, smoking habits, allergy history and education (medium, high, and superior)	Environmental exposure and occupational exposures: none, uncertain or certain Duration of occupational exposure: none, minimal to short, or long term	OR (95% CI) for prevalent NP: 1 Environmental exposure: evident vs. none: 15.0 (1.2–186.9) 2 Occupational exposure: evident vs. none: 21.4 (3.36–136.25) 3 Duration of occupational exposure: at least short vs. none: 4.91 (1.43–16.86)
Kim, 2002 ^{21b} PROBABLE CRS	Written survey: exposure to woodstoves, occupational exposures , indoor tobacco smoke, pets, and dust. Phone survey: duration and intensity of exposure to woodstoves	Adjusted for age, woodstove use, male sex, allergy, aspirin intolerance, occupational exposures, tobacco smoke, and pets	Yes/no to use/presence of exposure: 1 Woodstove use 2 Occupational exposure 3 Indoor tobacco smoke 4 Pets 5 Dust	OR (95% CI) for NP: 1 Woodstove use vs. no: 30.6 (6.9–135.6) 2 Occupational exposures vs. no: 7.2 (1.8–29.7) 3 Indoor tobacco smoke vs. no: 2.0 (0.6–7.1) 4 Pets vs. no: 0.2 (0.1–0.9)
Tammemagi, 2010 ^{9b} PROBABLE CRS	Phone survey: exposure to air pollution and chemicals or respiratory tract irritants at work, through hobbies, and from other sources	Matched on age, sex, and race	Yes/no: 1 Air pollution 2 Work exposure to chemicals 3 Hobby exposures to chemicals 4 Nonwork and nonhobby exposures to chemicals	Unadjusted OR (95% CI): 1 Air pollution vs. no: 1.59 (1.10–2.30) 2 Work exposure vs. no: 2.59 (1.58–4.24) 3 Hobby exposure vs. no: 2.92 (1.56–5.49) 4 Nonwork and nonhobby exposure vs. no: 1.52 (1.08–2.11)
Villeneuve, 2009 ²⁹ POSSIBLE CRS	GIS to determine distance between home and intensive hog farm	Adjusted for age, sex, cigarette smoking, and household income	Distance from home to hog farm (adults): 1 < 3 km 2 3 – < 9 km 3 9 km	OR (95% CI) for sinusitis in adults 1 vs. 3: 1.34 (0.78–2.30) 2 vs. 3: 0.67 (0.36–1.24)

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CRS probable: objective evidence of disease (by sinus CT scan, nasal endoscopy, X-ray), diagnosis by an ear, nose and throat (ENT) physician; or history of endoscopic sinus surgery for treatment of sinusitis. CRS possible: EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) CRS epidemiologic definition; diagnosis from a physician (ENT status not specified) based on a physical exam; or self-report of a physician diagnosis. Least likely CRS: CRS definitions that did not meet criteria for probable or possible CRS.

^d Study has both occupational and environmental data