

Chronic rhinosinusitis: Epidemiology and burden of disease

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is based on sinonasal symptoms coupled with sinonasal tissue inflammation. Establishing the epidemiology and prevalence of CRS, therefore, is challenging given that confirming objective evidence of sinonasal inflammation on a large scale is not feasible. Although the sinonasal symptoms are well documented at the sinonasal level, analysis of emerging data indicates that the impact on the general-health-related domains of health are the symptoms that are most bothersome to patients' quality of life.

Objective: To review the literature on the epidemiology and the societal and individual burdens of CRS.

Methods: A literature review.

Results: A refinement of questionnaire-based surveys coupled with sampling of respondents for accuracy likely provides the most accurate assessment of prevalence. There is geographic variation, but, in North American and European countries, the rates range from 4.5 to 12%. Although CRS is marked by sinonasal symptoms, the most problematic symptoms for patients seem to be the symptoms that affect general-health-related domains. Diminished sleep, productivity, cognition, mood, and fatigue are associated with the decision to elect surgical intervention and are associated with diminished healthy utility values. Direct costs of CRS have been well documented, but new data on the indirect costs of decreased productivity surpass direct costs, at \$12.8 billion dollars per year in the United States.

Conclusion: CRS is a common disease with a large and vast symptom burden with high indirect costs. Although clinicians are focused by guidelines on sinus-specific symptoms, patients seem to be most impacted by the general-health-related consequences of CRS. An expanded understanding of the extent and costs of these symptoms will allow for a cost-effective allocation of limited health care resources.

(Am J Rhinol Allergy 30, 134–139, 2016; doi: 10.2500/ajra.2016.30.4297)

Assessing the impact of chronic rhinosinusitis (CRS) on society is a challenging endeavor. One must estimate the proportion of a given population affected by CRS and simultaneously evaluate the degree to which individual health and well-being are influenced. Although CRS is clinically characterized by sinonasal symptoms, the impact on each individual is likely more comprehensive, which involves additional health-related domains. Emerging trends in clinical research are beginning to elucidate not only the extent and the reach of the symptomatology of CRS but also which symptoms are most bothersome or most valued by the individual and society. A refined understanding of the complete symptom profile of CRS as well as an understanding of what individuals value will help to accurately allocate limited health care resources. Furthermore, an accurate understanding of the prevalence of CRS is critical to extrapolate these values to a societal and health policy level. The goal of this review was to summarize available evidence regarding the population prevalence of CRS as well as to discuss data that explore the clinical and health economic impacts of CRS.

Epidemiology

CRS is widely thought to be a common disease, and many studies reflexively cite a prevalence of 10–15%.¹ The question remains whether this oft-quoted prevalence is an accurate approximation. Estimating the true prevalence of CRS in a reliable and reproducible way is valuable in that it allows for appropriate allocation of resources and provides a means of measuring the impact of time and

regional variables on the disease. Capturing the true prevalence of CRS has been challenging for a number of reasons. First, broadly accepted diagnostic criteria for CRS were not developed until relatively recently.^{2,3} Therefore, earlier epidemiologic studies may have had poor specificity and are often not directly comparable. In addition, the diagnosis of CRS is based on the combination of subjective symptoms as well as objective findings of tissue inflammation. The need for objective findings is critical because a purely symptom-based diagnosis will prove sensitive but will have a high false-positive rate due to overlap of CRS symptoms with other common diseases, *e.g.*, allergic rhinitis. Unfortunately, objective measures are not necessarily feasible on a large scale, and, therefore, population-level investigations into the prevalence of CRS are typically undertaken through questionnaire surveys.

Questionnaire-based Evaluation

National surveys provide a valuable resource for estimating disease prevalence across a society because they typically use complex sampling methods and large sample sizes to increase generalizability. The National Health Interview Survey (see Table 1 for commonly used abbreviations and definitions throughout the present text) is one such study carried out in the United States and was reported in 2012.⁴ This survey included 234,921 adults and found that 12.1% of the subjects reported having been given the diagnosis of sinusitis by a health care provider in the preceding year, which varied from 7.0% in Asians to 13.8% in whites. The Canadian analog, the National Population Healthy Survey, included 73,364 Canadian subjects with 4.5% of respondents reporting having been given a diagnosis of sinusitis.⁵ One important weakness of both studies is that they do not clarify whether the diagnosis is acute or chronic sinusitis, and this may lead to an overestimation of the prevalence of CRS. The 2008 Global Allergy and Asthma European Network (GA²LEN) questionnaire-based survey refined the questionnaire to adhere to clinical European Position Paper on Rhinosinusitis and Nasal Polyps criteria,² which includes the criterion that symptoms are present for >12 weeks, and still found that 10.9% of the 57,128 respondents met the subjective European Position Paper on Rhinosinusitis and Nasal Polyps criteria for CRS.⁶ Again, diagnoses were not confirmed by objective evidence of sinonasal inflammation, and, therefore, overestimation cannot be ruled out.

These large questionnaire-based studies also provide the best perspective on regional variation of CRS frequency. Although the meth-

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Presented at the North American Rhinology and Allergy Conference, Boca Raton, Florida, February 5, 2015.

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Table 1 Abbreviations and definitions

Abbreviations	Definitions
CFQ	Cognitive Failures Questionnaire: A 25-question instrument that captures patient-reported cognitive dysfunction
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
EQ-5D	Euroqol5 Dimension: Survey instrument used for measuring economic preferences for health states
GA ² LEN	Global Allergy and Asthma European Network: 2008 European survey of 57,128 adults
NHIS	National Health Interview Survey: U.S. 2012 survey of 234,921 adults
NPHS	National Population Health Survey: Canadian 1997 survey of 73,364 adults
QALY	Quality-adjusted life-year is a measure of the disease burden that includes both quality and quantity of life lived
SF-6D	Short Form 6 Dimension: A 6-question instrument used for measuring economic preferences for health states
SNOT-22	Sinonasal Outcomes Test-22: A disease-specific quality-of-life measure

Table 2 European geographic variation of prevalence

Country	CRS by EP ³ OS Criteria*	Total No. Respondents	Prevalence, %
Finland	125	1809	6.9
Denmark	264	3340	7.9
Macedonia	297	3613	8.2
Sweden	2296	26,675	8.6
Germany	318	3410	9.3
United Kingdom	316	3016	10.6
Italy	105	965	10.9
France	184	1385	13.3
Netherlands	456	3191	14.3
Poland	967	5711	17.1
Belgium	348	1851	18.8
Portugal	586	2162	27.1

CRS = chronic rhinosinusitis, EP³OS = European Position Paper on Rhinosinusitis and Nasal Polyps.
EP³OS criteria from Ref. 5.

odology of the Canadian and U.S. health surveys are imperfect, they do use relatively similar questions across massive sample sizes. Interestingly, the difference in CRS prevalence between the two countries is relatively large, with Canadian respondents reporting the diagnosis of sinusitis at less than half the rate of their U.S. neighbors. Whether this represents differences in CRS prevalence, health care access, or the diagnostic threshold of each country's physicians remains unknown. The European study also effectively highlights the wide range of prevalence across that continent (Table 2). Stratification of the European study data by each participating center reveals that the prevalence ranged from 6.9 to 27.1%.⁶ Because this study used symptom criteria as opposed to physician diagnosis, the variation cannot be explained by diagnostic thresholds or access to health care. Across all of the questionnaire studies, women were disproportionately affected with CRS (Table 3), which may represent a sex-specific susceptibility to the disease process.

Clinically-based Evaluation

Purely survey-based studies that lack confirmation of sinonasal inflammation may overestimate prevalence. For this reason, guidelines² recommend radiographic and/or endoscopic confirmation of disease to prevent misclassification of diseases that can masquerade (e.g., primary headache disorder, chronic rhinitis, septal deviation) as CRS. Perhaps one of the most striking examples of this phenomenon is a study of subjects recruited with self-diagnosed CRS in whom only 2% were found to have CRS.⁷ Another study that investigated the prevalence of CRS by the International Classification of Diseases, Ninth Revision codes in a single U.S. county found only 1.96% of subjects received the diagnosis in a single year.⁸ Another U.S. cohort study investigated the issue in 703 patients who presented for evaluation of CRS by an otolaryngologist found that 30% of subjects who

reported subjective symptoms of CRS had no radiographic evidence of disease.⁹

Results from these studies indicated that relying on patient reporting would lead to exaggerated prevalence estimates but that conclusion remains speculative. Each of these studies report on geographically isolated patient populations, range from one to three orders of magnitude smaller than the survey-based investigations, and likely have referral and/or selection biases. A follow-up study to the GA²LEN survey of CRS complicates this discussion even further. An otolaryngology evaluation was performed on respondents to the original study, and 30% of the CRS diagnoses were overturned by an otolaryngologist.¹⁰ Interestingly, 15% of the subjects who did not meet CRS criteria by the questionnaire were actually given a diagnosis of CRS by the otolaryngologist for a net increase in the number of overall CRS diagnoses, which may reflect the potential for minimized symptoms and/or objective disease (e.g., polyps) without symptoms.

Investigations into the true prevalence of CRS will likely always be imperfect and produce a range of findings across studies. Methodology does impact the detected rates of disease, and standardization of symptoms for diagnosis was a major step forward in triangulating the true prevalence of disease. At a minimum, standardized diagnostic criteria allows for a reproducible means by which to investigate the evolution of the disease over time and across regional and ethnic variations. For this reason, the GA²LEN data are unique in their robustness, which found a prevalence of ~10% in Europe. The U.S. data are comparable with these findings, at 12%, but potentially include past cases of acute sinusitis.

Individual Burden of CRS

Sinonasal Symptoms and Quality of Life. The clinical burden of CRS on an individual can be debilitating. The European Position Paper on Rhinosinusitis and Nasal Polyps¹¹ and the Adult Sinusitis Guidelines¹² focus clinicians onto the "cardinal" symptoms of CRS to establish a correct diagnosis and to monitor treatment success. An emphasis on cardinal symptoms optimizes positive and negative predictive values and allows for an accurate and efficient diagnosis. Problems with nasal congestion, purulent drainage, facial pain and/or pressure, and loss of smell are significantly bothersome to patients. However, CRS potentially produces wide-ranging consequences that extend beyond just sinonasal symptoms. Quality of life (QOL) has been established as an important end point for clinical study¹³ because it quantifies how the disease impacts daily functioning. Several sinus-specific QOL instruments exist that attempt to capture both the severity and the extent of the disease, and the literature that discusses QOL in patients with CRS is robust, and quality reviews exist.^{14,15} Although the significance of sinus-specific symptoms and QOL is undeniable, there is recent evidence that "extra-rhinologic" symptoms, such as poor sleep, cognitive dysfunction, and overall poor productivity, are also critically important. These extra-rhinologic impacts of CRS seem to significantly contribute to the overall health-related burden of disease and will be further discussed next.

Table 3 Survey-based epidemiologic studies on CRS

Study	Year	Survey	Location	No. Subjects	CRS, % Prevalence	CRS, % Male Sex
Chen <i>et al.</i> ⁵	2003	NPHS	Canada	73,364	5.2	32
Hastan <i>et al.</i> ⁶	2011	GA ² LEN	Europe	57,128	10.9	43
Blackwell <i>et al.</i> ⁴	2014	NHIS	United States	234,921	12.10	36

CRS = chronic rhinosinusitis; NPHS = National Population Health Survey; GA²LEN = Global Allergy and Asthma European Network; NHIS = National Health Interview Survey.

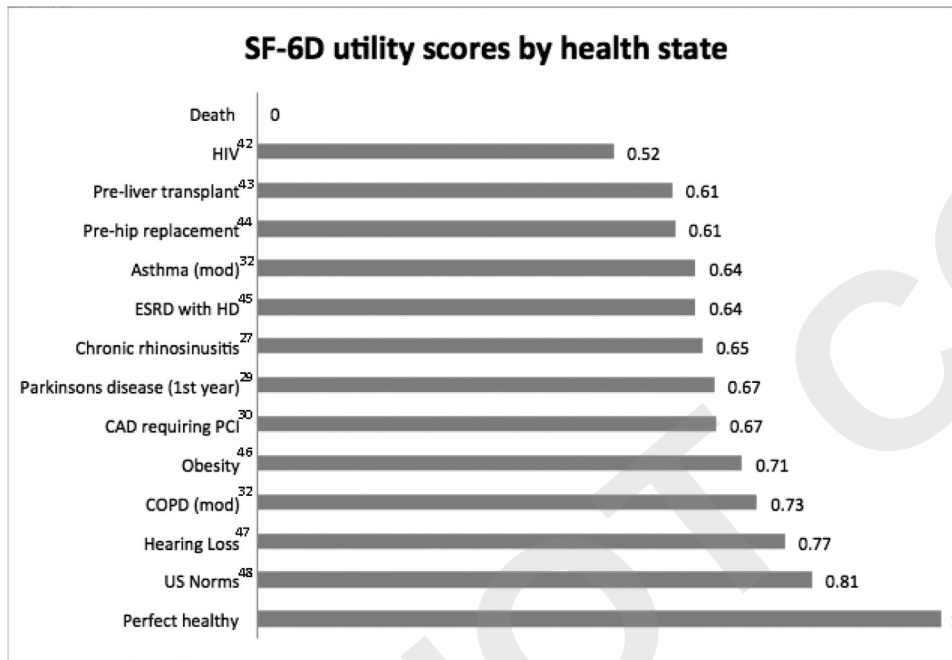


Figure 1. Utility scores for a variety of health states. HIV = human immunodeficiency virus; ESRD = end stage renal disease; HD = hemodialysis; CAD = coronary artery disease; PCI = percutaneous coronary intervention; COPD = chronic obstructive pulmonary disease.

Table 4 Individual costs of CRS

Costs	Annual U.S.\$ per Patient with CRS	No. Days per Year
Direct costs*		
Office-based expenditures	346	—
Prescription expenditures	397	—
Self-expenditures	90	—
Total health care expenses	772	—
Indirect costs#		
Presenteeism	3162	24.6
Absenteeism	4988	38.8
Lost household time	1927	21.2

CRS = chronic rhinosinusitis.

*2007 U.S.\$ spent beyond controls; from Ref. 38.

#Numbers in 2012 U.S.\$, with assumed median U.S. salary of \$30,875 and housekeeper wage of \$10.49 per hour for household time; from Ref. 39.

Extra-rhinologic Impacts. Sinus-specific QOL instruments are composite questionnaires that seek to capture all aspects of the impact of CRS. Some of these instruments are stratified into domains, whereas others are summed into one aggregate score. The rationale behind domains is that the questionnaires are measuring more than a single aspect of health. Examination of the underlying domains of an outcomes instrument can help to clarify what patients value. Specifically, examination of the Sinonasal Outcomes Test 22¹⁶ revealed that patients who elect surgical intervention over medical therapy are more likely to experience sleep and psychologic dysfunction.¹⁷ No difference was found in the rhinologic-specific domains between the pa-

tients who elected surgery and those who continued with medical therapy. These findings indicate that patients are more likely to take the riskier intervention when the disease process impacts sleep and psychologic function. The importance of extra-rhinologic impacts was highlighted in another recent study. Remenschneider *et al.*¹⁸ examined individual items from the Sinonasal Outcomes Test-22 instrument to examine which items most impacted health state utility scores. Health state utility scores represent a measure of the economic preference of a health state (see *Societal Burden of CRS* for further discussion of utility scoring). Indeed, the items that correlate most strongly with the utility score measure, the Euroqol 5 Dimension, are the questions that investigate sleep quality, fatigue, productivity, concentration, and frustration. These general-health-related domain symptoms have been relatively unexplored until recently.

Sleep and Fatigue. Patients with CRS commonly report sleep impairment; however, investigation into sleep outcomes by using validated clinical measures is a recent endeavor. A number of pathophysiologic mechanisms conceivably facilitate the relationship between CRS and sleep impairment, including nasal airway obstruction, impairment of mood, chronic pain, direct neural signaling, or *via* neural-immune cytokine signaling.¹⁹ A cross-sectional study of subjects with CRS found that 75% of the subjects reported a poor sleep quality. Furthermore, patient-reported CRS severity correlated with sleep quality.²⁰ Even when sleep questions are removed from CRS-specific instruments, the correlations of sleep quality and CRS symptom burden are maintained. To put this into perspective, the burden of CRS on sleep is comparable with obstructive sleep apnea and is higher than narcolepsy.²⁰ In patients with medically refractory CRS who underwent surgery, the odds of achieving good (<5 on the Pittsburgh Sleep Quality Index) sleep after endoscopic sinus surgery was quite high

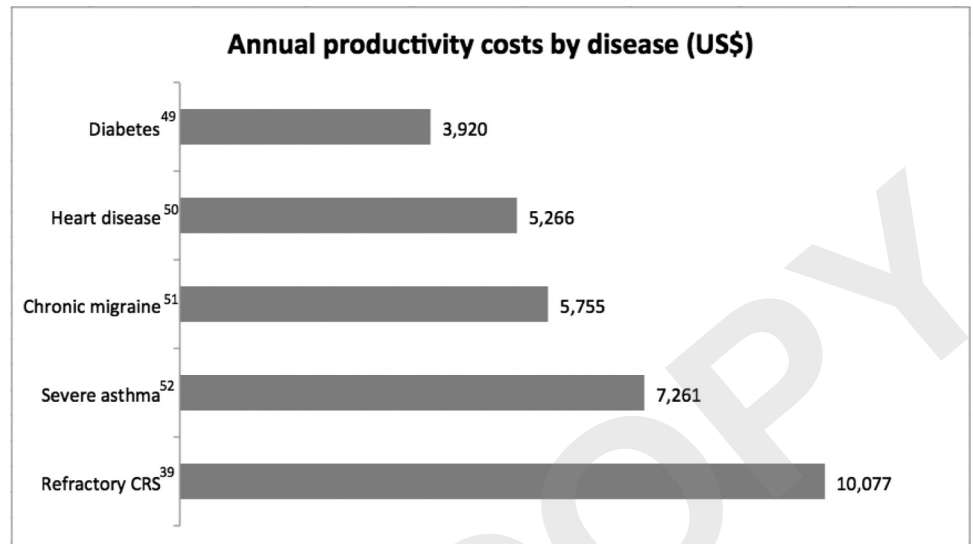


Figure 2. Annual productivity loss of various diseases. "Heart disease" includes acute coronary syndrome, heart failure, and atrial fibrillation.

(odds ratio 5.94 [95% confidence interval {CI}, 3.06–11.53]; $p < 0.001$).²¹ Sleep improvement after surgery was paralleled in a cohort of subjects with CRS without nasal polyps or septal deviation.²² These findings highlight that the impact of CRS on sleep is likely multifactorial, with nasal airway only one of several potential mechanisms.

Severe fatigue and bodily pain are also commonly reported by patients with CRS. A systematic review with meta-analysis, including data on 3427 patients from 28 studies, examined fatigue in patients with CRS.²³ The baseline median prevalence of fatigue was 54%, which ranged from 11 to 73% across studies. Another systematic review with meta-analysis examined bodily pain in 11 studies with 1019 patients. By primarily using the Short Form 36 instrument, pooled mean bodily pain scores were 0.89 standard deviations below national or local population norms ($p < 0.001$). Both fatigue and bodily pain were shown to significantly improve after sinus surgery, with combined effect sizes of 0.77 (95% CI, 0.59–0.95) for fatigue and 0.55 (95% CI, 0.45–0.64) for bodily pain. Further inquiry is necessary to understand the mechanisms of sleep dysfunction in CRS and to better understand any interrelationships between sleep and fatigue.

Cognitive Function. Patients with CRS commonly mention poor concentration and altered memory, but cognitive function in CRS has received relatively little attention. Most data come from individual questions isolated from broader QOL instruments and lack appropriate controls. A recent prospective, case-control study compared subjects with and without CRS by using the Cognitive Failures Questionnaire, a 25-question validated instrument that measures patient-reported cognitive dysfunction.²⁴ Patients with CRS were found to report significantly worse cognitive function compared with a control population. Furthermore, objective evaluation by using a battery of computerized tests revealed that reaction time scores were diminished in subjects with CRS compared with controls. Regression analysis found that these differences remained after controlling for potential confounding factors, such as age, education, antihistamine usage, obstructive sleep apnea, depression, and allergic rhinitis. Evaluation of cognitive function in CRS and elucidation of possible mechanisms is in its infancy, and much work remains to truly understand the impact of CRS on cognition.

Societal Burden of CRS

The relative high prevalence of CRS, coupled with significant symptoms and QOL impacts, leads to the assumption that CRS causes a substantial burden to society. However, understanding the relative societal impacts of CRS requires comparison with other diseases by using a common set of metrics. Health state utility values represent one such measure because they quantify how an individual values his

or her current health state. Economic measures are another means of evaluating societal impacts, including both direct and indirect costs associated with CRS. Taken together, health utility values and disease costs can inform policy makers who must make resource allocation decisions on a societal level.

Health Utility Value. Health utility value is a metric designed to determine the preference for a given health state. By definition, utility values range from 0 to 1, in which 0 represents death and 1 represents perfect health. The use of such a metric is important in that it allows for meaningful comparisons across heterogeneous diseases and interventions, and it provides a means to make an economic appraisal of each health state and intervention.²⁵ Determination of the utility value of an intervention allows for calculation of quality-adjusted life-years (QALY), which represent both the number of years of life that would be added and the quality of those years. This unit is important to efficiently allocate limited health care resources, and, in 1996, The U.S. Public Health Service Panel on Cost Effectiveness in Health and Medicine recommended that the QALY be used as the standard metric for cost-effectiveness research.²⁶

Utility scoring in CRS is in its nascency, with the first study on the subject within the past 5 years. Soler *et al.*²⁷ applied the Short Form 6 Dimension²⁸ to 232 subjects with medically refractory CRS who presented for endoscopic sinus surgery at baseline and with 6 months' follow-up. At baseline, the mean utility value for subjects with CRS was 0.65 (95% CI, 0.63–0.66). This utility value is a devastatingly low number in a relatively young cohort of patients (mean [standard deviation], 47.8 ± 14.1 years), with perhaps a mean of 25 years of life remaining if average life spans are assumed. To place this utility score in context of other medical conditions, this finding places CRS below Parkinson's disease,²⁹ coronary artery disease that requires percutaneous intervention,³⁰ congestive heart failure,³¹ and moderate chronic obstructive pulmonary disease (Figure 1).³² Remenschneider *et al.*³³ found similar baseline utility value comparisons by using the Euroqol 5 Dimension but found that severe chronic obstructive pulmonary disease, diabetes, and arthritis exhibit lower baseline health utility values.

By using the Short Form 6 Dimension, Soler *et al.*²⁷ found that interval utility values improved by 0.087 (95% CI, 0.06–0.12; $p < 0.001$) after primary surgery and 0.062 (95% CI, 0.04–0.09; $p < 0.001$) after revision surgery. Again, for context, these interval changes represent substantial improvements when considering that 0.03 is the minimal clinically important difference.³⁴ Improvement after endoscopic sinus surgery as an intervention has greater impact than other well-studied interventions, including continuous positive airway pressure³⁵ for

obstructive sleep apnea and joint replacement surgery for³⁶ for inflammatory joint disease. Primary surgery surpasses coronary angioplasty in utility improvement.³⁰

Costs of CRS and Cost-Effectiveness of Treatment. The direct costs to society of CRS have been well documented and are estimated to be high, at \$8.6 billion per year, in the United States.^{37,38} The indirect costs to society are represented by the loss of productivity associated with CRS. Productivity loss is measured through absenteeism (missed work), presenteeism (reduced work performance), and lost leisure time due to CRS.³⁹ For an individual with medically refractory CRS, this represents a cost of \$10,077 per year and nationally costs the United States an additional \$12.8 billion (Table 4; Fig. 2).³⁹ These metrics do not attribute an individual's preference for a given outcome (or society's preference), such as controlled or uncontrolled sinusitis. The QALY is the preferred metric to incorporate these judgments, and cost-effectiveness research can quantify the value of treatment of CRS.

A preliminary cost-effectiveness analysis has been performed that compared endoscopic sinus surgery to continued medical therapy for medically refractory CRS.³⁹ By using data from a North American cohort of patients with medically refractory CRS (Clinical Trials NCT00799097 NIH: R01 DC005805), endoscopic sinus surgery yielded 20.50 QALYs, whereas medical therapy alone resulted in 17.13 QALYs.⁴⁰ The willingness to pay threshold represents the maximum cost that society will accept for a QALY and is generally thought to be ~\$50,000 in the United States.⁴¹ A probabilistic sensitivity analysis found with 74% certainty that endoscopic sinus surgery represents the cost-effective decision over continued medical therapy for the conservative willingness to pay a threshold of \$25,000. Over time, this analysis found that endoscopic sinus surgery becomes the cost-effective intervention within the third year after surgery.

CONCLUSION

CRS is a common chronic disease with a massive impact on QOL and productivity. The impact of CRS has been well cataloged across a number of CRS-specific outcome measures, but it has only been within the past few years that there has been recognition of the health-related consequences of CRS on sleep quality, cognition, mood, productivity, and fatigue. These health-related consequences of CRS correlate with patient utility values and are associated with electing surgery over continued medical therapy in patients with medically refractory CRS. The indirect costs of medically refractory CRS in the United States is an order of magnitude greater than the direct costs. Endoscopic sinus surgery has been shown to be an effective way to reduce the indirect costs and, over a 3-year timeline, is more effective than continued medical therapy. CRS presents a significant burden at both the individual and societal level by way of its high prevalence, vast and burdensome symptom profile, and high indirect costs.

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