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Systematic literature review of humanistic and economic burdens of chronic rhinosinusitis with nasal polyposis

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ABSTRACT

Objectives: We conducted a systematic literature review (SLR) of randomized controlled trials and real-world evidence (RWE) studies to determine the humanistic (e.g. health-related/disease-specific quality of life [QOL]) and economic (e.g. direct and indirect costs) burdens of chronic rhinosinusitis with nasal polyposis (CRSwNP).

Methods: The SLR adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Embase, MEDLINE and Evidence-Based Medicine Reviews databases were searched using OVID. Relevant studies involving adult patients with CRSwNP published between 1 January 2008 and 16 February 2019 were included, with relevant conference abstracts from 1 January 2017, onward.

Results: Sino-Nasal Outcomes Test (SNOT)-22 was the most frequently used disease-specific health-related QOL/patient-reported outcomes instrument for patients with CRSwNP. Baseline SNOT-22 scores ranged from 25 to 73 for surgical candidates and from 14 to 56 for medically managed patients with CRSwNP. Mean baseline EuroQol-5 Dimensions (EQ-5D) index for patients with CRSwNP ranged from 0.81 to 0.86, and mean baseline Short Form-6 Dimensions (SF-6D) ranged from 0.67 to 0.75. Three months (EQ-5D) and 5 years (SF-6D) post-endoscopic sinus surgery (ESS), rates increased from 0.81 to 0.89 and from 0.69 to 0.80, respectively. One year post-diagnosis, patients with CRSwNP had significantly more systemic prescriptions, underwent significantly more medical procedures, demonstrated greater health care resource utilization and had significantly greater mean health care costs compared with matched controls (all $p < .001$). Overall, for patients with initial ESS, CRSwNP was associated with higher disease-related expenditures compared with CRS without nasal polyposis (NP), even for patients who did not undergo revision surgery.

Conclusions: This SLR identified substantial humanistic burden among surgery candidates. RWE shows that surgeries were used to treat relatively more severe CRSwNP patients as recommended by guidelines. Patient QOL is improved significantly after surgery; however, there is a lack of evidence on patients with revision surgery. Surgery is also associated with higher costs, and the presence of NP was a predictor of revision surgery. Patients with CRSwNP demonstrate greater health care resource utilization and costs compared to those with CRS without NP. Costs associated with different severity of CRSwNP and revision surgery need to be assessed further.

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Introduction


Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a chronic inflammatory condition associated with significant morbidity and decreased health-related quality of life (HRQOL)¹. It is generally a condition of middle age (with an average age of onset at 42 years), and is typically diagnosed at 40–60 years. CRSwNP may result from non-allergic disorders such as cystic fibrosis. CRSwNP is estimated to affect 25–30% of patients with chronic rhinosinusitis (CRS)¹.

The presence of polyps in CRSwNP may cause long-term symptoms such as prominent nasal obstruction, post-nasal drip, loss of smell and discharge, all of which can impact patients' HRQOL². Patients with CRSwNP have worse

subjective symptoms (evidenced by Sino-Nasal Outcome Test [SNOT]-22 scores), worse objective symptoms (demonstrated by Lund–Mackay scores [LMS]) and more frequently require revision surgery than patients with CRS without nasal polyposis (CRSsNP)³.

Treatment options for patients with CRSwNP remain limited. Both topical corticosteroids and nasal saline irrigations are recommended as initial medical therapies⁴. Intranasal corticosteroids (ICSs) can decrease polyp size, reduce sino-nasal symptoms and improve patient HRQOL^{5,6}. Oral corticosteroids (OCSs) can reduce polyp size and improve symptoms, but should be administered cautiously given their association with serious systemic adverse effects⁷. Antibiotics

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may be useful in treating infectious exacerbations of CRSwNP, but clinically significant efficacy (i.e. NP shrinkage) in large, randomized trials is lacking¹. Patients with serious disease or who have failed medical management may be eligible for sinus surgery. Functional endoscopic sinus surgery (FESS) can improve sinonasal symptoms and inflammation, but NP can still recur⁸, with rates as high as 50% (for patients followed over a period of 3 years)⁹.

Given the unmet need in recalcitrant CRSwNP, biologics have emerged as a novel treatment option owing to recent advancements in our understanding of the disease, particularly inflammation^{9,10}. Studies have demonstrated efficacy for biologics in the treatment of CRSwNP; therefore, biologics are anticipated to reduce the clinical, humanistic and economic burden of CRSwNP. A comprehensive review of this burden, which has not been conducted to date¹¹, is required to better understand the potential impact of biologics when more humanistic and economic data become available.

A systematic literature review (SLR) was conducted to understand the epidemiology, and clinical, humanistic and economic burdens of CRSwNP. The results of this SLR are published in two parts. This part covers the humanistic burden and economic burden of CRSwNP. Humanistic burden includes the impact of CRSwNP on a patient's HRQOL and activities of daily living. Economic burden includes health care resource utilization (HCRU), direct treatment costs and indirect costs. A companion article in this journal presents the results of the SLR describing the epidemiology and clinical burden of CRSwNP.

Methods

We performed all aspects of the SLR according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Using the OVID platform, we searched Ovid MEDLINE, including E-Pub Ahead of Print and In-Process & Other Non-Indexed Citations; Embase; and the following Evidence-Based Medicine Reviews databases, as applicable to each topic: the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, the NHS Economic Evaluation Database and the Cochrane Central Register of Controlled Trials. Details of the search strategies are provided in the [Appendix \(Supplementary Tables 1, 2, and 3\)](#).

For humanistic burden, additional randomized controlled trials (RCTs) were identified from the US National Library of Medicine's ClinicalTrials.gov. The School of Health and Related Research Health Utilities Database and the Health Economics Research Centre database of mapping studies were searched to validate findings for health utility and mapping studies, respectively. In addition, findings from published literature were validated against targeted literature searches and bibliographies of select review articles.

For economic burden, a review of the TUFTs Cost-Effectiveness Analysis (CEA) Registry, a comprehensive database of cost-utility analyses, was conducted to ensure all results were captured. In addition, findings from published

literature were validated against targeted literature searches and hand-searching of the bibliographies of included full-text journal articles.

Study selection

Literature searches were performed 16 February 2019, using the PICOS (Population, Intervention, Comparators, Outcomes, Study design) criteria. Studies of any design involving adult patients (≥ 18 years old) with CRSwNP published between 1 January 2008 and 16 February 2019 were included. The publication date limit from 1 January 2008 onwards was applied in order to capture the most recent and relevant studies, and to limit the scope of this assessment. Key outcomes for humanistic burden included patient-reported outcomes (PROs), disease-specific and general HRQOL measures, and health state utility values (HUVs). Key outcomes for economic burden included HCRU and costs associated with CRSwNP (including surgery and OCS use), work and school absenteeism and presenteeism, productivity loss, patient out-of-pocket expenditure to manage CRSwNP, caregiver burden, existing health economics models for CRSwNP, and economic impact of eosinophilic disease. Key exclusion criteria included pediatric studies (without adults), non-English articles, animal studies, commentaries, editorial reviews, expert opinion articles, letters and conference abstracts published prior to 1 January 2017. Detailed inclusion and exclusion criteria are shown in [Table 1](#).

Review process

Study screening (title and abstract) was performed using the systematic review software DistillerSR (Evidence Partners, Ontario, Canada) and was conducted by two reviewers who assessed study eligibility based on the pre-defined PICOS criteria. Citations considered to be eligible at the title-and-abstract stage were then independently reviewed by two reviewers in full-text form to determine formal inclusion in the final review. Reasons for exclusion were documented at the full-text stage. Any disagreements during screening were resolved by a third independent reviewer.

Data extraction

Details for selected articles were collected using a standardized data extraction template in Microsoft Excel. For both portions of the SLR, data extraction was performed by a single reviewer and validated by a second reviewer.

Quality assessment of included studies

A quality assessment of all publications reporting HUVs was performed using the quality assessment and relevance criteria presented in the National Institute for Health and Care Excellence (NICE) Technical Support Documents¹² and Papaioannou et al.¹³ by a single reviewer and validated by a second reviewer. A risk of bias assessment of other eligible humanistic or economic burden studies was not performed.

Table 1. Criteria for inclusion and exclusion of studies: humanistic and economic burdens.

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients aged ≥ 18 years old with CRSwNP	Only patients aged < 18 years All other diseases
Intervention/comparators	Any treatment for CRSwNP	None
Outcomes	Humanistic burden: Symptoms and patient-reported outcomes HRQOL, including anxiety/depression Functional impairment and activity limitations Caregiver burden The role of high EOS Economic burden: HCRU and costs associated with CRSwNP, including surgery/OCS use Work and school absenteeism and presenteeism Productivity loss Patient out-of-pocket expenditure to manage CRSwNP Caregiver burden Existing health economics models for CRSwNP Economic impact of high EOS	Outcomes not related to the humanistic or economic burden of CRSwNP
Study design	Any study type (e.g. clinical trials, observational studies, surveys, registries, economic evaluations) Articles published 1 January 2008 to 16 February 2019 Conference abstracts published 1 January 2017 to 16 February 2019	Animal studies, <i>in vitro</i> studies, case reports, expert opinion articles, commentaries, letters Articles published before 1 January 2008 Conference abstracts published before 1 January 2017
Language	Articles in English ^a	All non-English articles

^aCitation retrieval was not limited by language. Records were categorized based on language during title-and-abstract screening stage, and non-English abstracts were excluded. English abstracts with non-English articles were excluded at the full-text screening stage.

Abbreviations. CRSwNP, Chronic rhinosinusitis with nasal polyposis; EOS, Eosinophils; HCRU, Health care resource utilization; HRQOL, Health-related quality of life; OCS, Oral corticosteroid.

Results

Humanistic burden: summary of search results for randomized controlled trials

In total, 5466 records of RCTs were identified; 2979 records were available for title-and-abstract screening after duplicates were removed. After assessment of all records based on title and abstract, 325 were selected for full-text review. After full-text review and additional searches, 59 published articles, five conference abstracts and five clinical trial records, representing 63 unique studies, were found to fulfill the inclusion criteria (Figure 1(A)).

Humanistic burden: summary of search results for real-world evidence studies

In total, 4117 real-world evidence (RWE) records (defined as non-randomized studies, including prospective observational studies, phase 4 studies, etc.) were identified, and 2809 records were available for title-and-abstract screening after duplicates were removed. After assessment, 544 records were selected for full-text review. Full-text review and additional searches identified 231 published articles and 10 conference abstracts, representing 209 unique studies that met the inclusion criteria (Figure 1(B)).

Disease-specific health-related quality of life

While there were many instruments used to assess HRQOL for patients with CRSwNP, SNOT-22 was the most commonly reported disease-specific instrument used (reported in 19 RCTs and 82 RWE studies) (Table 2). Seventy-one studies reported individually measured symptoms related to CRSwNP. Individually measured symptoms were typically

assessed using a Likert scale or visual analog scale (VAS). The six most frequently measured symptoms were nasal congestion, olfactory disturbance, nasal discharge, headache, facial pain and post-nasal drip.

Baseline health-related quality of life: SNOT-22, SF-6D and EQ-5D

Ten RCTs^{14–23} and 42 RWE studies^{24–65} reported mean or median baseline SNOT-22 scores for study populations consisting of surgical candidates. In all studies, baseline SNOT-22 score was assessed prior to surgical interventions. Overall, SNOT-22 scores ranged from 25⁴⁴ to 73⁵⁷ for surgical candidates. Six RCTs^{66–71} and 16 RWE studies^{56,72–86} reported mean or median baseline SNOT-22 scores for study populations consisting of medically managed patients (i.e. patients not identified as surgical candidates at baseline). Baseline SNOT-22 scores in these medically managed patients ranged from 14 (value was interpreted from primary source using Digitizelt software)⁷⁶ to 56⁷⁵.

Three studies^{87–89} reported baseline HUVs for patients with CRSwNP using the SF-6D (Table 3). Soler et al.⁸⁷ reported a mean baseline HUV of 0.67 for a prospective cohort of patients with CRSwNP undergoing surgery. Luk et al.⁸⁸ conducted a prospective cohort study that provided baseline HUVs for three sub-populations of medically refractory CRSwNP patients who were considered candidates for endoscopic sinus surgery (ESS): patients electing continued medical management (baseline HUV = 0.75); patients undergoing surgery (baseline HUV = 0.72); and patients initially electing medical management who elected to change therapy to include ESS (baseline HUV = 0.68). Ference et al.⁸⁹ conducted a cross-sectional study that reported a baseline HUV of 0.73 for a population of patients with CRSwNP.

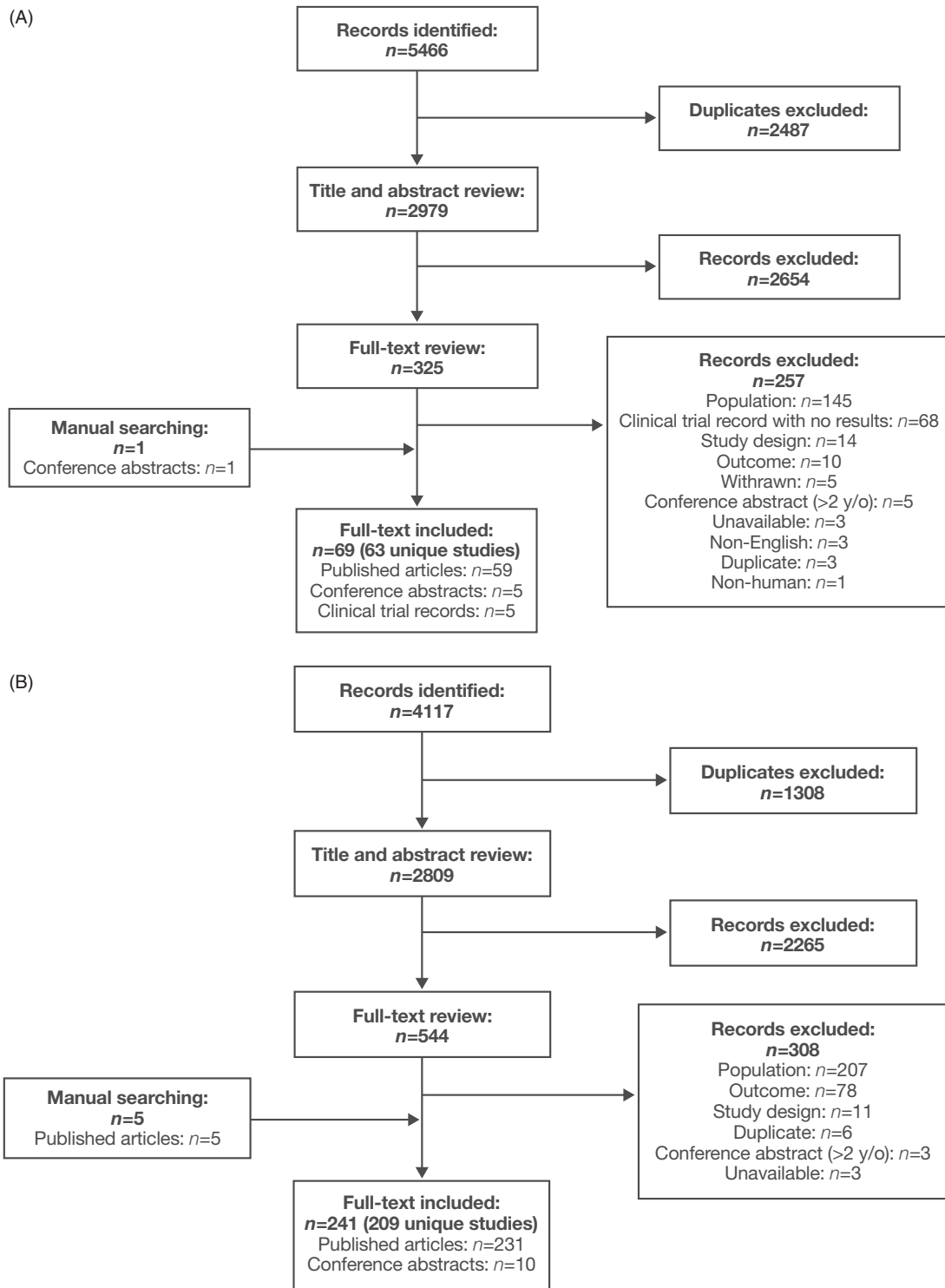


Figure 1. (A). PRISMA diagram for RCTs: humanistic burden. (B). PRISMA diagram for RWE studies: humanistic burden. (C). PRISMA diagram: economic burden. Abbreviations. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized controlled trial; RWE, real-world evidence; y/o, Years old.

Two studies reported baseline HUVs for patients with CRSwNP using the EQ-5D^{23,90}. Bachert et al.²³ conducted a multinational RCT that assessed the efficacy of mepolizumab versus placebo for patients with recurrent NP receiving topical corticosteroids who required surgery. At baseline, the mean HUV reported for the mepolizumab and placebo

groups was 0.88 and 0.84, respectively, with a weighted mean of 0.86. Remenschneider et al.⁹⁰, in a prospective cohort study conducted in the United States, described HUVs in the CRS population and measured the impact of sinus surgery on HRQOL over time. The HUV reported at baseline was 0.806.

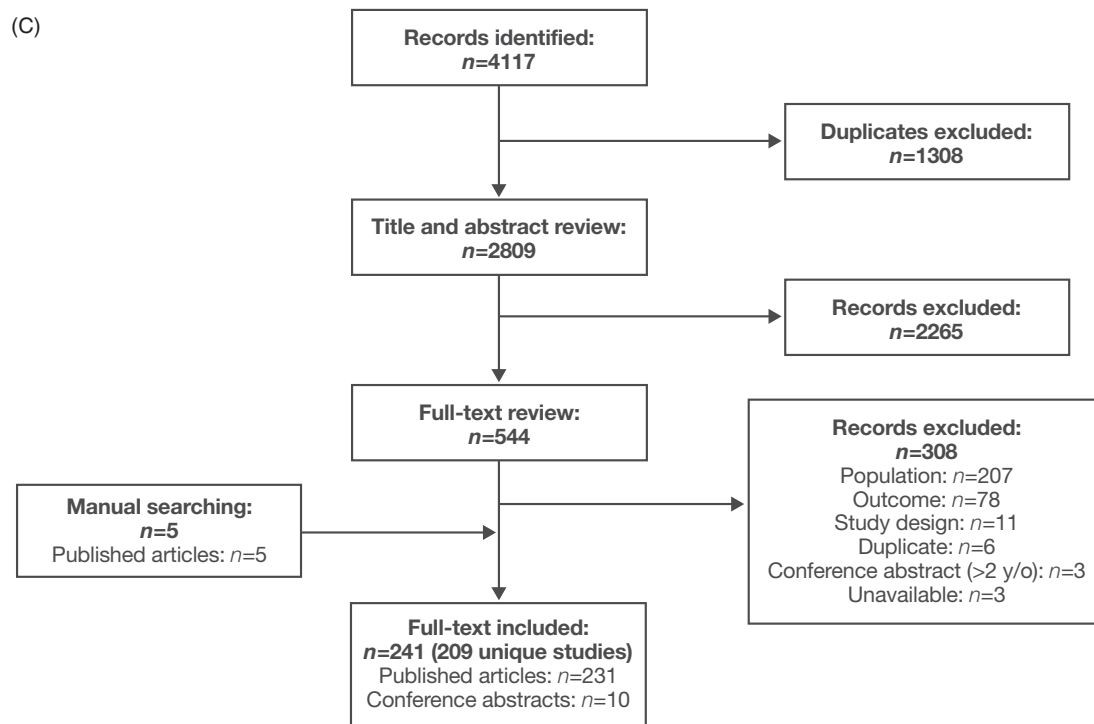


Figure 1. Continued

Table 2. Top 10 instruments used to assess health-related quality of life.

Test	Studies reporting instrument results
Sino-Nasal Outcome Test 22 (SNOT-22)	19 RCTs; 82 RWE studies
Sino-Nasal Outcome Test 20 (SNOT-20)	12 RCTs; 23 RWE studies
Rhinosinusitis Disability Index (RSDI)	6 RCTs; 8 RWE studies
Chronic Sinusitis Survey (CSS)	1 RCT; 4 RWE studies
Nasal Obstruction Symptom Evaluation (NOSE)	3 RCTs; 2 RWE studies
Lund-Kennedy Symptom Score	2 RCTs; 1 RWE study
Rhinosinusitis Outcome Measure (RSOM-31)	1 RCT; 2 RWE studies
Questionnaire of Olfactory Disorders (QOD)	2 RWE studies
Questionnaire of Olfactory Disorders-Negative Statements (QOD-NS)	2 RWE studies
Rhinosinusitis Symptom Inventory (RSI)	2 RWE studies

Abbreviations. RCT, Randomized controlled trial; RWE, Real-world evidence.

Table 3. Studies reporting health utility value for patients with CRSwNP: SF-6D.

Study	Design	Region	Population characteristics	Population (n)	CRSwNP population (n)	Mean baseline HUV for CRSwNP
Soler et al. ⁸⁷	Prospective cohort study	US	CRS patients undergoing surgery	232	103	0.67
Luk et al. ⁸⁸	Prospective cohort study	US and Canada	CRS surgical candidates electing continued medical management	40	17	0.75
			CRS patients undergoing surgery	152	56	0.72
			CRS patients initially electing medical management who elected to change therapy to include ESS (crossover)	20	10	0.68
Ference et al. ⁸⁹	Cross-sectional study	US	CRS patients in baseline, exacerbation, recalcitrant or remitted states	137	61	0.73

Abbreviations. CRS, Chronic rhinosinusitis; CRSwNP, Chronic rhinosinusitis with nasal polyposis; ESS, Endoscopic sinus surgery; HUV, Health utility value; SF-6D, Short Form-6 Dimensions.

Table 4. SNOT-22 severity for patients prior to surgery⁹¹.

Severity (SNOT-22 range)	Studies with surgical candidates	
	RWE studies with mean baseline SNOT-22 in range, n (%)	RCTs with mean baseline SNOT-22 in range, n (%)
Mild (8–20)	0 (0)	0 (0)
Moderate (>20–50)	25 (60)	5 (50)
Severe (>50)	17 (40)	5 (50)

Abbreviations. RCT, Randomized controlled trial; RWE, Real-world evidence; SNOT, Sino-Nasal Outcome Test.

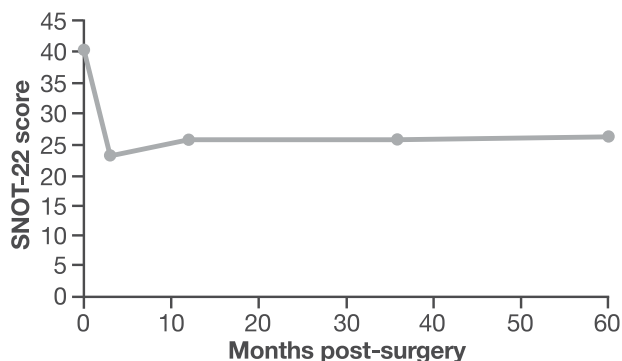


Figure 2. Longitudinal trends in SNOT-22 score following surgery³⁸. Abbreviation. SNOT, Sino-Nasal Outcome Test.

Health-related quality of life related to surgery

Stratification of SNOT-22 scores prior to surgery

Of the 10 RCTs^{14–23} and 42 RWE studies^{24–65} reporting baseline SNOT-22 scores for surgical candidates, all ranged from moderate to severe (Table 4)⁹¹. Five RCTs^{14–18} and 25 RWE studies^{24–47,65} reported mean baseline SNOT-22 scores in the moderate range. Five RCTs^{19–23} and 17 RWE studies^{48–64} reported severe mean baseline SNOT-22 scores. These findings were consistent with the treatment plan for CRSwNP provided by Fokkens et al.⁹², which recommended surgery as treatment for patients with more severe symptoms or with polyps that are recalcitrant to medical management.

Change in SNOT-22 score following surgery

Surgery was associated with clinically meaningful reduction in SNOT-22 scores for patients with CRSwNP. Based on a minimal clinically important difference (MCID) of 8.9 in SNOT-22 scores for patients with CRS after surgery⁹³, the majority of studies reported a clinically meaningful reduction in SNOT-22 score for each study subgroup at each follow-up period. A study based on the National Comparative Audit Study³⁸, which had the longest follow-up and largest sample size of the relevant studies in the SLR, included 1952 patients in England and Wales with CRSwNP at baseline and 1045 patients with CRSwNP who completed 5 years of follow-up. Mean baseline SNOT-22 score was 40.6, and a clinically meaningful reduction to 23.0 was reported at 3 months after surgery³⁸. This reduction remained clinically meaningful through 5 years, with mean values of 25.7, 25.6 and 26.2 reported at 1, 3 and 5 years post-surgery, respectively (Figure 2).

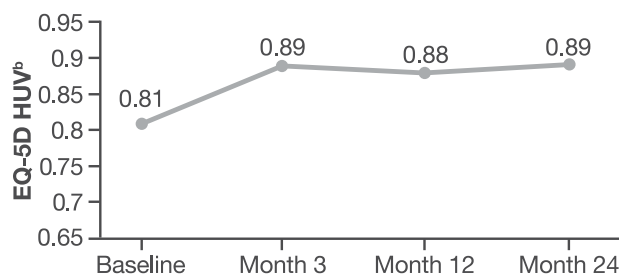


Figure 3. HUVs before and after surgery for patients ($n = 242^a$) with CRS (with and without nasal polyposis)⁹⁰. ^aPatient response rate was 70% at 3 months, 72% at 12 months and 61% at 24 months. ^bData from Remenschneider et al.⁹⁰. Abbreviations. CRS, Chronic rhinosinusitis; EQ-5D, EuroQol-5 Dimension; HUV, Health utility value.

SF-6D health utility values after endoscopic sinus surgery for patients with chronic rhinosinusitis with nasal polyposis

Rudmik et al.⁹⁴, which reported the long-term follow-up for the cohort of patients in Soler et al.⁸⁷, was the only study that reported a long-term follow-up SF-6D HUV for patients with CRSwNP after surgery. Mean SF-6D HUV changed from 0.69 at baseline to 0.80 at 5 years post-ESS for patients with CRSwNP⁹⁴. Walters and Brazier⁹⁵ estimated that the MCID in SF-6D was 0.033. Therefore, the change from baseline reported by Rudmik et al.⁹⁴ was considered clinically meaningful.

EQ-5D health utility values after endoscopic sinus surgery for patients with chronic rhinosinusitis

One study⁹⁰ reported EQ-5D HUV after surgery. However, the reported values were based on a population of patients with CRS (i.e. with and without NP with no specific HUV reported for patients with CRSwNP). The HUVs reported were 0.81 pre-surgery, 0.89 at Month 3 post-surgery, 0.88 at Month 12 post-surgery, and 0.89 at Month 24 post-surgery (Figure 3). Because McClure et al.⁹⁶ estimated that the MCID in EQ-5D ranged from 0.037 to 0.069, the change from baseline post-surgery reported by Remenschneider et al.⁹⁰ was considered clinically meaningful.

Comparison with other diseases: SF-6D and EQ-5D

Soler et al.⁸⁷ and Luk et al.⁸⁸ compared the baseline SF-6D HUVs with those for patients with other chronic disease states (e.g. back pain, Parkinson's disease and type 2 diabetes) and found that baseline HUVs for patients with CRSwNP were comparable to those for patients with other chronic illnesses, and lower than US norms (i.e. the difference from the US norm of 0.81 was greater than the MCID for SF-6D)⁹⁵.

Remenschneider et al.⁹⁰ compared the mean baseline EQ-5D HUV from their study with those from patients with 17 other disease states. The mean baseline EQ-5D HUV for patients with CRSwNP (0.806) and with CRSsNP (0.809) was less than those for patients with conditions such as seasonal allergies (0.94), peptic ulcer disease (0.92), prostate hypertrophy (0.83), hemorrhoids (0.83) and mild asthma (0.82–0.92).

Table 5. Comparison of methods of assessing health utility in CRS.

Measure	Overall	CRS + Exacerbation + Recalcitrant	Disease state			
			CRS	Exacerbation	Recalcitrant	Remitted
SF-6D	0.72	0.71	0.74	0.68	0.71	0.76
VAS	0.69	0.68	0.70	0.61	0.68	0.87
TTO	0.80	0.78	0.76	0.78	0.81	0.98
SG	0.93	0.93	0.93	0.92	0.94	1.00
SNOT-22	35.1		36.9	43.4	34.2	14.6

Abbreviations. CRS, Chronic rhinosinusitis; SF-6D, Short-Form 6-Dimension; SG, Standard gamble; SNOT, Sino-Nasal Outcome Test; TTO, Time trade-off; VAS, Visual analog scale.

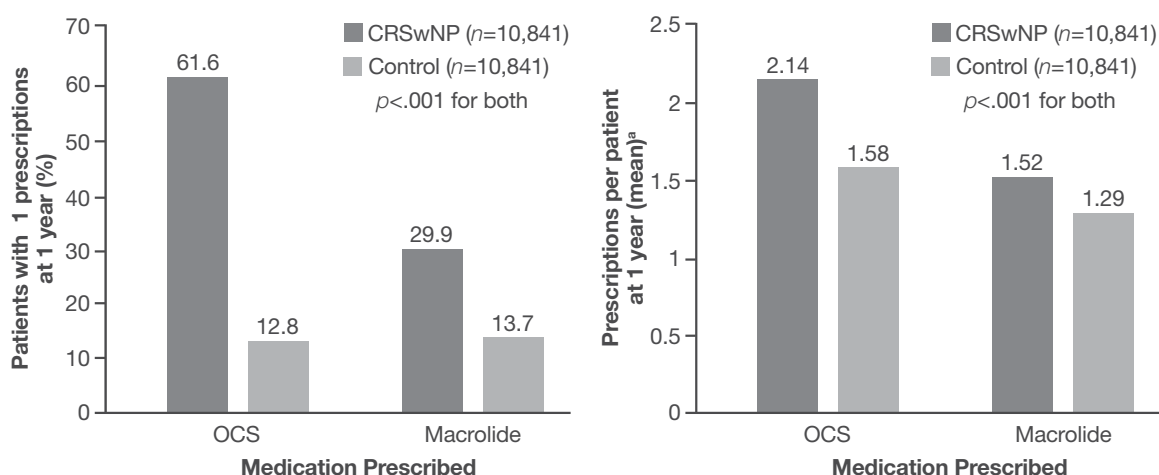


Figure 4. Medication use for patients with CRSwNP at 1 year follow-up⁹⁷. ^aFor patients with at least one prescription. Abbreviations. CRSwNP, Chronic rhinosinusitis with nasal polypsis; OCS, Oral corticosteroid.

Comparison of methods of assessing health utility for patients with chronic rhinosinusitis

Ference et al.⁸⁹ used several methods of assessing health utility (i.e. SF-6D, VAS, time trade-off [TTO] and standard gamble [SG]) and compared them with SNOT-22 (Table 5). SF-6D and VAS scores were consistent across different disease states, with the exacerbation having the lowest utility values followed by the recalcitrant and CRS states. With all measures, the remitted state had the greatest utility value, ranging from 0.76 to 1.00. SF-6D, VAS and TTO scores were significantly associated with SNOT-22 ($p < .001$ for all), while SG was not.

Economic burden: summary of search results

A total of 1185 records were identified through the database searches. After removing duplicates, 1157 records were available for title-and-abstract screening. Eighty-three records were selected for full-text review. After full-text review and additional searches, 27 unique studies were found to fulfill the inclusion criteria (Figure 1(C)).

Direct costs

Health care resource utilization and costs

HCRU and costs related to CRSwNP were reported in five studies (Supplementary Table 15)^{97–101}. Four studies were conducted in the United States^{97,99–101} and one study in

China⁹⁸. Two studies were retrospective database analyses^{99,100}, one was a retrospective case-control study⁹⁷, one was a randomized controlled trial⁹⁸ and one was a population-based survey¹⁰¹.

One US case-control study⁹⁷ reported data on systemic prescription usage, medical procedures, HCRU and total health care costs for patients with CRSwNP compared with a matched control group 1 year after diagnosis. A significantly greater percentage of patients with CRSwNP compared with controls were prescribed OCSs (61.6% vs. 12.8%, $p < .001$) and macrolides (29.9% vs. 13.7%, $p < .001$; Figure 4). In addition, the mean numbers of OCS and macrolide prescriptions per patient with at least one prescription were significantly greater in the CRSwNP cohort compared with controls (2.14 vs. 1.58 OCS prescriptions, and 1.52 vs. 1.29 macrolide prescriptions, $p < .001$). In a population-based survey, Mahmoud et al.¹⁰¹ found that in the previous year 92.5% of patients with CRSwNP had used conventional steroid nasal sprays, 71.2% had used oral steroids and 52.2% had a history of surgery.

In the US case-control study, patients with CRSwNP underwent significantly more medical procedures compared with the control cohort; FESS was the primary surgical procedure, with 42.7% of patients undergoing the surgery (with or without polypectomy; Figure 5). Compared with patients who did not undergo FESS, patients with CRSwNP who underwent FESS incurred incremental costs of \$13,532 (2016 USD)⁹⁷. Wu et al.⁹⁸ compared cohorts of patients with CRSwNP undergoing FESS with or without enhanced-

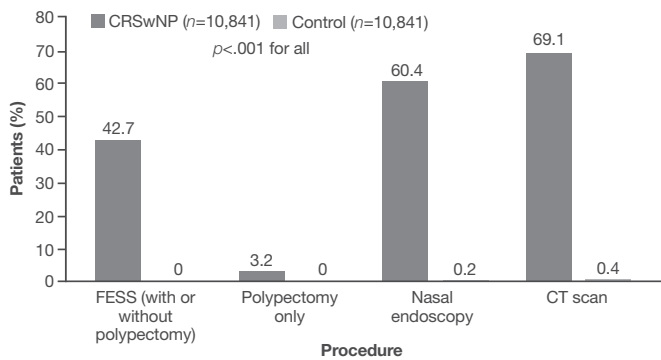


Figure 5. Medical procedures for patients with CRSwNP at 1 year follow-up⁹⁷. Abbreviations. CRSwNP, Chronic rhinosinusitis with nasal polyposis; CT, Computerized tomography; FESS, Functional endoscopic sinus surgery.

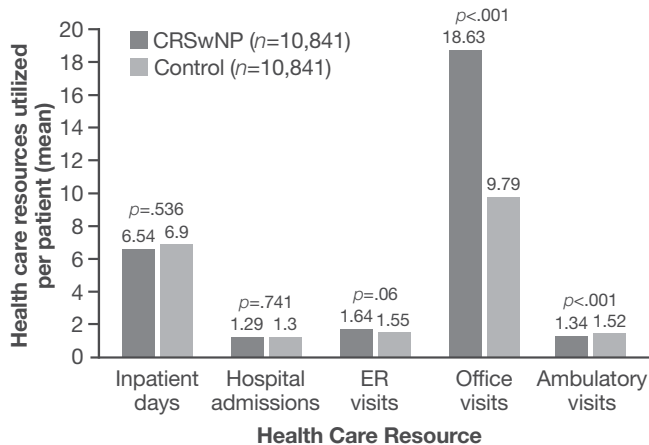
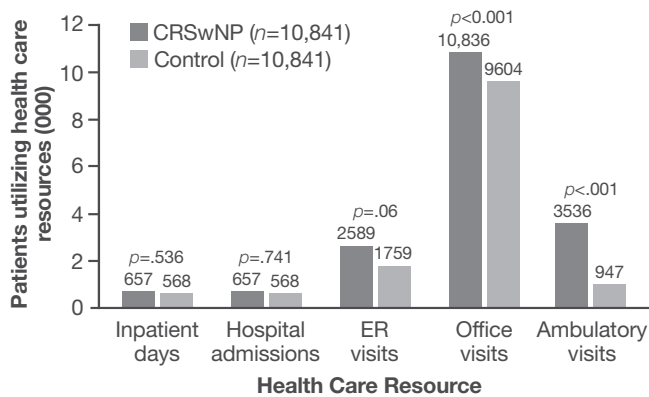


Figure 6. Health care resource utilization for patients with CRSwNP at 1 year follow-up⁹⁷. Abbreviations. CRSwNP, Chronic rhinosinusitis with nasal polyposis; ER, Emergency room.

recovery-after-surgery protocols. FESS followed by the protocols both reduced length of hospital stays (median 5 vs. 8 days, with vs. without), and lowered hospitalization expenses (median \$2670 vs. \$3129, with vs. without).

Bhattacharyya et al.⁹⁷ also demonstrated greater utilization of health care resources (including inpatient days, hospital admissions, emergency room [ER] visits, office visits and ambulatory visits) compared with matched controls. Specifically, patients with CRSwNP had 3.7 times the usage of ambulatory care services compared with controls (32.6% vs. 8.7%, $p < .001$). In addition, patients with CRSwNP had a

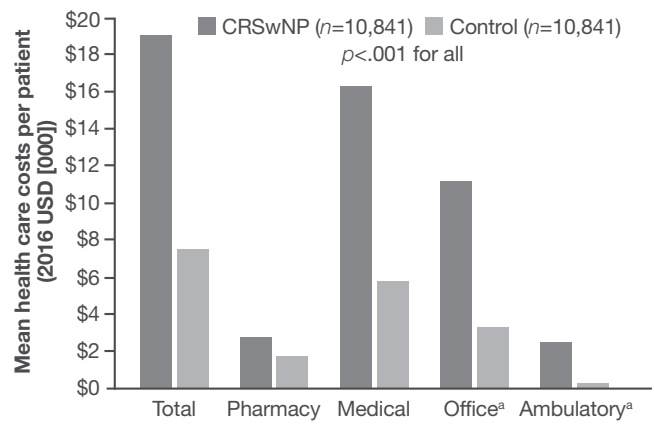


Figure 7. Health care costs for patients with CRSwNP at 1 year follow-up⁹⁷. ^aOffice costs and ambulatory costs make up medical costs. Abbreviations. CRSwNP, Chronic rhinosinusitis with nasal polyposis; USD, United States dollars.

significantly greater number of office visits compared with controls (mean 18.63 vs. 9.79 visits, $p < .001$; Figure 6)⁹⁷. In another study, in-office balloon catheter dilation procedures did not result in a significant decrease in health care utilization for patients with CRSwNP, but Sillers et al.¹⁰⁰ found that patients with CRSwNP had greater health care resource use at all time points in the study compared with CRSwNP patients.

Bhattacharyya et al.⁹⁷ found that the mean total health care cost per patient (including pharmacy and medical costs) was \$11,507 (2016 USD) greater for the CRSwNP group compared with controls after 1 year (\$18,964 vs. \$7457, $p < .001$; Figure 7). Medical costs (including office and ambulatory costs) made up the greatest portion of health care costs in the CRSwNP population, equating to \$16,247 of the total health care cost. In extrapolation to a US population, patients with CRSwNP were estimated to have had an annual overall health care cost burden of \$5.7 billion (2016 USD).

Resource utilization and costs related to surgery

Resource utilization and costs related to surgery were reported in seven studies (see study characteristics in Supplementary Table 16)^{99,102–107}. Six studies were conducted in the United States^{99,102–105,107} and one in the UK¹⁰⁶, including Scotland and Wales. The UK study used data from the Chronic Rhinosinusitis Epidemiology Study (CRES)¹⁰⁶. Four studies were retrospective database analyses^{99,103,104,107}, one was a retrospective cohort study¹⁰⁵ and two were cross-sectional studies^{102,106}.

One US study¹⁰² reported the median charge for ESS procedures. Using the State Ambulatory Surgery Databases for the regions of Florida, Maryland and New York, Ferenc et al.¹⁰² found that ESS procedures were associated with a median total charge of \$13,264 (Figure 8). In addition, pan-ESS was found to be a more expensive procedure compared to mini-ESS (median total charge of \$17,272 vs. \$11,213). Data from four regions (Florida, Maryland, New York and California) were available to determine the number of each procedure type that was performed for patients with CRSwNP between 2009 and 2011: ethmoidectomy ($n = 25,345$) was the most common procedure, followed by

Procedure Type	Median Total Charge ^c in 2009–2011 (USD)
Pan-ESS ^a	\$17,272
Mini-ESS ^b	\$11,213
All ESS Procedures	\$13,264

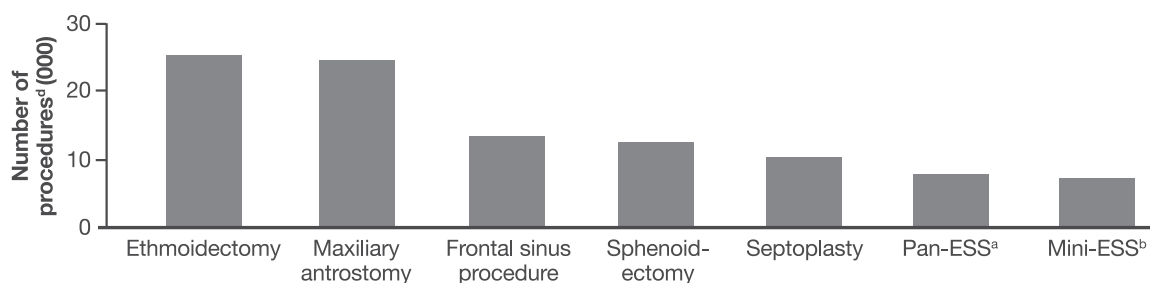


Figure 8. Costs and procedures for patients with CRSwNP undergoing surgery 2009–2011¹⁰². ^aPan-ESS defined as maxillary antrostomy, sphenoidotomy, and frontal sinus exploration via endoscopic or balloon techniques and ethmoidectomy. ^bMini-ESS defined as a maxillary antrostomy either via endoscopic or balloon techniques and ethmoidectomy. ^cCharge data available for Florida, Maryland and New York. Total charge data do not include professional fees and noncovered charges, and professional fees are removed from the total charge during Health Care Cost and Utilization Project (HCUP) processing. ^dStates included: California, Florida, Maryland, New York; selected to gain a wide geographic distribution. Abbreviations. CRSwNP, Chronic rhinosinusitis with nasal polyposis; ESS, Endoscopic sinus surgery; USD, United States dollars.

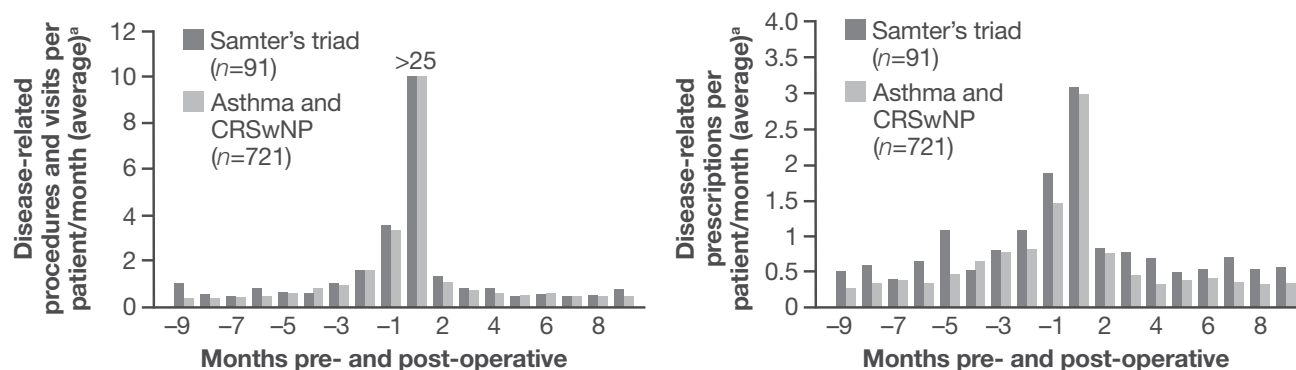


Figure 9. Procedures and prescriptions during the pre- and post-operative period¹⁰³. ^aValues were interpreted from primary source using Digitizelt software. Samter's triad: adult cases ($n=85$), pediatric cases ($n=6$); asthma and CRSwNP: adult cases ($n=669$), pediatric cases ($n=52$). Abbreviation. CRSwNP, Chronic rhinosinusitis with nasal polyposis.

maxillary antrostomy ($n=24,833$), frontal sinus ($n=13,336$), sphenoidotomy ($n=12,497$), septoplasty ($n=10,128$), pan-ESS ($n=7777$) and mini-ESS ($n=7250$).

In a 2015 claims-based study, Purcell et al.¹⁰⁷ found that total CRS-related health care costs for patients with CRSwNP (not including costs that occurred 7 days prior to surgery) were \$541 (2011 USD) per patient in the year before ESS. In post-operative Years 2 and 3, <50% of patients with CRSwNP filed a CRS-related claim resulting in a median cost of \$0.

Three studies discussed HCRU relative to time of surgery (Figure 9). Benninger and Holy¹⁰³ reported that, for patients with Samter's triad and those with CRSwNP and comorbid asthma, health care needs such as outpatient medical procedures and visits, and prescriptions increased approximately 6 months prior to ESS but decreased post-operatively

reaching baseline levels within 3–4 months. In addition, regardless of the presence of NP or asthma, early surgical intervention after diagnosis of CRS was associated with lower post-operative health care utilization compared with surgical intervention after years of medical treatment¹⁰⁴.

Three studies reported results related to revision surgery. Hunter et al.⁹⁹ reported that, in the first year following ESS, CRSwNP doubled the risk of revision surgery compared with CRSsNP (Figure 10). In addition, revision ESS within the first year after primary surgery increased mean 1 year expenditures by \$13,549 for CRSwNP versus \$11,306 for CRSsNP (USD year not reported). Stein et al.¹⁰⁵ found that the presence of NP was predictive of revision surgery (hazard ratio: 1.19; 95% confidence interval [CI] 1.11–1.27, $p<.001$). Philpott et al.¹⁰⁶ reported that, for a cohort of patients with CRS, the greatest rate of revision surgery was for those with

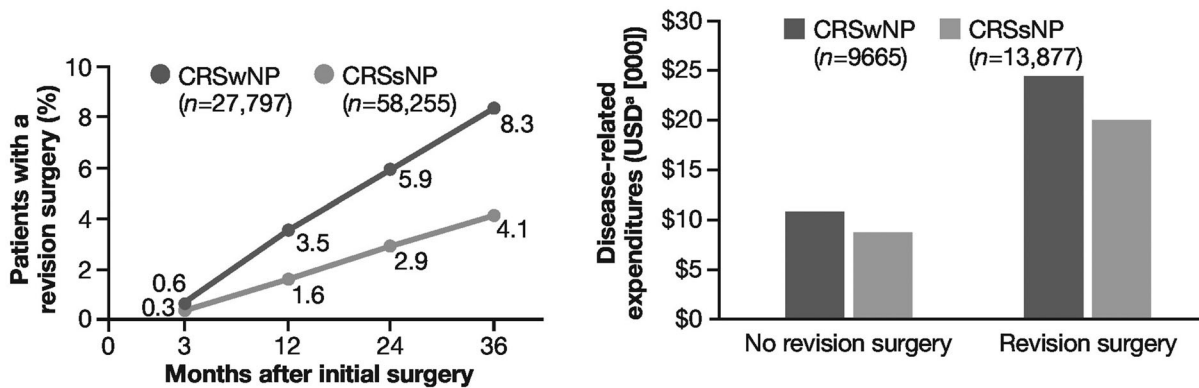


Figure 10. Risk for revision surgery and health care expenditures for patients with CRS who had ESS⁹⁹. ^aYear of cost not reported. Abbreviations. CRSsNP, Chronic rhinosinusitis without nasal polypsis; CRSwNP, Chronic rhinosinusitis with nasal polypsis; ESS, Endoscopic sinus surgery; USD, United States dollars.

CRSwNP and allergic fungal rhinosinusitis (AFRS), with rates of revision surgery almost twice that of those without NP.

Indirect costs

Productivity

Absenteeism and presenteeism related to CRSwNP were reported in three studies (Supplementary Table 17)^{39,108,109}. Two were conducted in the United States^{108,109} and one in Sweden³⁹. One study was a prospective consecutive series¹⁰⁸, one was a pooled analysis of clinical trials¹⁰⁹ and one was a prospective multicenter study³⁹. The pooled analysis was a US study¹⁰⁹ that reported absenteeism of patients with primary and recurrent polyps. Bhattacharyya¹⁰⁸ reported that, one year prior to diagnosis and treatment of CRS, patients with recurrent polyps missed more work days on average compared with those with a primary polyp occurrence (3.6 vs. 3.0, respectively). Sahlstrand-Johnson et al.³⁹ found that, of 113 patients with CRSwNP, 60 reported 0 days of absenteeism (53%), 24 reported 1–7 days (21%) and 29 reported ≥ 8 days (26%) in the past year.

A US study¹⁰⁹ reported absenteeism and presenteeism related to treatment with an exhalation delivery system with fluticasone (EDS-FLU) for patients with CRSwNP. There, Velez et al. (2018)¹⁰⁹ reported that, when absenteeism results were projected to 1 year, treatment with EDS-FLU was associated with an average of 0.54 workdays lost per patient, compared with 3.1 workdays lost with placebo. In addition, when presenteeism results were projected to 1 year, treatment with EDS-FLU was associated with 5.3 workdays per patient, compared to 10.9 workdays with placebo.

Productivity costs associated with CRSwNP were reported in five studies (see study characteristics in Supplementary Table 18)^{109–113}, all of which were conducted in the United States. Three studies were observational cohort studies^{111–113} one was a pooled analysis of clinical trials¹⁰⁹ and one was a 30-year Markov model¹¹⁰.

Two studies were identified that reported productivity loss associated with treatment of CRSwNP with EDS-FLU^{110,111}. Velez et al.¹⁰⁹ used the human capital approach to estimate lost wages per year. Treatment with EDS-FLU resulted in less wages lost annually compared with placebo treatment (\$1185 vs. \$1823, respectively; 2017 USD). Velez

et al. (2019)¹¹⁰ reported results of a 30-year Markov model using the human capital approach to estimate work productivity gains with EDS-FLU. Treatment with EDS-FLU was associated with 1.6 years and \$74,978 of lost productivity, while standard medical therapy was associated with 2.9 years and \$134,823 of lost productivity (2018 USD).

Estimates of mean annual productivity cost associated with refractory CRSwNP were high, but varied across studies. Chowdhury et al.¹¹¹ reported a mean annual productivity cost per patient of \$9845 (2012/2013 USD) for patients with refractory CRSwNP. In addition, this study found that productivity cost was significantly correlated to the total SNOT-22 score and the psychological and sleep dysfunction subdomains scores. Rudmik et al.¹¹² reported a mean annual productivity cost per patient of \$7182 (2012/2013 USD) for patients with refractory CRSwNP. Rudmik et al.¹¹³ reported a decrease in mean annual productivity cost per patient after continued medical therapy for patients with refractory CRSwNP from \$3927 at baseline to \$2259 after therapy (2012/2013 USD).

Cost-effectiveness evaluations

Cost-effectiveness evaluations were reported in six studies (see study characteristics in Supplementary Table 19)^{114–119}. Five of these studies were US-based^{114–117,119} and one was Canadian¹¹⁸. Four US studies^{114–117} reported treatments that were considered cost-effective at a willingness-to-pay (WTP) threshold of \$50,000 (USD) per quality-adjusted life-year (QALY). Cost-effective treatments included ESS compared with medical management alone^{114,116} for patients with or without comorbid asthma¹¹⁵, and EDS-FLU versus ESS¹¹⁷.

One US study¹¹⁵ and one Canadian study¹¹⁸ reported treatments that were not considered cost effective, including the addition of endoscopic frontal sinusotomy (EFS) to ESS versus ESS alone¹¹⁶ and ESS versus endoscopic polypectomy in-clinic (EPIC)¹¹⁸. One US study¹¹⁹ reported cost-effectiveness results for the use of a steroid-eluting implant for patients with refractory CRS. Rudmik and Smith¹¹⁹ reported that steroid-eluting implants demonstrated an incremental cost-effectiveness ratio (ICER) of \$5490 per post-operative intervention avoided within 60 days after ESS.

Discussion

SNOT-22 was the most commonly used disease-specific instrument used to assess HRQOL for patients with CRSwNP. Overall, SNOT-22 scores were greater for surgical candidates than medically managed patients. Pre-surgical SNOT-22 scores in surgical candidate populations were indicative of moderate to severe CRSwNP. A clinically meaningful reduction in SNOT-22 scores following surgery was observed for most study subgroups and at most follow-up periods. However, a formal meta-analysis of this data is lacking and recommended.

Although many studies reported SNOT-22 scores for patients with CRSwNP, there was a limited number of studies from key regions such as Brazil, Japan, China and Australia. Furthermore, there was a paucity of studies reporting SNOT-22 scores at periods greater than 1 year post-surgery for patients with CRSwNP, especially in RCTs.

The burden of illness according to baseline HUVs reported for patients with CRSwNP was comparable to those for patients with other chronic diseases and was lower than US norms. The long-term follow-up for a cohort of CRSwNP patients undergoing surgery showed a change from a mean SF-6D HUV of 0.69 at the pre-surgery time point to 0.80 at approximately 5 years post-surgery.

Except for one study by Bachert et al.²³, all studies that reported HUVs for patients with CRSwNP were conducted within North America. The lack of HUVs for patients with CRSwNP from regions outside of North America is an important gap in the literature. In addition, none of the identified studies reported HUVs for various CRSwNP-specific health states (e.g. mild, moderate and severe states; exacerbations). Such health states may be useful for informing economic models that are specific to patients with NP. We also identified a lack of studies reporting HUVs for patients with eosinophilic CRSwNP.

Regarding the economic burden, one year following diagnosis, patients with CRSwNP had significantly more systemic prescriptions, underwent significantly more medical procedures, demonstrated greater utilization of health care resources and had significantly greater mean health care costs compared with matched controls. Ethmoidectomy was the most commonly performed procedure for patients with CRSwNP. For patients with CRSwNP and respiratory comorbidities, health care needs increased approximately 6 months before ESS, but decreased after surgery, reaching baseline levels within 3–4 months. For patients who underwent ESS, CRSwNP was associated with greater risk for revision surgery and greater health care expenditures compared with CRSsNP. CRSwNP was associated with approximately three missed workdays per year. Estimates of mean annual productivity cost associated with refractory CRSwNP were high, but varied across studies. ESS was reported to be cost effective compared with medical management alone, as was EDS-FLU compared with ESS for the treatment of CRSwNP.

A lack of published data on patient out-of-pocket expenditures to manage CRSwNP and on caregiver burden was noted. No data on the economic burden of eosinophilic CRSwNP, or the economic burden related to various CRSwNP

severities (e.g. mild, moderate, severe) or symptoms were identified. In addition, there was a paucity of economic data from countries other than the United States.

A major strength of this study is that we adhered to best practices for the conduct and reporting of systematic reviews. Notably, the literature searches were performed and peer-reviewed by experienced information specialists. Detailed search strategies (Supplementary Tables 2 and 3) and a full list of included studies (Supplementary Table 20) are available in the Appendix, as per PRISMA guidelines. A limitation of this SLR is that the included studies were restricted to the English language at the study-selection stage. Because the majority of studies are published in English-language journals, this is likely a minor limitation.

Conclusions

This SLR identified substantial humanistic burden among surgery candidates. RWE shows that surgeries were used to treat relatively more severe CRSwNP patients as recommended by guidelines. Patient quality of life is improved significantly after surgery; however, there is a lack of evidence, specifically on patients with revision surgery. Surgery is also associated with higher costs, and the presence of NP was found to be a predictor of revision surgery. Patients with CRSwNP demonstrate greater health care resource utilization and costs compared to those with CRSsNP. Costs associated with different severity of CRSwNP and revision surgery need to be assessed further.

Transparency

Declaration of funding

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Declaration of financial/other relationships

S.C. and B.E. have disclosed that they are employees of AstraZeneca. A.Z., D.G. and E.R. have disclosed that they are employees of Eversana. CMRO peer reviewers on this manuscript have received an honorarium from CMRO for their review work. One of these peer reviewers discloses receiving a NIHR grant for chronic rhinosinusitis. The peer reviewers have no other relevant financial relationships to disclose.

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