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REVIEW ARTICLE

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Systematic literature review of the epidemiology and clinical burden of chronic rhinosinusitis with nasal polyposis

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ABSTRACT

Objectives: We conducted a systematic literature review (SLR) to determine the epidemiology and clinical burden of chronic rhinosinusitis with nasal polyps (CRSwNP) and to describe how the addition of biologics has affected outcomes for patients with 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 published between 1 January 2008 and 8 February 2019, for epidemiology, and 1 January 2008 and 16 February 2019, for clinical burden, and relevant conference abstracts from 1 January 2017 to 7 March 2019, for epidemiology and 1 January 2017–16 February 2019 for clinical burden were included.

Results: For the epidemiology and clinical burden SLR, 147 and 119 records, respectively, met the inclusion criteria. We found the prevalence of CRSwNP was 1–2.6% and was greater in men. Asthma, allergy, and allergic rhinitis were the most common comorbidities identified. Reported risk factors included asthma, gene polymorphisms, age, and eosinophilia. Studies indicated that dupilumab, mepolizumab, and omalizumab each improved different clinical outcomes. Non-biologics (drugs such as corticosteroids or antibiotics, surgery, or aspirin desensitization) improved clinical outcomes as well.

Conclusions: CRSwNP is fairly prevalent in the general population. Despite the significant efficacy of existing treatments, several unmet needs remain. The high burden of uncontrolled symptoms, frequent recurrence of nasal polyps after surgery, and long-term adverse effects of oral corticosteroids indicate that new therapies addressing these unmet needs should be developed. Although data on biologics from randomized controlled trials look promising, the efficacy of biologics in the real world has yet to be established.

The SLR of the epidemiology and clinical burden of CRSwNP revealed key gaps in the literature. There was a paucity of prevalence data across many geographic areas, and no prevalence projections could be determined. Studies showed varying efficacy of non-biologics and no studies directly compared biologics for efficacy. Data regarding clinical efficacy of agents for eosinophilic CRSwNP or severe CRSwNP were lacking, and these patient populations would be served by more trials.

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Introduction

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a chronic inflammatory condition associated with significant morbidity[1]. CRSwNP is estimated to affect 1–4% of the general population and 25–30% of patients with chronic rhinosinusitis (CRS)[1,2]. CRSwNP can cause long-term symptoms such as prominent nasal obstruction, post-nasal drip, loss of smell, and discharge, all of which negatively affect patients' health-related quality of life (HRQOL)[1]. Generally a condition of middle age with 42 years being an average age of onset, CRSwNP is typically diagnosed at 40–60 years[1].

The exact cause of nasal polyposis (NP) is unknown, but allergy, asthma, infection, and aspirin sensitivity have been associated with this complex refractory disease in adults[1]. Inflammatory mediators that may play roles in the development of NP include the cytokines IL-4, IL-5, and IL-13, and the chemokines CCL24 and CCL26[3,4]. Furthermore, microbial colonization contributes to the development of NP, including *Alternaria* species and *Staphylococcus aureus*[3]. NP may also result from non-allergic disorders such as cystic fibrosis[1]. CRSwNP is associated with more severe symptoms than for patients without NP[1].

Treatment options for patients with CRSwNP remain limited. According to US guidelines, both topical corticosteroids and nasal saline irrigations are recommended as initial medical therapies[5]. Intranasal corticosteroids (ICS) can decrease NP size, reduce sinonasal symptoms, and improve patient HRQOL[6,7]. Oral corticosteroids (OCS) can reduce polyp size and improve disease symptoms, but should be administered cautiously, given their association with serious systemic adverse effects[8]. Antibiotics may be useful in treating

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infectious exacerbations of CRSwNP, but information regarding clinically significant efficacy (i.e. NP shrinkage) from large, randomized trials is lacking[1]. 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 may still recur[9], with rates as high as 50% (for patients observed over a period of 3 years)[10].

A systematic literature review (SLR) was conducted to understand the epidemiology, and the clinical, humanistic, and economic burdens of CRSwNP. The results of this SLR are published in two parts. This part covers the epidemiology and clinical burden of CRSwNP. A companion article in this journal presents the results of the SLR describing the humanistic and economic burdens of CRSwNP.

The authors' overall objective was to determine the epidemiology and clinical burden of CRSwNP described in the literature by conducting an SLR. The objective of the epidemiology portion of the SLR was to summarize the literature on the following specific epidemiological aspects of CRSwNP: prevalence, incidence, mortality risk, comorbidities, symptoms, severity, surgery as a treatment option, most commonly used drugs for treatment, and risk factors. The objective of the clinical burden portion of the SLR was to review randomized controlled trials (RCTs) and real-world evidence (RWE) studies of therapies used for the treatment of patients with CRSwNP, to assess the efficacy of current treatment options, and to determine unmet needs for CRSwNP. In particular, the authors wanted to see how the addition of biologics has affected outcomes for patients with CRSwNP.

Methods

The SLR was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11]. Databases searched *via* the OVID platform included Ovid MEDLINE, containing E-Pub Ahead of Print and In-Process & Other Non-Indexed Citations; Embase; and the following Evidence-Based Medicine Reviews (EBMR) 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 Cochrane Central Register of Controlled Trials, and the NHS Economic Evaluation Database. Details of the search strategies are provided in the Appendix (Supplementary Tables 1 and 2).

Available government websites, professional organization websites, and patient advocacy group websites were searched for the epidemiology SLR to validate the findings from published literature. The countries with demographic websites searched included the United States, Canada, France, Germany, Spain, the United Kingdom, and Japan. For the clinical burden SLR, results of the searches were validated and supplemented by searching the US National Library of Medicine's ClinicalTrials.gov website and reviewing Cochrane systematic reviews. In addition, findings from published literature were validated against targeted literature searches and the bibliographies of select review articles.

Study selection

Epidemiology searches were performed 8 February 2019, while clinical burden searches were conducted 16 February 2019. Inclusion criteria were patients with CRSwNP $\geq$18 years old, any treatment for CRSwNP (clinical burden SLR only), outcomes relevant to epidemiology or clinical burden (as described in further detail below), and RCTs and non-RCTs/RWE studies (e.g. retrospective database analyses or chart reviews; case-control, cross-sectional survey, longitudinal, pilot, cohort, and single-arm studies). Exclusion criteria included pediatric studies (without adults), non-English articles, animal studies, commentaries, editorial reviews, expert-opinion articles, letters, articles published prior to 1 January 2008, and conference abstracts published prior to 1 January 2017. Detailed inclusion and exclusion criteria are shown in Tables 1 and 2.

Key epidemiology outcomes of interest included prevalence, incidence, mortality, comorbidities, risk factors, symptoms, and commonly used drugs for the treatment of CRSwNP. For clinical burden, studies reporting outcomes related to the current standard of care for CRSwNP, and the clinical outcomes of different therapies (e.g. non-biologics, surgery, and biologics) were included.

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 extractions were performed by a single reviewer and validated by a second reviewer.

Results

Epidemiology

A total of 16,669 records were identified through the database searches. After de-duplication, 8967 records were screened at the title-and-abstract stage. After assessing all records based on title and abstract, 886 records were selected for full-text review. Full-text review and additional searches identified 147 studies that met the inclusion criteria for epidemiology studies. The SLR identified six studies reporting prevalence, one study reporting incidence, one study reporting mortality risk, 98 studies reporting comorbidities, 26 studies reporting symptoms, and 41 studies

Table 1. Detailed criteria for inclusion/exclusion of studies for epidemiology SLR.

Criteria	Inclusion criteria	Exclusion criteria
Population	• Patients aged ≥18 years old with chronic rhinosinusitis with nasal polyposis (CRSwNP)	• Only patients aged <18 years • All other diseases
Intervention/Comparators	• Epidemiology and burden of illness studies were not restricted by treatment	• None
Outcomes	• Prevalence in key regions[a] • Incidence in key regions[a] • Key comorbidities (e.g. asthma, allergic rhinitis) • Morbidity (e.g. exacerbations, symptoms, severity) • Mortality risk • Percentage of patients who require surgery, and the frequency of surgery and repeated surgery • Risk factors • Percentage of patients with high EOS • OCS burden and pattern (including OCS use and consequences of OCS use)	• Outcomes not related to the epidemiology of CRSwNP
Study design	• Any study type (e.g. prospective and retrospective cohort studies, survey studies, case-control studies) • Articles published 1 January 2008, to 8 February 2019 • Conference abstracts published 1 January 2017, to 7 March 2019	• Animal studies, *in vitro* 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[b]	• All non-English articles

[a]Key regions included: US, Canada, EU5 (France, Germany, Italy, Spain, United Kingdom), China, Japan, Australia, Brazil.
[b]Citation 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, eosinophil; EU5, European Union 5; HTA, health technology agency; N/A, not applicable; OCS, oral corticosteroid; SLR, systematic literature review; US, United States.

Table 2. Detailed criteria for inclusion/exclusion of studies for clinical burden SLR.

Criteria	Inclusion criteria	Exclusion criteria
Population	• Patients aged ≥18 years old with CRSwNP	• Only patients aged <18 years old
Intervention	• Any treatment for CRSwNP	• Treatments not for CRSwNP
Comparators	• Any treatment for CRSwNP	• Treatments not for CRSwNP
Outcomes	• The current SoC for CRSwNP • Clinical outcomes of different therapies, including consequences of OCS use	• Outcomes not related to the clinical burden of CRSwNP

Study design	• RCTs
	• Non-randomized studies:
	  • Observational studies (e.g. case-control, cross-sectional, longitudinal, and cohort studies)
	  • Single-arm studies
	  • Pilot studies
	• Articles published 1 January 2008 to 16 February 2019
	• Conference abstracts published 1 January 2017 to 16 February 2019
		• Animal studies, *in vitro* 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

[a]Citation 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; OCS, oral corticosteroid; RCTs, randomized controlled trials; SLR, systematic literature review; SoC, standard of care.

reporting risk factors. In addition, 16 studies reported surgery statistics, 23 studies reported previous treatment, 67 studies reported severity of CRSwNP, and 17 studies reported eosinophilia-related results. The results of each stage of the screening process are presented as a PRISMA diagram in Figure 1. Note that data for some of the outcomes of interest (e.g. risk factors, severity, symptoms, and comorbidities) extracted from smaller studies with a total study population of fewer than 500 were not considered population-representative and are therefore not summarized herein.

Prevalence

The prevalence of CRSwNP in the general population was reported in six studies. In South Korea, the prevalence was 2.5–2.6% of the general population[12–15], which was greater than that reported for the United States (1.1% of the general population)[16]. CRSwNP was more prevalent for males (3.2–3.7%) than for females (2.0–3.3%), and the greatest prevalence was observed for the 60- to 69-year age group[12,17]. The prevalence of NP was reported to be

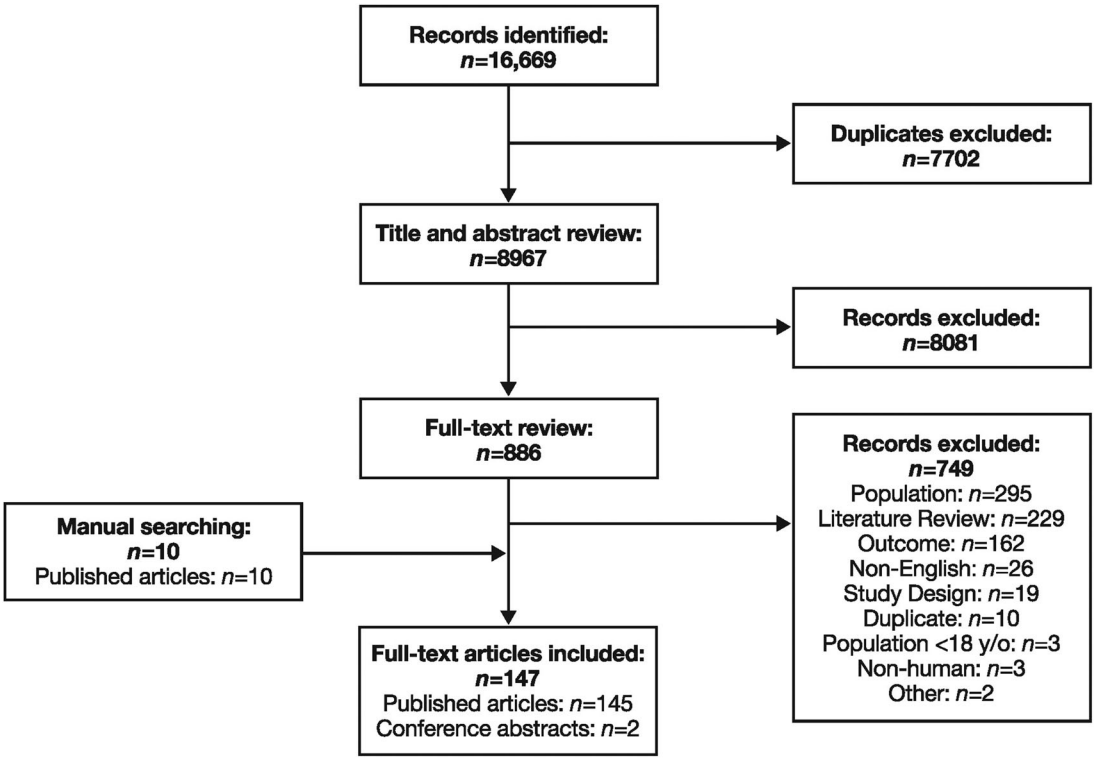

Figure 1. PRISMA diagram: Epidemiology. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; y/o, years old.

6.1–31% of the population with CRS in the United States, and 24% of the population with CRS in Denmark[18–21].

Uncontrolled (i.e. inadequately controlled) CRSwNP is defined as three or more of the following: nasal blockage present on most days of the week, rhinorrhea/postnasal drip on most days of the week, facial pain/pressure on most days of the week, impaired smell, sleep disturbance/fatigue, and nasal endoscopy with diseased mucosa; symptoms (as above) persist despite rescue treatment(s) in the last 6 months[2]. The prevalence of uncontrolled CRSwNP among the general CRSwNP population is not reported in the literature. Only two studies from Belgium have reported 41.8% and 40% uncontrolled CRSwNP among the CRSwNP population who previously had surgery for NP[22,23].

The prevalence of eosinophilic CRSwNP (eCRSwNP) varied by region[24,25]. In Europe, the prevalence estimates for eCRSwNP in the CRSwNP population ranged from 84–91%, with the lowest prevalences noted for Belgium, The Netherlands, and Luxembourg. The highest prevalence was reported for patients in Berlin, Germany[25]. In Asia, the estimated prevalence for eCRSwNP in the CRSwNP population ranged from 65% for Chengdu, China, to 89% for Tochigi, Japan[25]. The prevalence of eCRSwNP in the CRSwNP population was estimated to be 91% for Adelaide, Australia[25].

Incidence

Our search of multiple medical-literature databases identified one report of the incidence of CRSwNP in community practice clinics and hospitals in a 31-county region of central and northeastern Pennsylvania[26]. Between 2007 and 2009, the reported average incidence of CRSwNP was 83 cases per 100,000 person-years in the region.

Mortality risk

Our search identified one report of mortality risk among 27,005 patients diagnosed with CRS in the Utah Population Database. Mortality risk for this population was greater for patients with CRSwNP compared with patients who had CRS without NP (CRSsNP) (hazard ratio [HR] = 1.38; 95% confidence interval [CI] 1.09–1.77)[18].

Comorbidities

Most studies reported comorbidities of CRSwNP from a US population. Asthma (percentage of patients, range 5–56%), allergy (12–77%), and allergic rhinitis (17–76%) were the most commonly reported comorbidities for patients with CRSwNP. Details of studies reporting prevalence of these comorbidities are summarized in Table 3.

Symptoms

Facial pain, nasal congestion, loss of smell, sneezing, and headache were the most commonly reported symptoms for patients with CRSwNP. Facial pain was reported for 60–92.2% of patients in North America[16,27], 31–45% of patients in Europe[28,29], and 19–100% of patients in Asia[30–33]. Nasal congestion was reported in 95–100% of patients with CRSwNP in North America[17,27], 73–88% of patients in Europe[34,35], and 76–81% of patients in Asia[31,36]. Loss of smell was reported for 56–84% of patients with CRSwNP in North America[16,27], 35–90% of patients in Europe[28,34,35,37,38], and 30–100% of patients in Asia[30–32,36,39]. Sneezing was reported for 88% of patients in North America[26], 12–73% of patients in Europe[28,34,35,38], and 27–51% of patients in Asia[31,33]. Headache was reported for 33–95.8% of patients in North

Table 3. Most commonly reported comorbidities for patients with CRSwNP[a].

Comorbidity	Study	Country	Time frame	Study design	Population	Total study population (*n*)	CRSwNP population (*n*)	CRSwNP age, years (mean ± SD)	Percentage of patients with CRSwNP and comorbidity (%)	Description
Asthma	[14]	Korea	2010–2012	Cross-sectional survey	CRS	17,506	Not stated	52.7 ± 0.9	Physician-diagnosed: 6.7 ± 1.5 Self-reported: 9.4 ± 1.6% Past: 3.9 ± 1.0 Current: 5.4 ± 1.4	Asthma
	[37]	Japan	2005	Prospective study	CRS	553	309	51.5 ± 18.8	23.1	Asthma
	[67]	US	2013–2014	Retrospective case-control study	CRSwNP	21,682	10,841	45.84 ± 11.86	At baseline: 12.4 At follow-up: 20.8	Asthma
	[23]	US	2001–2010	Retrospective longitudinal cohort study	CRS	446,480	595	48.4 ± 19.1	23.9	Asthma
	[19]	US	1996–2016	Retrospective database analysis	CRS	29,934	9,177	44.8 ± 15.2	30.1	Asthma
	[71]	US	2003–2013	Retrospective cross-sectional study	CRS	1,393	488	46	53.6	Asthma
	[74]	US	2002–2012	Chart review	CRS	507 + 874	874	50.35 ± 14.4	56	Asthma
	[22]	Europe, Asia, Australia	Not stated	Prospective study	CRS	573	Benelux: 125 Berlin: 72 Adelaide: 68 Beijing: 152 Chengdu: 114 Tochigi: 42	Not stated	Benelux: 44.44 Berlin: 36.36 Adelaide: 42.42 Beijing: 13.68 Chengdu: 7.25 Tochigi: 33.3	Asthma
Allergy/Atopy/ Atopic dermatitis	[19]	US	1996–2016	Retrospective database analysis	CRS	29,934	9,177	44.8 ± 15.2	12.6	Allergy
	[91]	US	Not stated	Prospective case series	Adults presenting with inflammatory paranasal sinus disease	514	18–39 years: 203 40–59 years: 213 60+ years: 98	Not stated	18–39 years: 77.4 40–59 years: 74.7 60+ years: 59.1	Environmental allergy
	[40]	Belgium	NR	Questionnaire	CRS	1,281	420	Not stated	47.6	Allergy
	[22]	Europe, Asia, Australia	Not stated	Chart review	CRS	573	Benelux:125 Berlin: 72 Adelaide: 68 Beijing: 152 Chengdu:114 Tochigi: 42	Not stated	Benelux: 44.44 Berlin: 54.55 Adelaide: 57.58 Beijing: 36.84 Chengdu: 34.78 Tochigi: 33.33	Allergy
	[23]	US	2001–2010	Retrospective longitudinal cohort study	CRS	446,480	595	48.4 ± 19.1	4.2	Atopic dermatitis
	[68]	Europe	2007–2009	Cross-sectional case-control study	CRS	869	445	46.8 ± 11.2	46.8	Atopy
	[71]	US	2003–2013	Retrospective cross-sectional study	CRS	1,393	488	46	66.4	Atopy
Allergic rhinitis	[67]	US	2013–2014	Observational, retrospective, case-control study	CRSwNP	21,682	10,841	45.84 ± 11.86	At baseline: 25.6 At follow-up: 53.3	Allergic rhinitis
	[74]	US	2002–2012	Chart review	CRS	507 + 874	874	50.35 ± 14.4	76	Allergic rhinitis
	[68]	Europe	2007–2009	Cross-sectional case-control study	CRS	869	445	46.8 ± 11.2	~2/3 participants	Allergic rhinitis
	[14]	Korea	2010–2012	Cross-sectional survey	General adult population	17,506	Not stated	52.7 ± 0.9	17.4	History of allergic rhinitis
	[23]	US	2001–2010	Retrospective longitudinal cohort study	CRS	446,480	595	48.4 ± 19.1	42.7	Allergic rhinitis

[a]Studies with populations ≥500 included.

Abbreviations. AERD, aspirin-exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis; Benelux, Belgium, the Netherlands, Luxembourg; COPD, chronic obstructive pulmonary disorder; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; GERD, gastroesophageal reflux disease; SD, standard deviation; US, United States

America[27,40], 20–41% of patients in Europe[33,34], and 2–76% of patients in Asia[33,36].

Risk factors

Asthma, gene polymorphisms, and aging were the most commonly reported risk factors for developing CRSwNP. Other risk factors included male sex, smoking, allergy, presence of polyps, CRS-related symptoms, tobacco use, chronic bronchitis, aspirin intolerance, occupation (e.g. firefighter), high serum concentrations of cytokines IL-5 or IL-13, lower education levels, obesity, lower S100A8/9 (calprotectin) protein concentrations, first- or second-degree relatives with CRSwNP, greater Lund-Mackay score (LMS), and high tissue and blood eosinophil counts.

Asthma as a risk factor was reported in five studies[12,15,41–43], with reported odds ratios (ORs) of 5.9 (95% CI 1.79–19.65)[42], 2.20 (95% CI 1.41–3.45)[12], and 5.85 (no 95% CI given)[41]. Won et al.[15] reported relative risk of 3.18 (95% CI 1.8–5.6). Pearlman et al.[43] reported that the association was significant (p=.0019).

The extent to which gene polymorphisms are risk factors for developing CRSwNP varied by gene. Bernstein et al.[44] reported that an allele in a single nucleotide polymorphism located in the tumor necrosis factor-α gene was associated with developing CRSwNP (OR 1.86; 95% CI 1.14–3.09). Sitarek et al.[45] reported that the C/G genotype of the proto-oncogene c-met (hepatocyte growth factor receptor; OR 2.83; 95% CI 1.74–4.61) and the −765 G/C genotype of the cyclooxygenase-2 gene (OR 7.79; 95% CI 4.88–12.4) were associated with developing CRSwNP. Zielinska-Blizniewska et al.[46] found that the A/G genotype of the lactoferrin gene (OR 4.78; 95% CI 3.07–7.24) and the C/G and G/G genotypes (OR 3.48; 95% CI 2.19–5.52; OR 16.45; 95% CI 6.71–40.30, respectively) of the osteoblast-specific factor-2 gene increased the likelihood of developing CRSwNP.

Age as a risk factor was reported in two studies. The first study reported cross-sectional data from more than 35,000 patients in the Korean National Health and Nutrition Examination Survey from 2008 through 2012[12]. The second study was a case-control study of 367 patients in Sweden[38]. Both studies reported an OR of 1.03 (95% CI 1.02–1.04).

Eosinophilia may be a risk factor for developing CRSwNP. Putman et al.[47] reported that an eosinophil count ≥240 cells/μL was a greater risk factor for CRSwNP than for CRSsNP (HR 1.39; 95% CI 1.22–1.58 versus 1.13; 95% CI 1.10–1.27). Chen et al.[48] found that peripheral eosinophils were a risk factor for NP (OR 2.02; 95% CI 1.08–3.72). Eosinophilia was associated with CRSwNP recurrence (RR 3.68; 95% CI 0.19–11.38)[49] and with recurrence of NP (RR 6.18; 95% CI 1.29–29.42)[50]. Furthermore, eosinophilia was also associated with worse respiratory function[37,51–57], disease severity[32,51,58–61], and greater CRSwNP recurrence rates[49,62,63]. Guo et al.[62] reported that blood eosinophil counts of 0.25×10^3/μL (OR 3.63; 95% CI 0.73–18.10) or 2.6% blood eosinophils (OR 5.12; 95% CI 0.62–42.58) predicted multiple recurrences of CRSwNP after FESS.

Severity of CRSwNP

Severity as assessed by LMS was found to vary by geographic region and to depend on factors such as eosinophilia and comorbidities. In North America, LMS ranged from 12.0[64] to 26.0[65]. In Europe, LMS ranged from 6.2[59] to 17.6[37] for patients with low mucosal eCRSwNP and CRSwNP patients with asthma, respectively. In Asia, the lowest LMS was 11.6 and the greatest LMS was 22, reported for a CRSwNP population without atopy and a CRSwNP population characterized by marked tissue eosinophilia[66,67]. One Australian study reported a mean LMS of 16.79 for patients who underwent ESS[68].

Surgery for CRSwNP

Surgery is a common treatment option for patients with CRSwNP. The percentage of patients who had undergone surgery as reported in five studies varied by geographic region: United States, 43–52%; UK, 55%; Europe, 46%; and Belgium, 84%[16,69–72]. In five studies, 21–59% of patients with CRSwNP were reported to have undergone revision surgery[20,70,73–75]. Two studies reported that 6% and 6.5% of patients with CRSwNP had undergone two revision surgeries over study durations of 20 and 5 years, respectively[20,70]. Patients with CRSwNP were reported to undergo a mean number of 1.4–2.98 surgeries, with women found to have 1.2-times more surgeries than men[71,73,76].

Most commonly used drugs for CRSwNP

Corticosteroids (percentage of patients, intranasal: range 90–93%; oral: range 23–71%), antibiotics (29–55%), and antihistamines (34%) were the most commonly used drugs for CRSwNP, as reported in six studies. These studies are summarized in Table 4. A summary of evidence for the efficacy of these drugs, as well as for biologics, is included in the clinical burden results section.

Clinical burden

A total of 5466 records were identified for RCTs. After removal of duplicates, the titles and abstracts of 2979 records were examined. Of these, 417 were selected for full-text review. Full-text review and additional searches yielded 119 records, representing 97 unique RCTs. Treatments investigated in the RCTs included biologics, corticosteroids, antibiotics, antifungals, aspirin desensitization, surgical treatments, and alternative therapies. The PRISMA flow chart of record selection for RCTs is presented in Figure 2.

A total of 4117 records were identified for RWE studies. After removing duplicates, 2809 records were evaluated at the title-and-abstract stage. Of these, 404 were selected for full-text review. In all, 276 records representing 263 unique RWE studies that fulfilled the inclusion criteria were identified. Treatments investigated in the RWE studies included biologics, corticosteroids, aspirin desensitization, and ESS, among others. The PRISMA flow chart of record selection for RWE studies is presented in Figure 3.

Table 4. Drugs most commonly used for CRSwNP[a].

Treatment	Study	Country	Time frame	Study design	Population	Total study population (*n*)	CRSwNP population (*n*)	CRSwNP age, years (mean ± SD)	Percentage who received prior treatment (%)	Treatment description
Intranasal corticosteroids	[68]	Europe	2007–2009	Cross-sectional case-control study	CRS	869	445	46.8 ± 11.2	90.4	Ever having received medical treatment for their sinus condition – intranasal corticosteroids
	[15]	US	2014–2015	Cross-sectional survey	General adult population	1189	1.1%	Not stated	92.5	Treated with nasal spray in the past 12 mo
	[23]	US	2001–2010	Retrospective longitudinal cohort study	CRS	446,480	595	48.4 ± 19.1	7–24 mo before CRS diagnosis: 0.3 (1.0) 0–6 mo before CRS diagnosis: 0.3 (0.6)	Overall nasal steroid use Number of orders (by physician), mean (SD)
Oral corticosteroids	[68]	Europe	2007–2009	Cross-sectional case-control study	CRS	869	445	46.8 ± 11.2	61.3	Ever having received medical treatment for their sinus condition – OCS
	[67]	US	2013–2014	Retrospective case-control study	CRSwNP	21,682	10,841	45.84 ± 11.86	At baseline: 29.2 At follow-up: 61.6	OCS prescription
	[71]	US	2003–2013	Retrospective cross-sectional study	CRS	1393	488	Not stated	23.4	% having taken oral steroids
	[15]	US	2014–2015	Cross-sectional survey	General adult population	1189	1.1%	Not stated	71.2	Taken oral steroids for nasal or sinus symptoms in the past 12 mo
	[23]	US	2001–2010	Retrospective longitudinal cohort study	CRS	446,480	595	48.4 ± 19.1	7–24 mo before CRS diagnosis: 0.4 (0.9) 0–6 mo before CRS diagnosis: 0.2 (0.7)	Overall systemic steroid use Number of orders, mean (SD)
Antibiotics	[67]	US	2013–2014	Retrospective case-control study	CRSwNP	21,682	10,841	45.84 ± 11.86	At baseline: 28.5 At follow-up: 29.9	Macrolide prescription
	[68]	Europe	2007–2009	Cross-sectional case-control study	CRS	869	445	46.8 ± 11.2	54.9	Ever having received medical treatment for their sinus condition – antibiotics
	[23]	US	2001–2010	Retrospective longitudinal cohort study	CRS	446,480	595	48.4 ± 19.1	7–24 mo before CRS diagnosis: 1.5 (2.4) 0–6 mo before CRS diagnosis: 0.9 (1.7)	Overall antibiotic use Number of orders, mean (SD)
Antihistamines	[68]	Europe	2007–2009	Cross-sectional case-control study	CRS	869	445	46.8 ± 11.2	33.6	Ever having received medical treatment for their sinus condition – antihistamines

[a]Studies with populations ≥500 included.
Abbreviations. CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; mo, months; OCS, oral corticosteroids; SD, standard deviation.

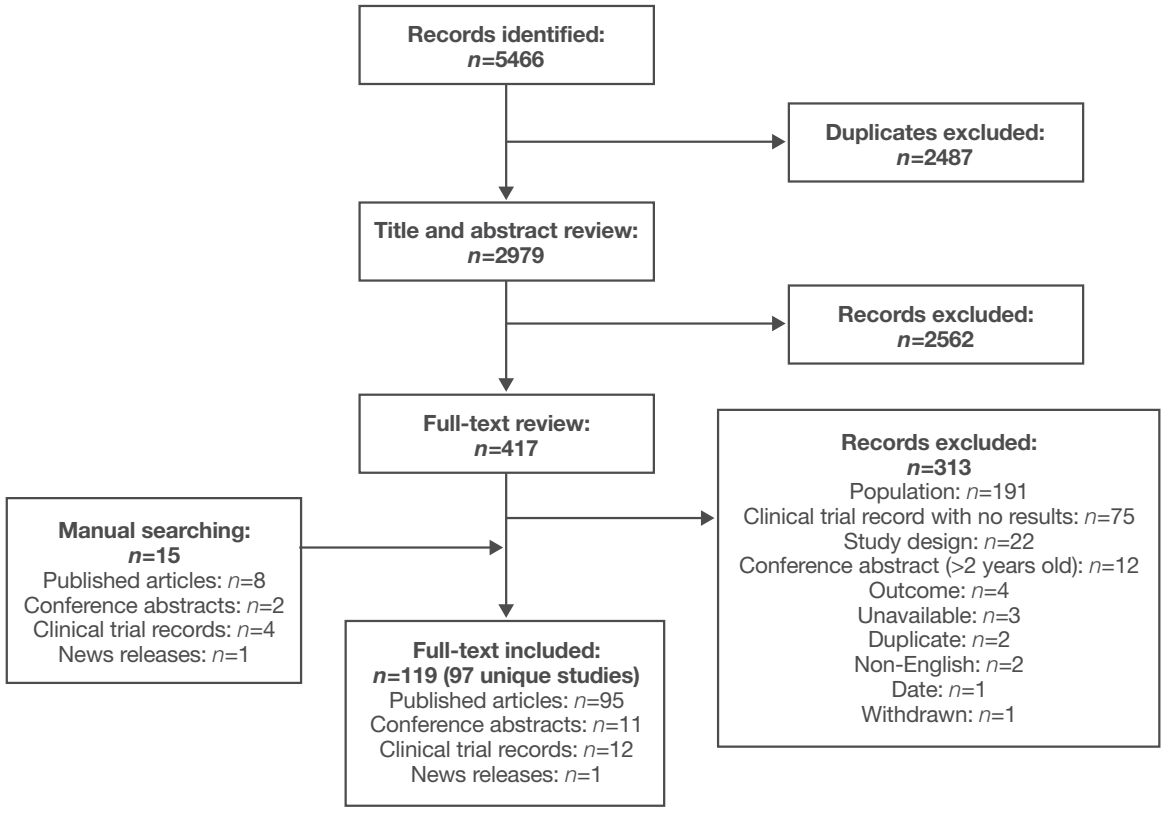

Figure 2. PRISMA diagram for RCTs: Clinical Burden. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized clinical trials.

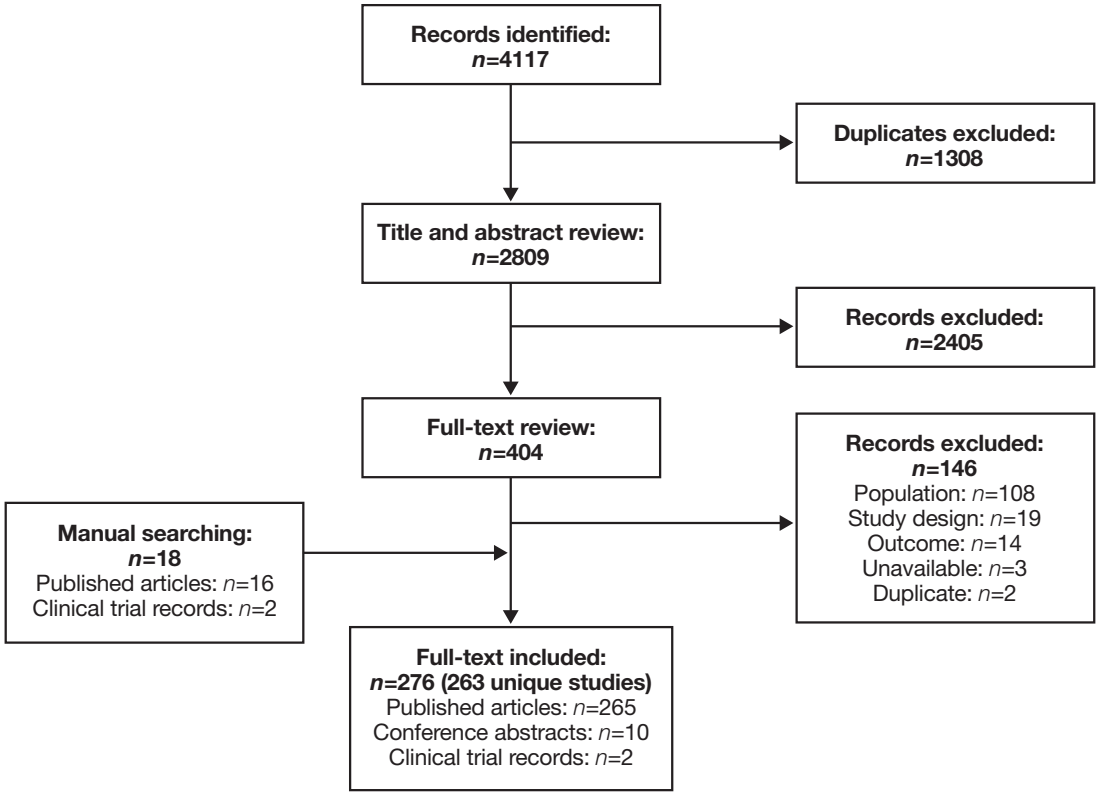

Figure 3. PRISMA diagram for RWE studies: Clinical Burden. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RWE, real-world evidence.

Table 5. RCTs and RWE studies investigating biologics[a].

Reference	Biologic	Study type	NCT# (study name)	Phase	*N*	Population
Bachert, 2019[86]	Dupilumab	placebo-controlled, multicenter RCT	NCT02898454 (SINUS-52)	3	448	Adults with severe CRSwNP previously treated with systemic corticosteroids and/or NP surgery, on daily mometasone furoate
Han, 2019[85]	Dupilumab	placebo-controlled, multicenter RCT	NCT02912468 (SINUS-24)	3	276	Adults with severe CRSwNP, with or without comorbid asthma, on daily mometasone furoate
Bachert, 2016[87]	Dupilumab	placebo-controlled, multicenter RCT	NCT01920893	2	60	Adults with CRSwNP refractory to intranasal corticosteroids
Bachert, 2017[90]	Mepolizumab	placebo-controlled, multicenter RCT	NCT01362244	2	107	Adult patients with severe recurrent bilateral nasal polyposis requiring surgery
Gevaert, 2011[91]	Mepolizumab	placebo-controlled, single-center RCT	NR	NR	30	Adult patients with severe nasal polyposis (grade 3/4 or recurrent after surgery) refractory to corticosteroid therapy
Tuttle, 2018[92]	Mepolizumab	retrospective study	N/A	N/A	14	Patients with AERD
NLM, 2009[93]	Omalizumab	placebo-controlled, single-center RCT	NCT01066104	2	27	Adult outpatients with CRSwNP, without uncontrolled moderate-to-severe asthma
Gevaert, 2013[94]	Omalizumab	placebo-controlled, 2-center RCT	NR	NR	24	Adult CRSwNP patients with comorbid asthma for >2 years
Bidder, 2018[95]	Omalizumab	prospective cohort study	N/A	N/A	37	CRSwNP patients with severe allergic asthma

[a]Only biologics RCTs with results available at the time of the literature search are listed in this table. Ongoing Phase III studies identified by the literature search for omalizumab in CRSwNP: POLYP 1 and POLYP 2; ongoing Phase III study identified for mepolizumab in severe bilateral nasal polyposis: SYNAPSE; ongoing Phase III study identified for benralizumab in severe nasal polyposis: OSTRO.

Abbreviations. AERD, aspirin-exacerbated respiratory disease; CRSwNP, chronic rhinosinusitis with nasal polyposis; NP, nasal polyposis; NR, not reported; N/A, not applicable; RCT, randomized controlled trial; RWE, real-world evidence.

Results for non-biologics

Non-biologics for the treatment of CRSwNP included intranasal and oral corticosteroids; surgery, such as ESS; nasal irrigation; antibiotics, such as clarithromycin and doxycycline; antifungals; aspirin desensitization; and alternative therapies. RCTs demonstrated that non-biologics improved the following commonly reported clinical outcomes: Sino-Nasal Outcomes Test (SNOT)-22 scores (Supplementary Table 4), Lund-Mackay CT scores (Supplementary Table 6), nasal obstruction scores (Supplementary Table 8), total symptom scores by visual analog scale (VAS) (Supplementary Table 10), and total endoscopic NP scores (Supplementary Table 12). In addition to improvements in the above outcomes, RWE studies reported that non-biologics improved SNOT-22 scores, Lund-Kennedy CT and endoscopic scores, total symptom scores by VAS, and nasal polyp scores (Supplementary Tables 5, 7, 9, 11, 13, and 14). Four RCTs[77–80] and 4 RWE studies[81–84] reported on non-biologics (corticosteroids and ESS) for patients with eCRSwNP. All eight studies demonstrated improvement in clinical outcomes. Despite clinical efficacy provided by non-biologics, these treatments do not remove polyps completely or eliminate disease symptoms. The burden of CRSwNP symptoms for patients, as measured by SNOT-22 and NP scores after treatment (Supplementary Tables 4, 8, 10, and 12), remains high. Moreover, although OCS are effective in improving symptoms and size of polyps in the short term and the adverse events associated with their use have been described in other disease, their long-term adverse effects have not been studied in this patient population.

Results for biologics

Seven RCTs with published results for three biologics were found: dupilumab (three studies), omalizumab (two studies), and mepolizumab (two studies). These studies are summarized in Table 5.

Three RCT studies for dupilumab, the Phase III SINUS-24[85] and SINUS-52[86] studies, and a Phase II study[87] were retrieved. No RWE studies were found for dupilumab. In the SINUS-24 study, dupilumab significantly improved endoscopic nasal congestion, and NP, Lund-Mackay, University of Pennsylvania Smell Identification Test (UPSIT), and SNOT-22 scores relative to placebo for patients with severe CRSwNP (Figure 4(A))[85]. At 24 weeks, dupilumab reduced rescue treatment (systemic corticosteroids) or NP surgery by 73% versus placebo ($p < .001$)[88,89]. Also at 24 weeks, dupilumab significantly improved Asthma Control Questionnaire (ACQ)-6 scores ($p < .0001$) and forced expiratory volume in 1 second (FEV_1) ($p < .001$) versus placebo for patients with severe CRSwNP plus comorbid asthma[85]. In the SINUS-52 trial, dupilumab significantly improved endoscopic nasal congestion and NP, Lund-Mackay, UPSIT, and SNOT-22 scores relative to placebo for patients with severe CRSwNP (Figure 4(B))[86].

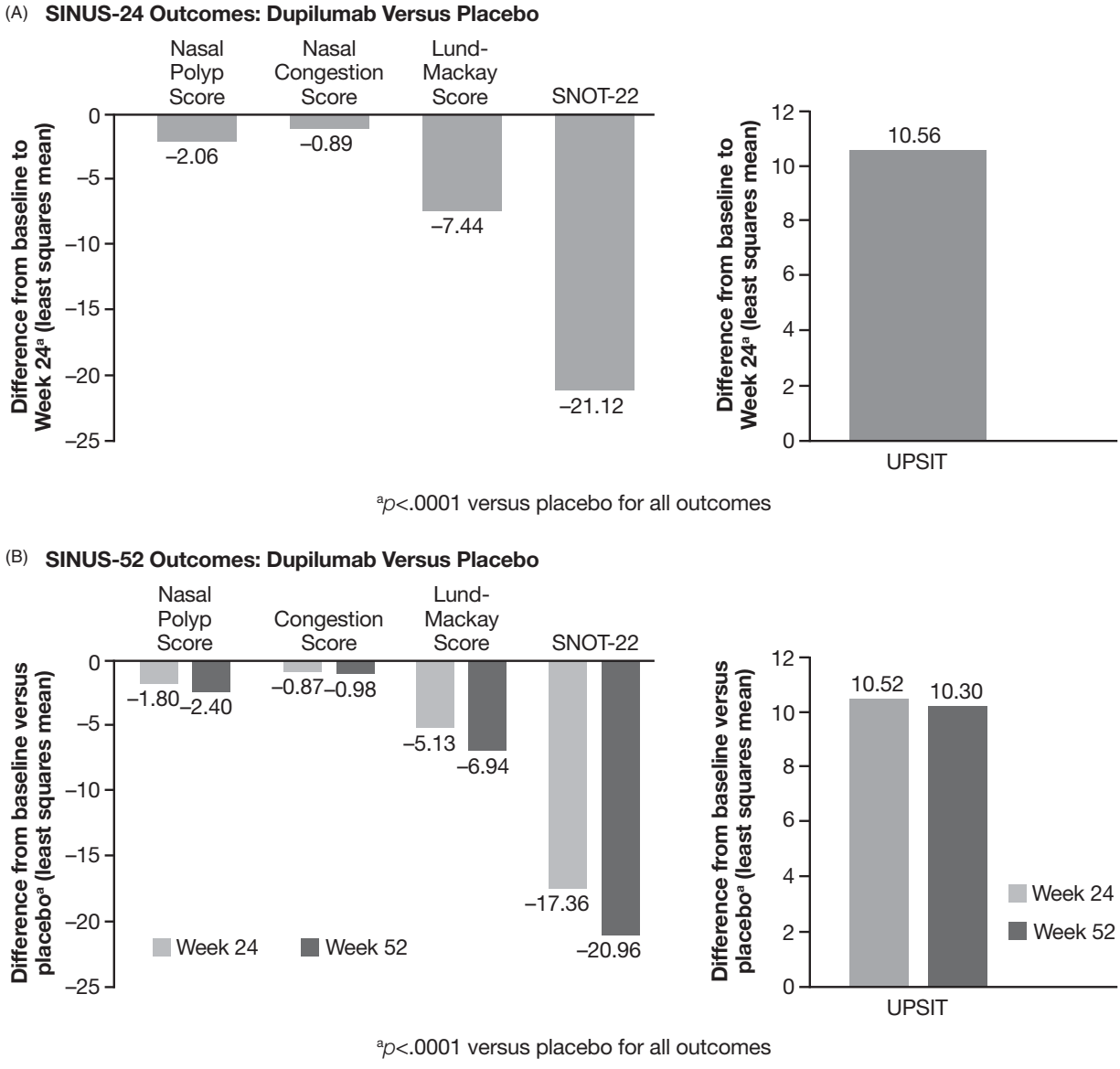

Figure 4. Clinical outcomes scores for dupilumab versus placebo from SINUS-24 and SINUS-52 Phase III RCTs.

At 52 weeks, dupilumab reduced rescue treatment (systemic corticosteroids) or NP surgery by 76% versus placebo ($p < .0001$)[88]. Also at 52 weeks, dupilumab significantly improved both ACQ-6 scores ($p < .0001$) and FEV_1 ($p < .0001$) versus placebo for patients with severe CRSwNP plus comorbid asthma[86]. The Phase II trial (NCT01920893) demonstrated that dupilumab significantly improved endoscopic nasal congestion and NP, Lund-Mackay, UPSIT, and SNOT-22 scores compared with placebo for patients with CRSwNP refractory to intranasal corticosteroids[87].

Searches for mepolizumab retrieved one Phase II study (NCT01362244)[90] and one study not specifying phase[91]. Bachert et al.[90] found that the NP severity VAS scores and mean individual symptom VAS scores (mucus in throat, loss of smell, rhinorrhea and nasal blockage) were significantly improved in the mepolizumab group compared with the placebo group at Week 25 (Figure 5(A)). In the second study, treatment difference reflected by the total polyp score demonstrated that mepolizumab resulted in improvement compared with placebo (Figure 5(B))[91]. In one RWE study of mepolizumab for patients with aspirin-exacerbated respiratory disease (AERD)[92], after three or more doses of mepolizumab, the SNOT-22 score decreased significantly by 17.7 points[92].

For omalizumab, one Phase II study[93] and one study of unspecified phase were retrieved[94]. In the Phase II trial (NCT01066104), omalizumab had no significant effect on polypoid mucosal thickening in the anterior ethmoid and maxillary sinuses, or on volume of polypoid mucosal tissue in the noses and sinuses of patients with CRSwNP (Figure 6(A))[93]. In a smaller clinical study of 24 patients (no phase specified), omalizumab significantly improved total endoscopic NP score compared with baseline and placebo for patients with CRSwNP and comorbid asthma (Figure 6(B))[94]. In one RWE study, omalizumab treatment significantly

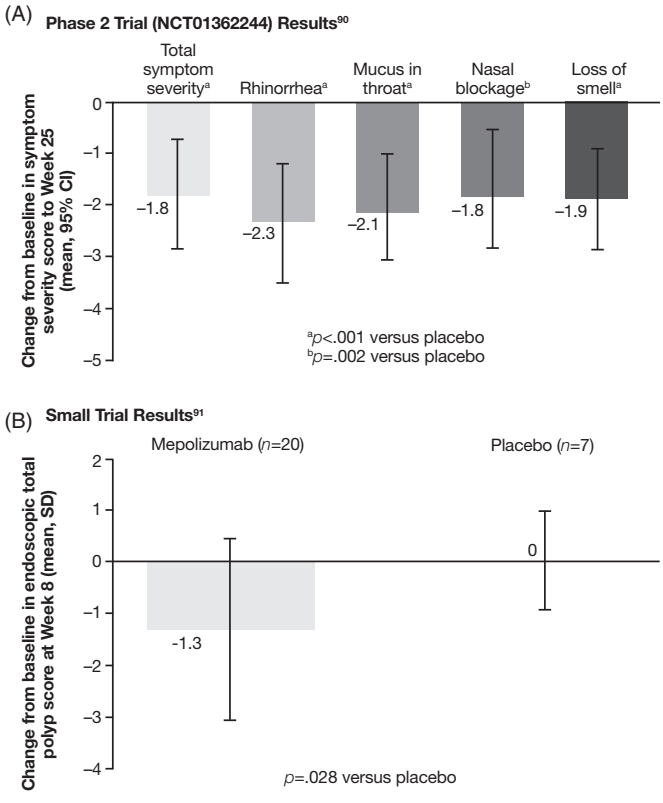

Figure 5. Mepolizumab clinical trial results.

improved SNOT-22 scores after 4 and 16 weeks relative to baseline (Figure 5(C))[95]. ACQ-7 scores also improved significantly at Weeks 4 ($p < .005$) and 16 ($p < .03$)[95].

Discussion

A major strength of this SLR was that it 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. A limitation of this SLR was that it included studies restricted to the English language at the study-selection stage. This is likely a minor limitation, given that the majority of studies are published in English-language journals. This SLR included only RCTs and RWE studies with results available at the time of the literature searches. Results for ongoing Phase III trials for biologics may have become available after the completion of this review. As well, novel biologics, which will affect disease management for patients with CRSwNP, may be in future trials.

The epidemiology SLR found that CRSwNP affects approximately 1–3 of 100 people and is more common in men and older individuals[96]. The prevalence varies across geographic regions. In particular, the prevalence of eCRSwNP within the CRSwNP population was reported to range from 65% in Asia to 91% in Europe[24,25]. CRSwNP has a greater mortality risk compared with CRSsNP. Asthma, allergy, and allergic rhinitis were the most commonly reported comorbidities identified for CRSwNP. Common symptoms of CRSwNP were nasal congestion, loss of smell, sneezing, headache, and facial pain. Asthma, gene polymorphisms, and aging can increase the likelihood of developing CRSwNP.

Although Fokkens et al.[2] in the European Position Paper (EPOS) published in 2020 describe an association between asthma and CRS, eosinophilia and asthma are identified in the literature covered in this review as risk factors for CRSwNP and disease recurrence. Eosinophilia is also associated with worse respiratory function, and greater disease severity and recurrence rates. The most common treatments for CRSwNP were corticosteroids, followed by antibiotics and antihistamines.

Prevalence data were reported more often for CRS than for CRSwNP. Prevalence data for patients with CRSwNP were available only for South Korea and the United States in articles published from 2008 onward. The lack of prevalence data from Europe, South America, and other regions is a notable gap in the literature. In addition, there were few reports on incidence or mortality, and no projected prevalence data. Finally, few studies focusing on severe CRSwNP and eCRSwNP were retrieved.

Symptoms remain highly prevalent among CRSwNP patients, indicating a large percentage of patients with disease not well-controlled with current treatment options. A short course of OCS might be used for patients with CRSwNP who failed initial therapy. Despite the fact that long-term OCS adverse effects were not directly assessed in CRSwNP patients, the impact for patients with other conditions, such as asthma, is well-documented[97]. Therefore, the long-term deleterious effects of steroid use should be weighed against any gains in symptom relief.

Patients with disease refractory to medical intervention often have surgery. However, recurrence rates of symptoms and polyps are high. The GA^{2}LEN study found that 59% of patients who had undergone surgery also later received revision surgery, and nearly 23% of patients experienced four or more revision surgeries[98]. Another study reported that within 18 months of surgery, 40% of patients reported recurrence of polyps and within 3–5 years of surgery, 80% of patients reported inadequately-controlled symptoms[99].

Three biologics had published literature attesting to efficacy, but the efficacy metrics varied. Of them, omalizumab had efficacy only in the more limited setting of patients with AERD. This implies that head-to-head trials are needed to determine potential superiority for one biologic over another.

Key data gaps identified by the clinical burden portion of the SLR included lack of head-to-head Phase III trials for biologics in CRSwNP. Moreover, there was a lack of evidence on the effects of prolonged treatment with biologics, and on the duration of efficacy after treatment with biologics. The efficacy and safety of biologics for patients with CRSwNP in the real-world setting requires further study. There was also a lack of RCTs and RWE studies of patients with eCRSwNP. Finally, there was variability in how outcomes were measured, both between RCTs and between RCTs and RWE studies. Such variation in data reporting made robust comparisons not feasible.

There was heterogeneity across the studies included in the review in terms of factors such as patient inclusion criteria,

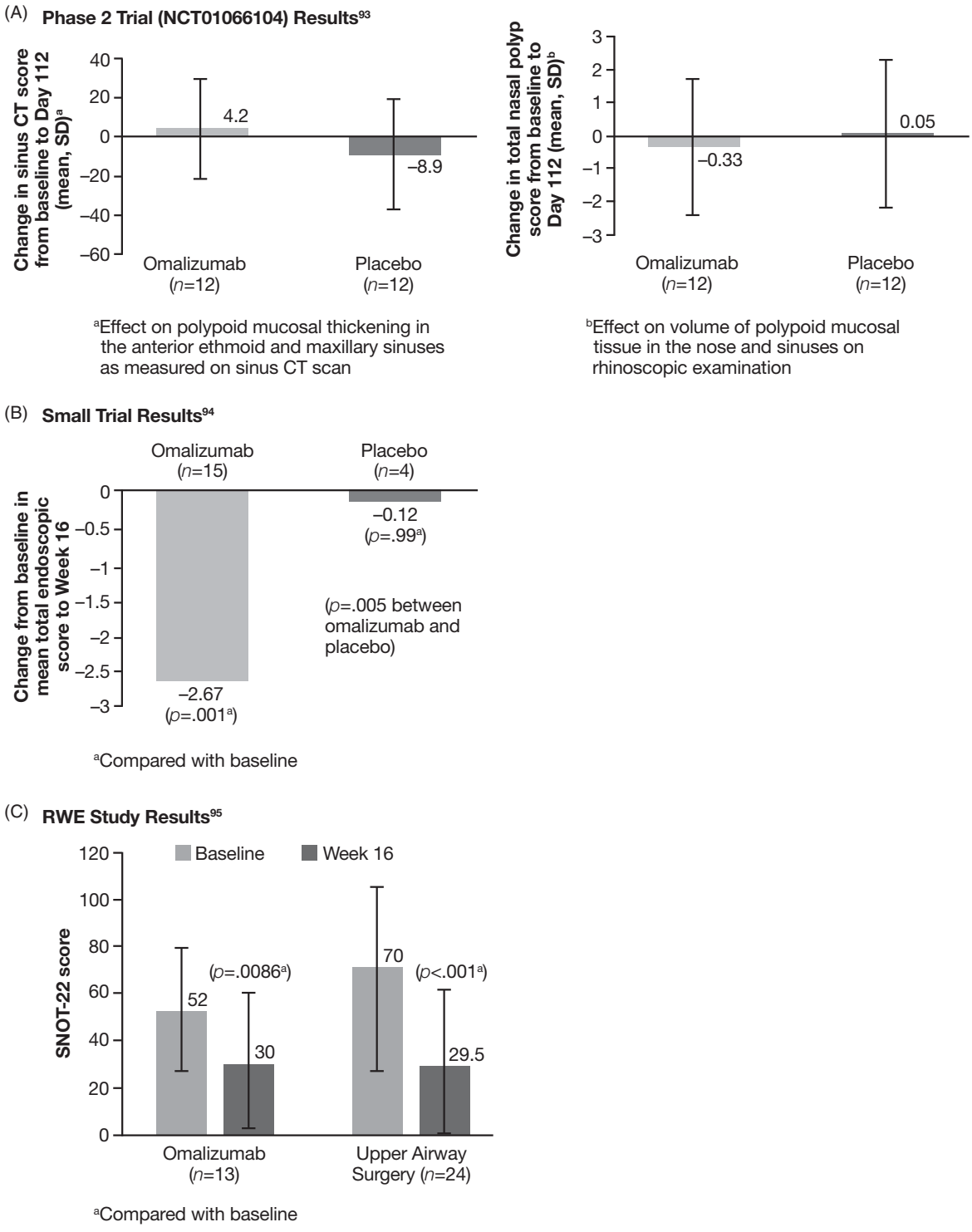

Figure 6. Omalizumab clinical trial and RWE study results.

patient characteristics, and study setting (e.g. recruitment at secondary or tertiary clinics), which may have contributed to the wide ranges observed in the results. Future studies should clarify how these factors may have influenced the results.

Conclusions

CRSwNP is fairly prevalent in the general population. Despite the significant efficacy of existing treatments, several unmet needs remain. The high burden of uncontrolled symptoms, frequent recurrence of nasal polyps after surgery, and long-term adverse effects of OCS indicate that new therapies addressing these unmet needs should be developed. Although data on biologics from RCTs look promising, the efficacy of biologics for CRSwNP in the real world has yet to be established.

The SLR of the epidemiology and clinical burden of CRSwNP revealed key gaps in the literature. There was a paucity of prevalence data across many geographic areas, and

no prevalence projections could be determined. Studies showed varying efficacy of non-biologics and no studies directly compared biologics for efficacy. Data regarding clinical efficacy of agents for eCRSwNP or severe CRSwNP were lacking, and these patient populations would be served by more trials.

Transparency

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Declaration of financial/other relationships

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