

SUPPLEMENTARY MATERIAL

Supplementary table S1. Search terms and strategies developed for this systematic review.

Number	Term	Synonyms
#1	Chronic rhinosinusitis with nasal polyps	((Chronic Rhinosinusitis with nasal polyps) OR CRSwNP OR (nasal polyposis))
#2	Smell impairment	((Olfact* OR smell) AND (impairment OR dysfunction OR alteration OR disorder OR loss)) OR anosmia OR hyposmia)
#3	Medical treatment	((oral cortico*) OR (nasal cortico* OR intranasal cortico*) OR (systemic cortico*) OR (topic cortico*) OR (antibiotic) OR (medical treatment))
#4	Surgical treatment	((endoscopic sinus surgery) OR (endoscopic nasal surgery) OR (surg*))
#5	Biological treatment	(biologic* OR (omalizumab OR dupilumab OR mepolizumab OR benralizumab))
#6	Outcomes	((olfact* OR anosmia OR hyposmia OR smell OR outcome*)
#7	Tests	((sniffin* stick) OR UPSIT OR "University of Pennsylvania Smell Identification Test" OR VAS OR "visual analogue scale" OR BSIT OR "Brief Smell Identification Test" OR BAST-24 OR "Barcelona Smell Test-24" OR CCCRC OR "Connecticut Chemosensory Clinical Research Center" OR (Likert scale))
SEARCH STRATEGIES		
#1 AND #2 AND (#3 OR #4 OR #5)		
#1 AND #6 AND #7		

Supplementary table S2a. Quality assessment of studies selected for inclusion according to the CASP system.

Study reference	Type of study	Quality level	CASP results ^a		
			Design	Methods	Outcomes
Biologic treatment					
(Bachert, Mannent et al. 2016)	RCT	High	+++	++0++	++
(Bachert, Sousa et al. 2017)	RCT	High	+++	++0++	++
(Bachert, Han et al. 2019)	Pooled analysis from 2RCTs	Very high	+++	+++++	++
(Desrosiers, Mannent et al. 2021)	Pooled subgroup analyses from 2 RCTs	Very high	+++	+++++	++
(Gevaert, Omachi et al. 2020)	2RCTs	Very high	+++	+++++	++
(Gevaert, Saenz et al. 2022)	OLE from RCTs	Medium-High	+++	+++00	++
(Han, Bachert et al. 2021)	RCT	High	+++	+----	++
(Mullol, Bachert et al. 2022)	Pooled analyses from the SINUS-24 and SINUS-52 phase 3 trials	Very High	+++	+++++	++
(Mullol, Laidlaw et al. 2021)	Pooled analyses from the 2RCTs	Medium-High	++-	+++++	++
(Naclerio et al., 2017) ABSTRACT	Phase 2a trial	Very low	++-	00000	++
Surgical treatment					
(Andrews, Poirrier et al. 2016)	Prospective cohort study	Very high	+++	+++++	++
(Arancibia, Langdon et al. 2022)	Prospective cohort study	Medium	+++	-+++	+0
(Baradaranfar, Ahmadi et al. 2014)	Prospective non-randomized clinical trial	Medium-low	+0	---++	++
(Bardaranfar, Ranjbar et al. 2014)	RCT	Medium	++0	+0++0	++
(Beswick, Smith et al. 2021)	Observational, prospective, multicenter study	Medium-low	+++	+----	+-
(Bogdanov, Walliczek-Dworschak et al. 2020)	Prospective, randomized study	Medium-low	+++	----+	++
(Chen, Deng et al. 2016)	Prospective, single-center, cohort study	Low	+++	--0+	+-
(Dadgarnia, Rahmani et al. 2019)	Prospective study	Medium	+++	+00+-	++
(DeConde, Mace et al. 2015)	Prospective, observational, multi-center cohort study	Medium	+++	-----	+-
(Djukic, Dudvarski et al. 2015)	Prospective study	Medium-low	+++	---0+	++
(Galletti, Gazia et al. 2019)	Retrospective study	Lowow	+0+	----+	++
(Haxel, Boessert et al. 2017)	Prospective study	High	+++	+++0+	++
(Haxel, Fischer et al. 2022)	Prospective study	Medium-High	+++	++++-	+-
(Hema, Rebekah et al. 2021)	Prospective observational study	Medium-low	+++	+--0-	++
(Levy, Mace et al. 2016)	Prospective, multi-center, observational cohort study	Medium-High	+0+	+++--	++

(Lind, Joergensen et al. 2016)	Prospective cohort study	High	+++	++++-	++
(Lötsch, Hintschich et al. 2021)	Prospective open cohort study	Medium	+++	+00+-	++
(Nguyen et al., 2015)	Prospective observational study	Low	+00	+0+--	++
(Nguyen et al., 2016)	Prospective observational study	Medium	+++	+--++	+-
(Paksoy et al., 2019)	Prospective observational study	Medium	+++	+--+	++
(Szaleniec, 2015)	Observational				
Medical treatment					
(Alobid, Benitez et al. 2014)	RCT	Medium-low	+++	----+	++
(Antonio, Marson et al. 2021)	RCT	Medium-low	+++	----+	++
(Kern, Stolovitzky et al. 2018)	RCT	Medium-High	+++	+--++	++
(Papadakis et al., 2021)	Randomized non-blinded clinical study	Low	++0	---+-	++
(Poletti et al., 2017)	Prospective clinical trial pseudo-randomized	Medium-High	+++	+00++	++
(Van Gerven, 2018)	Prospective, randomized, open-label trial	Medium-High	+++	---++	++

^aQuality assessment was performed using CASP checklists for each type of study (<https://casp-uk.net/casp-tools-checklists/>). Results depicted in the table correspond to questions related to design (questions 1-3), methodology (questions 4-6) and outcomes (questions 7-8) in the corresponding checklists. Each positive (yes) response in the questionnaire is depicted as (+), negative it is indicated as (-), and “can’t tell” is depicted as (0). The increasing number of (+) indicates a greater quality assessment score. Quality judgment as been assigned as an indicative measure (not given in the CASP assessment checklist).

RCT: randomized clinical trial.

Supplementary table S2b. Quality assessment of systematic reviews with meta-analysis selected for inclusion according to the CASP system.

Study reference	Type of study	Quality assessment	CASP results ^a		
			Design	Methods	Outcomes
Biologic treatment					
(Cai, Xu et al. 2022)	SRL and MA of 7 RCTs:	Very high	++	+++	++
Ohkyman, Paramo et al., 2022	NMA of RCT	Very high	++	+++	++
(Peters et al., 2021)	SRL and indirect treatment comparison of 4 RCTs	High	++	++	++
(Tsetsos, 2020)	SRL and MA of 7 RCTs	Very high	++	+++	++
(Wang, 2022)	SRL and MA of 7 RCTs	Very high	++	+++	++
Surgical treatment					
(Kohli, Naik et al. 2016)	SRL and MA (31 prospective cohort studies)	Medium-high	+-	++	++
(Zhao, 2021)	SRL and MA (35 studies: 29 cohort studies, 4 RCT, 2 case-control studies)	Very high	++	+++	++

^aQuality assessment was performed using CASP checklists for each type of study (<https://casp-uk.net/casp-tools-checklists/>). Results depicted in the table correspond to questions related to design (questions 1-2), methodology (questions 3-5) and outcomes (questions 6-7) in the corresponding checklists. Each positive (yes) response in the questionnaire is depicted as (+), negative it is indicated as (-), and “can’t tell” is depicted as (0). The increasing number of (+) indicates a greater quality assessment score. Quality judgment as been assigned as an indicative measure (not given in the CASP assessment checklist).

SRL: systematic review of literature; MA: Meta-analysis

Supplementary table S3. Methodological design and population characteristics of the studies included for qualitative synthesis.

Publication	Study design	Population /sample size	Comorbid asthma (%)	Comorbid NSAID-ERD (%)	Previous sinus surgery (%)	Follow-up time	Specific intervention	Comparator
BIOLOGICAL TREATMENT								
(Bachert, Mannent et al., 2016)	Randomized, double-blind, placebo-controlled parallel-group study	Adults with CRSwNP refractory to INS corticosteroids (<i>n</i> = 60)	63.3% in the placebo group; 53.3% in the dupilumab group	30% in the placebo group; 20% in the dupilumab group	63.3% in the placebo group and 53.3% in the dupilumab group	16 weeks	Dupilumab + mometasone furoate nasal spray	Placebo + mometasone furoate nasal spray
(Bachert, Sousa et al. 2017)	Randomized, double-blind, placebo-controlled trial	Adults with recurrent CRSwNP requiring surgery (<i>n</i> = 105)	75% in placebo group; 81% in mepolizumab group	NA	100%	24 weeks	Mepolizumab + intranasal steroids (fluticasone propionate)	Placebo + INS (fluticasone propionate)
(Bachert, Han et al. 2019)	Pooled analysis from two multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies	Adults with severe, uncontrolled CRSwNP (<i>n</i> = 724)	59%	28%	63.4%	24 weeks/52 weeks	Dupilumab	Placebo
(Desrosiers, Mannent et al. 2021)	Pooled subgroup analyses from the SINUS-24 and SINUS-52 phase 3 trials	Adults with CRSwNP with (<i>n</i> = 538) /without (<i>n</i> = 186) prior SCS use and with (<i>n</i> = 459)/without (<i>n</i> = 265) prior ESS	With/without prior SCS use: 60.2%/ 55.9%; With/without prior ESS: 66.2%/ 46.8%	With/without prior SCS use: 27.5%/ 30.1%; With/without prior ESS: 34.6%/ 17.0%	With/without prior SCS use: 54.3%/ 89.8%	24 weeks/ 52 weeks	Dupilumab	Placebo
(Gevaert, Omachi et al. 2020)	Randomized, multicenter, double-blind, placebo-controlled phase 3 studies (POLYP 1 and POLYP 2)	Adults with CRSwNP with inadequate response to INS (<i>n</i> = 265)	48.5 – 61.3 %	16.7 – 38.7%	54.2 – 62.9%	24 weeks	Omalizumab	Placebo + INS (mometasone)
(Gevaert, Saenz et al. 2022)	Open-label extension study of patients who completed POLYP 1 or POLYP 2	Adults with CRSwNP with inadequate response to INS (<i>n</i> = 249)	57%	26.9%	59%	52 weeks	Omalizumab	Placebo + INS (mometasone)

(Han, Bachert et al., 2021)	Randomized, double-blind, placebo-controlled, phase 3 trial	Adult patients with recurrent, refractory, severe CRSwNP and at least one NP surgery (<i>n</i> = 407)	71%	26.5%	100%	49 weeks/52 weeks	Mepolizumab	Placebo
(Mullol, Bachert et al., 2022)	Pooled analyses from the SINUS-24 and SINUS-52 phase 3 trials	Adults with severe, uncontrolled CRSwNP (<i>n</i> = 724)	59%	28.2%	63.4%	24 weeks/52 weeks	Dupilumab	Placebo
(Mullol, Laidlaw et al., 2021)	Pooled analyses from the SINUS-24 and SINUS-52 phase 3 trials	Adults with severe, uncontrolled CRSwNP (<i>n</i> = 724)	With/without NSAID-ERD: 88.7%/ 47.5%	28.2	With/without NSAID-ERD: 77.9%/ 57.7%	24 weeks/52 weeks	Dupilumab	Placebo
(Naclerio et al., 2017) ABSTRACT	Phase 2a trial	Adults with CRSwNP (<i>n</i> = 60)	NA	NA	NA	16 weeks	Dupilumab	Placebo + mometasone furoate nasal spray
(Cai, Xu et al., 2022)	Systematic review and meta-analysis (7 RCT)	Adults with CRSwNP (<i>n</i> = 1913)	53.6% – 78.1%	NA	58.3% – 100%	Ranges from 24 to 56 weeks	Benralizumab, dupilumab, mepolizumab, omalizumab	Depending on the RCT, the comparison was placebo, standard of care, or no treatment.
Ohkyman, Paramo et al., 2022	Network meta-analysis of RCT	29 RCT evaluating 8 interventions (<i>n</i> = 3461)	Mean of means: 77%	Mean of means: 34%	Mean of means: 73%	NA	Benralizumab, dupilumab, mepolizumab, omalizumab	NA
(Peters et al., 2021)	Systematic review and indirect treatment comparison (4 RCT)	Adults with CRSwNP (<i>n</i> = 989)	53.6% – 60.6%	NA	57.2% – 71.7%	24 weeks	Dupilumab, omalizumab	Placebo
(Tsetsos, 2020)	Systematic review and meta-analysis (7 RCT)	Adults with CRSwNP (<i>n</i> = 957)	NA	NA	NA	Ranges from 16 to 52 weeks	Dupilumab, omalizumab, mepolizumab	Placebo
(Wang, 2022)	Systematic review and meta-analysis (7 RCT)	Adults with CRSwNP (<i>n</i> = 799)	30 – 88%	NA	NA	Ranges from 24 to 76 weeks	Benralizumab, mepolizumab, reslizumab	Placebo

SURGERY								
(Andrews Poirrier et al., 2016)	Prospective cohort study	Adults with CRS ($n = 113$; CRSwNP $n = 60$)	NA	NA	11.5%	6 months	ESS	Before and after surgery
(Arancibia, Langdon et al., 2022)	Prospective cohort study	Adults with moderate-to-severe CRSwNP refractory to medical treatment ($n = 76$, n at 12 years = 39)	55.4%	31.1%	19.7%	12 years	ESS	Before surgery and 12 years after surgery
(Baradaranfar, Ahmadi et al., 2014)	Prospective non-randomized clinical trial	Patients with CRSwNP ($n = 60$)	NA	NA	0%	12 weeks	FESS + postoperative Fluticasone propionate nasal spray for 8 weeks	FESS + medical treatment vs. medical treatment alone
(Bardaranfar, Ranjbar et al., 2014)	Double-blind randomized controlled trial	Patients with CRSwNP who had complaints of olfactory dysfunction ($n = 60$)	NA	NA	NA	8 weeks	Triamcinolone+ ESS + Gelfoam (Triamcinolone group) vs. ESS + Gelfoam (control group)	2 weeks before surgery and 8 weeks after surgery
(Beswick, Smith et al., 2021)	Observational, prospective, multicenter study	Adults with CRSwNP who underwent ESS ($n = 165$)	56%	19%	63%	18 months	ESS	2 months before surgery and every 6 months after surgery until 18 months
(Bogdanov, Walliczek-Dworschak et al., 2020)	Prospective, randomized study	CRSwNP patients ($n = 52$) divided into control group ($n = 31$) and treatment group ($n = 21$)	NA	0%	NA	3 months	ESS without preoperative OCS (control group); ESS with preoperative OCS (treatment group)	Comparison of control and treatment group before surgery vs. 2 weeks, 1 month and 3 months after surgery
(Chen, Deng et al., 2016)	Prospective, single-center, cohort study	Patients with CRSwNP and asthma ($n = 47$) undergoing EESS ($n = 23$) or FESS ($n = 24$)	100%	NA	25% in the EESS group and 22.7% in the FESS group	1 year	EESS or FESS + prednisolone 30 mg once a day for 7 days before surgery + budesonide nasal spray 128 µg twice a day for at least 3 months or until achieving good control.	Before and after surgery

(Dadgarnia, Rahmani et al., 2019)	Prospective study	Patients with CRSwNP undergoing ESS (<i>n</i> = 40)	NA	NA	NA	3 months	ESS + 5-day course of prednisolone 0.5 mg/kg in a single dose every morning before surgery + topical fluticasone 100 µg in each nostril daily after surgery for 6 weeks.	Before surgery and 3 months after surgery
(DeConde, Mace et al., 2015)	Prospective, observational, multi-center cohort study	Adult patients with medical refractory CRS (<i>n</i> = 342) who either continued medical management (<i>n</i> = 69) or underwent ESS (<i>n</i> = 273)	30.4% in medical management group and 37% in ESS group	11.6% in medical management group and 8.4% in ESS group	58% in medical management group and 52% in ESS group	At least 6 months and up to 18 months	ESS	Baseline and at least 6-months after continued medical therapy or ESS procedure.
(Djukic, Dudvarski et al., 2015)	Prospective study	Adult patients with NP who underwent FESS after failure of medical treatment or surgical treatment (<i>n</i> = 85)	38.8%	25.9%	44.7%	12 months	FESS + postoperative intranasal corticosteroid for 3 months	Before surgery and 6 and 12 months after surgery
(Galletti, Gazia et al., 2019)	Retrospective study	Patients with CRS refractory to medical treatment (<i>n</i> = 96), divided into group A (who underwent ESS with computer navigation system) (<i>n</i> = 48), and group B (who underwent conventional ESS) (<i>n</i> = 48).	NA	NA	NA	12 months	Group A: ESS with use of the Medtronic FUSION Compact ENT NAVIGATION system. Group B: conventional ESS; + third generation cephalosporins for 5 days, nasal douching with beclomethasone dipropionate, thiamphenicol, acetylcysteine and saline solution twice a day for a month.	Group A: ESS with use of the Medtronic FUSION Compact ENT NAVIGATION system. Group B: conventional ESS + third generation cephalosporins for 5 days + nasal douching with beclomethasone dipropionate, thiamphenicol, acetylcysteine and saline solution twice a day for a month.
(Haxel, Boessert et al., 2017)	Prospective study	Adult patients with CRS (with and without NP), who	NA	NA	58.5%	6 months	ESS + nasal irrigation with saline at least twice a day +	Before surgery, and 2 weeks and 6 months after surgery

		underwent ESS because of unsuccessful conservative treatment with topical and/or systemic steroids ($n = 41$)					topical nasal steroid (fluticasone furoate) once a day (27.5 mg), beginning after the surgical intervention and continuing for the entire study period.	
(Haxel, Fischer et al., 2022)	Prospective study	Patients with CRSwNP undergoing ESS ($n = 47$)	40%	11%	19%	3 months	ESS + topical nasal steroid after surgery	Before surgery and 3 months after surgery
(Hema, Rebekah et al., 2021)	Prospective observational study	Patients with medically refractory CRS ($n = 96$; 65.6% with NP).	11%	NA	19%	6 months	FESS	Before surgery and 6 months after surgery
(Levy, Mace et al., 2016)	Prospective, multicenter, observational cohort study	Adult patients with medically recalcitrant CRS ($n = 122$), with NP ($n = 38$) and without NP	31.1%	7%	51%	6, 12 and 18 months	ESS	Before surgery and at 6, 12 and 18 months after surgery
(Lind, Joergensen et al., 2016)	Prospective cohort study	Patients with CRS with inadequate response to INS ($n = 97$), with CRSwNP ($n = 75$) or CRSsNP ($n = 22$)	28% in the CRSwNP group and 10% in the CRSsNP group	0% (excluded from study)	31% in the CRSwNP group and 5% in the CRSsNP group	6 months	ESS	Before surgery, and 1 month and 6 months after surgery
(Lötsch, Hintschich et al., 2021)	Prospective open cohort study	Patients with CRSwNP ($n = 158$) that had undergone surgery.	NA	NA	NA	4 months	ESS	Before surgery and 4 months after surgery
(Nguyen et al., 2015)	Prospective observational study	Patients endoscopically operated for NP ($n = 96$)	58.33%	NA	54.17%	6 weeks	ESS + INS before and after surgery.	Before surgery and 6 weeks after surgery
(Nguyen et al., 2016)	Prospective observational study	Patients who underwent endoscopic surgery for NP ($n = 65$)	NA	NA	NA	7 months	ESS (radical ethmoid surgery for NP) + topical steroids once daily after surgery	Before surgery, and 6 weeks and 7 months after surgery
(Paksoy et al., 2019)	Prospective observational study	Patients with CRSwNP undergoing surgery for NP ($n = 30$)	NA	NA	NA	3 months	ESS + standard medical treatment pre and post operative	Before surgery and 3 months after surgery

(Szaleniec, 2015)	Observational	CRS refractory to medical treatment ($n = 153$)	35%	13%	Polypectomy 17%; ESS 17%	12 months	ESS	Before surgery and 3-6 months after ESS (121 individuals) and 12 months after ESS (58 individuals)
(Kohli, Naik et al., 2016)	Systematic review and meta-analysis (31 prospective cohort studies)	Patients with CRSwNP ($n = 599$)	NA	NA	NA	Ranges from 6 weeks to 30 months	ESS	Before and after surgery
(Zhao, 2021)	Systematic review and meta-analysis (35 studies: 29 cohort studies, 4 RCT, 2 case-control studies)	Patients with CRS ($n = 3164$)	NA	NA	NA	Ranges from 1 month to 46 months	ESS	NA
MEDICAL TREATMENT								
(Alobid, Benitez et al., 2014)	RCT	Patients with moderate-to-severe CRSwNP ($n = 89$)	61% (treatment group), 63% (control group)	24% (treatment group), 23% (control group)	6.7%	14 weeks	Standardized oral prednisone for 2 weeks (30 mg daily for four days followed by a 2-day reduction of 5 mg) and INS budesonide 400 µg BID for 12 weeks	The control group received no corticosteroid treatment for 2 weeks
(Antonio, Marson et al., 2021)	RCT	Adults with CRSwNP ($n = 30$)	26.7% (control group), 26.7% (treatment group)	13.3% (control group), 26.7% (treatment group)	46.7% (control group), 60% (treatment group)	12 weeks (T1) and 24 weeks (T2)	INS 0.05% budesonide + 0.1% tretinoin	0.05% budesonide
(Kern, Stolovitzky et al., 2018)	Randomized, sham-controlled, double-blind phase 3 trial	Adults with refractory CRSwNP, candidates for repeated surgery ($n = 300$)	73.6% (treatment group), 61.6% (control group)	14.9% (treatment group), 17.2% (control group)	100%	90 days	Mometasone furoate 200 µg nasal spray and nasal implants containing 1350 µg of mometasone or placebo (shams)	Placebo
(Papadakis et al., 2021)	Randomized non-blinded clinical study	Adults with CRSwNP with hyposmia ($n = 140$)	NA	NA	NA	12 weeks and 24 weeks	Group A: 7-day course of oral steroids with a 12-weeks course of INS and douching. Group B: 12-weeks course of INS and douching.	Group A vs. group B

(Poletti et al., 2017)	Prospective clinical trial pseudo-randomized	Patients with CRS (with and without NP) (<i>n</i> = 29)	NA	NA	NA	2 weeks and 6 weeks	1) conventional nasal spray and (2) a device using pressure and vibration to distribute steroid aerosol endonasally (AMSA®).	Group A vs. group B
(Van Gerven, 2018)	Prospective, randomized, open-label trial	Patients with CRSwNP after surgery (<i>n</i> = 72)	54%	28%	NA	1 year	INS + montelukast	INS

CRS, chronic rhinosinusitis; NP, nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; CRSsNP, chronic rhinosinusitis without nasal polyposis; INS, intranasal corticosteroids; NSAID-ERD, non-steroid anti-inflammatory drug-exacerbated respiratory disease; NA, not available; SCS, systemic corticosteroids; ESS, endoscopic sinus surgery; EESS: extensive endoscopic sinus surgery; FESS, functional endoscopic sinus surgery; RCT, randomized controlled trial; OCS, oral corticosteroids; BID, twice per day