

## SUPPLEMENTARY MATERIAL

**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))
<b>SEARCH STRATEGIES</b>		
#1 AND #2 AND (#3 OR #4 OR #5)		
#1 AND #6 AND #7		

**Table S2a.** Quality assessment of studies selected for inclusion according to the CASP system.

Study reference	Type of study	Quality level	CASP results <sup>a</sup>		
			Design	Methods	Outcomes
<b>Biologic treatment</b>					
(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	++
<b>Surgical treatment</b>					
(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				
<b>Medical treatment</b>					
(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	+++	---++	++

<sup>a</sup>Quality 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.

**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 <sup>a</sup>		
			Design	Methods	Outcomes
<b>Biologic treatment</b>					
(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	++	+++	++
<b>Surgical treatment</b>					
(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	++	+++	++

<sup>a</sup>Quality 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

**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
<b>BIOLOGICAL TREATMENT</b>								
<b>(Bachert, Mannent et al., 2016)</b>	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
<b>(Bachert, Sousa et al. 2017)</b>	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)
<b>(Bachert, Han et al. 2019)</b>	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
<b>(Desrosiers, Mannent et al. 2021)</b>	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
<b>(Gevaert, Omachi et al. 2020)</b>	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)
<b>(Gevaert, Saenz et al. 2022)</b>	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)

<b>(Han, Bachert et al., 2021)</b>	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
<b>(Mullol, Bachert et al., 2022)</b>	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
<b>(Mullol, Laidlaw et al., 2021)</b>	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
<b>(Naclerio et al., 2017) ABSTRACT</b>	Phase 2a trial	Adults with CRSwNP ( <i>n</i> = 60)	NA	NA	NA	16 weeks	Dupilumab	Placebo + mometasone furoate nasal spray
<b>(Cai, Xu et al., 2022)</b>	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.
<b>Ohkyman, Paramo et al., 2022</b>	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
<b>(Peters et al., 2021)</b>	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
<b>(Tsetsos, 2020)</b>	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
<b>(Wang, 2022)</b>	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								
<b>(Andrews Poirrier et al., 2016)</b>	Prospective cohort study	Adults with CRS ( $n = 113$ ; CRSwNP $n = 60$ )	NA	NA	11.5%	6 months	ESS	Before and after surgery
<b>(Arancibia, Langdon et al., 2022)</b>	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
<b>(Baradaranfar, Ahmadi et al., 2014)</b>	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
<b>(Bardaranfar, Ranjbar et al., 2014)</b>	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
<b>(Beswick, Smith et al., 2021)</b>	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
<b>(Bogdanov, Walliczek-Dworschak et al., 2020)</b>	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
<b>(Chen, Deng et al., 2016)</b>	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

<b>(Dadgarnia, Rahmani et al., 2019)</b>	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
<b>(DeConde, Mace et al., 2015)</b>	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.
<b>(Djukic, Dudvarski et al., 2015)</b>	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
<b>(Galletti, Gazia et al., 2019)</b>	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.
<b>(Haxel, Boessert et al., 2017)</b>	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.	
<b>(Haxel, Fischer et al., 2022)</b>	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
<b>(Hema, Rebekah et al., 2021)</b>	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
<b>(Levy, Mace et al., 2016)</b>	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
<b>(Lind, Joergensen et al., 2016)</b>	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
<b>(Lötsch, Hintschich et al., 2021)</b>	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
<b>(Nguyen et al., 2015)</b>	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
<b>(Nguyen et al., 2016)</b>	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
<b>(Paksoy et al., 2019)</b>	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

<b>(Szaleniec, 2015)</b>	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)
<b>(Kohli, Naik et al., 2016)</b>	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
<b>(Zhao, 2021)</b>	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
<b>MEDICAL TREATMENT</b>								
<b>(Alobid, Benitez et al., 2014)</b>	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
<b>(Antonio, Marson et al., 2021)</b>	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
<b>(Kern, Stolovitzky et al., 2018)</b>	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
<b>(Papadakis et al., 2021)</b>	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

<b>(Poletti et al., 2017)</b>	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
<b>(Van Gerven, 2018)</b>	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