Effect of different therapeutic strategies on olfactory outcomes in patients with chronic rhinosinusitis with nasal polyps: a systematic review

Running title: Effect of interventions on olfaction in CRSwNP

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Abstract

Introduction: Olfactory impairment is one of the cardinal symptoms of chronic rhinosinusitis with nasal polyps (CRSwNP), yet the effect of the currently available therapeutic options on the recovery of the sense of smell is not well defined. The aim of this systematic review was to compile the evidence on the impact of medical, surgical, and biological therapies on the olfactory outcomes in patients with CRSwNP.

Methods: This review was conducted by two reviewers, according to the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) guidelines. The quality of evidence of all studies included in the qualitative synthesis was evaluated using the Critical Appraisal Skills Programme (CASP).

Results: Forty-four studies were included in the qualitative synthesis (assessing sinonasal surgery [*n* = 23], biologics [*n* =15], and conventional medical treatment [*n* = 6]); most had moderate-to-high methodological quality. Overall, significant improvements in the sense of smell were detected with all analyzed interventions measured by either an objective or a subjective tool (or both). However, most studies used different outcome measurements, hindering comparisons between interventions, and data on clinically relevant changes were missing.

Conclusion: Oral corticosteroids, biologics and sinonasal surgery improve olfactory impairment associated with CRSwNP, but the high variability among existing studies does not allow accurate comparisons.

Key words: CRSwNP. Olfaction. Impairment. Biologics. Surgery. Corticosteroids.

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Resumen

Introducción: el deterioro del olfato es uno de los síntomas cardinales de la rinosinusitis crónica con rinosinusitis crónica con pólipos nasales (RSCcPN), pero el efecto de las opciones terapéuticas actualmente disponibles sobre la recuperación del sentido del olfato no está bien definido. El objetivo de esta revisión sistemática es recopilar datos sobre el impacto de los tratamientos médicos, quirúrgicos y biológicos en los resultados sobre el olfato de los pacientes con RSCcPN.

Métodos: la revisión se llevó a cabo de acuerdo con las directrices *Preferred Reporting Items for Systematic Reviews and meta-Analyses* (PRISMA), y el proceso fue realizado por dos revisores. La calidad de la evidencia de todos los estudios incluidos para la síntesis cualitativa se evaluó mediante el *Critical Appraisal Skills Programme* (CASP).

Resultados: se incluyeron cuarenta y cuatro estudios para la síntesis cualitativa (que evaluaban la cirugía sinonasal [n = 23], los productos biológicos [n = 15] o el tratamiento médico convencional [n = 6]), la mayoría de ellos con una calidad metodológica de moderada a alta. En general, se detectaron mejoras significativas en el sentido del olfato con todas las intervenciones analizadas medidas mediante una herramienta objetiva o subjetiva (o ambas). Sin embargo, la mayoría de los estudios utilizaron diferentes pruebas de medición de resultados, lo que dificultó las comparaciones entre intervenciones, y se ofrecían datos sobre el cambio clínicamente relevante.

Conclusión: los corticosteroides orales, los fármacos biológicos y la cirugía sinonasal mejoran la alteración olfativa asociada a la RSCcPN, pero la elevada variabilidad entre los estudios existentes no permite realizar comparaciones precisas.

Palabras clave: RSCcPN. Olfato. Deterioro. Biológicos. Cirugía. Corticosteroides.

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Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a complex disorder characterized by chronic inflammation of the sinonasal mucosa and presence of nasal polyps [1] that confers a significant long-term symptom burden [2]. It affects about 4% of the population globally [3] and, in most patients, it is associated with type 2 inflammation, a pathway involved in other airway diseases. For this reason, CRSwNP often coexists with comorbid asthma and/or non-steroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) [4]. Among the range of clinical symptoms usually present in CRSwNP patients, olfactory impairment is a common complaint that can be troublesome and impact substantially on patients´ quality of life (QoL) [5].

The conventional approach to improve olfactory outcomes consists of medical treatment with intranasal corticosteroids (INCS), nasal washing, antibiotics and/or oral corticosteroids (OCS)[6]. In refractory cases, surgical endoscopic resection of nasal polyps is recommended, and recently, biological agents have been approved as an alternative treatment for this cases [7]. However, despite the increasing number of studies assessing olfactory outcomes in patients with CRSwNP [8], the effect of the available therapeutic options on olfactory recovery is not well defined.

The aim of this systematic review, then, was to analyze the literature, in order to compile and summarize the existing evidence on the effect of medical, surgical, and biological therapy on olfactory dysfunction associated with CRSwNP.

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Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) guidelines [9] and the recommendations of the Cochrane handbook for systematic reviews [10]. The search protocol was entered in the international Prospective Register Of Systematic Reviews (PROSPERO) of the National Institute for Health Research under number CRD42022336668.

Search strategy

The research question was defined using the PICO structure. The population comprised patients with CRSwNP, and the considered interventions included treatments with biologic therapies, medical therapies, or surgery. Outcome was the change in the sense of smell at different timepoints after surgery or after the beginning of the treatment, measured with one or more of the following psychophysical and/or subjective tests: Sniffin´ Sticks test, Connecticut Chemosensory Clinical Research Center (CCCRC) test, Brief Smell Identification Test (BSIT), University of Pennsylvania Smell Identification Test (UPSIT), Barcelona Smell Test-24 (BAST-24), Visual Analogue Scale (VAS), Likert scale, and smell item of the 22-item Sinonasal Outcome Test (SNOT-22). The comparator was the change in outcome after the intervention, or another intervention, or placebo.

A search strategy which also included Medical Subject Heading [Mesh] terms was developed (Table S1). Searches for publications in English and/or Spanish were performed on the PubMed, Web of Science and SCOPUS databases on April 1st, 2022, using a publication timeframe from January 2014 to March 2022.

Study selection and data extraction

Two reviewers screened the title, abstract and full text of all articles (one reviewer screened the records and the other checked the decisions) and applied eligibility standards based on inclusion/exclusion criteria to select the studies. The final articles comprised systematic reviews with meta-analyses, clinical trials (both randomized or not), *post hoc* studies of randomized trials, and observational studies specifically focusing on the effects of the medical, surgical, or biological treatment of CRSwNP on smell impairment measured by one the previously mentioned tests. Exclusion criteria were: systematic reviews without meta-analysis, case reports or case series, narrative reviews, studies with chronic rhinosinusitis without nasal polyps (CRSsNP) or mixed CRS population (CRSwNP and CRSsNP), studies with patients presenting comorbidities not related with T2-inflamation, studies with a sample size smaller than 25 patients (we estimated the sample size for between-groups mean comparison with an alpha level of 0.05 and a power of 80%, assuming a mean difference in the UPSIT score of 5 points and a SD of 4), publications where explicit olfactory outcomes could not be retrieved, and sub-analyses of an already included study with repeated outcome data. Data extracted from the studies were collected using a standardized Microsoft Excel® template by a single reviewer and validated by a second reviewer, and included information about the study design and methodology, percentage of participants with asthma, N-ERD and previous surgery at baseline, follow-up time, outcomes before and after the intervention, data on olfactory status and clinically relevant change when available, and conclusions.

Methodological quality assessment

The quality of evidence of all included studies was evaluated to determine risk of bias using the Critical Appraisal Skills Programme (CASP) (https://casp-uk.net/casp-tools-checklists/). Two independent reviewers assessed both study design/methodology and outcomes/results, using the appropriate checklist depending on the type of study. In the absence of a numeric score, the articles were classified as low, moderate, or high-quality evidence according to the type of study/design and the number of questions in the corresponding checklist that answered positive or negative.

Results

A total of 1659 records were identified through the database searches. After eliminating duplicates and performing the title, abstract and full text screening, 44 publications were selected for inclusion. Figure 1 contains a PRISMA diagram detailing the workflow of the screening process. Articles finally selected for the qualitative synthesis included clinical trials, subgroup and *post hoc* analyses, systematic reviews with meta-analysis, and observational studies. The methodological quality of the reviewed references is represented in Table S2a and Table S2b.

Effect of biological treatment on olfaction

Fifteen articles addressed biological treatment, with either dupilumab, mepolizumab, omalizumab, benralizumab, or reslizumab. Of these, 10 were randomized controlled

trials (RCT) and 5 were systematic reviews with meta-analysis. The population sample in most studies comprised non-controlled CRSwNP patients with an inadequate response to INCS and/or previous endoscopic surgery.

The UPSIT was used in almost all articles (*n* = 13) that addressed the efficacy of either dupilumab or omalizumab and in the meta-analyses which included several biologics. In general terms, significant improvements in UPSIT scores were detected after treatment with biologics (ranging from 16 to 52 weeks), all of which showed a statistically significant mean change from baseline (Table 1). In studies where the comparator was placebo, the least square (LS) mean difference (95% CI) in the UPSIT scores between the two arms at 24 weeks of follow-up ranged from 3.81 (1.38–6.24) (p = 0.0024) for omalizumab (POLYP 1 trial) [11] to 10.56 (8.79–12.34) (p<0.0001) for dupilumab (LIBERTY NP SINUS 24 trial) [12]. According to three network meta-analysis and indirect comparisons, the mean difference in UPSIT scores (95% CI) for dupilumab versus omalizumab was 6.70 (4.67 – 8.73)[13], 7.21 (5.20 – 9.23)[14], and 6.70 (4.59 – 8.80)[15], all favoring dupilumab. The latter was also superior to mepolizumab, with a mean difference (95% CI) of 4.83 (2.43 – 7.22), and to benralizumab, with a mean difference (95% CI) of 8.01 (5.73 – 10.29). Besides the UPSIT test, the Sniffin´ Sticks test was the only non-subjective smell test used in just one study, revealing a mean difference between mepolizumab and placebo at 24 weeks of treatment of 0.7 (-0.5 – 1.9) (p = 0.233)[16].

In 10 out of the 15 publications, one or more subjective measurements of olfaction were used. These outcomes were usually in line with those derived from the objective tests (Table 1). However, none of the included studies provided complete data on the

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clinically relevant change based on the olfactory condition, evaluated as the percentage of patients that were normosmic, hyposmic and anosmic, before and after treatment. Only a pooled analysis of the LIBERTY NP SINUS-24 and SINUS-52 phase 3 trials reported that 77.6% of 724 patients were anosmic at baseline versus 28% after treatment with dupilumab [17]. Detailed extracted data for all outcomes and included studies are shown in Table 1.

Effect of surgical treatment on olfaction

In 23 of the included references, the study intervention was sinus surgery, and most were prospective observational studies (*n* = 17). The remaining articles were systematic reviews with meta-analysis (*n* = 2), randomized or non-randomized clinical trials (*n* = 3), and a retrospective study (*n* = 1). In 12 studies, an objective olfactory test was used, whereas a subjective test was used in 11 studies. Six studies combined the use of an objective and subjective tool, and eight included data on the percentage of patients with each clinical olfactory status before and after the intervention. Globally, all studies concluded that sinus surgery significantly improved the CRSwNP patient´s perceived and measured sense of smell. The follow-up time ranged from six weeks to 12 years, and the analyzed population were mostly patients with CRSwNP refractory to medical treatment (Table S3). One study showed very long-term postoperative improvement in olfaction according to the BAST-24 test: at baseline, the median percentage (IQR) of smell detection, smell memory and smell identification were 0 (0–5), 0 (0–5) and 0 (0–0), respectively, while at a 12-year follow-up, they were 65 (0–100)(p <0.001), 15 (0 – 46.2) (p=0.031) and 30 (0 – 55) (p <0.001).

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Two studies that reported separate CRSwNP and CRSsNP data observed a higher response to surgery in patients with CRSwNP [18, 19]. From the analyses including data on the clinical olfactory status, one study reported a change in the proportion of anosmic patients, from 36.6% preoperatively to 17.1% at 6 months after surgery. Almost half (46.5%) were hyposmic both before surgery and 6 months after surgery, while the proportion of normosmic patients rose from 17.1% before surgery to 36.6% after 6 months from surgery [20]. According to Bardaranfar *et al*., combined surgical and medical treatment had a better effect (CCCRC mean [± *SD*] score: 1.10 [± 0.344] pretreatment vs. CCCRC mean [± *SD*] score: 7.0 [± 0.0] posttreatment) than surgery alone (CCCRC mean [±*SD*] score: 1.33 [± 0.32] pretreatment vs. CCCRC mean [± *SD*] score: 6.37 [± 0.24] posttreatment), and these results correlated with the clinical olfactory status (Table 1) [21]. In a different study, CRSwNP patients were significantly more likely to report complete restoration of smell or taste following sinus surgery compared to medical management (23.8% vs. 4.0%; $p = 0.026$) [22]. A trial compared the difference in olfactory outcomes between extensive endoscopic sinus surgery (EESS) and functional endoscopic sinus surgery (FESS). The difference in the VAS score (mean ± *SD*) one year after surgery was 6.00 ± 3.67 in the EESS group ($n = 23$) and 3.30 ± 3.44 in the FESS group ($n = 24$)($p = 0.015$).

Effect of medical treatment on olfaction

Of the 44 references included in the qualitative synthesis, only six reported a medical intervention other than surgery or biologics, all of which were randomized clinical trials. Thus, one of these trials assessed the administration of oral prednisone for two weeks (30 mg daily for four days followed by a 2-day reduction of 5 mg) plus intranasal

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budesonide spray twice daily (400 µg) for 12 weeks. The control group did not receive the two-week oral prednisone treatment [23]. The association of oral and INCS improved smell and nasal congestion while decreasing nasal inflammation as compared to the control group (p <0.05). These results were in line with another study in which olfactory recovery was better when initial medical treatment consisted of a short course of oral dexamethasone and intranasal budesonide compared to INCS alone (p <0.001) (Table 1) [24].

Kern*et al*. performed a sham-controlled trial with a sample size of 300 refractory CRSwNP patients. Patients who received absorbable mometasone-eluting furoate 200 µg nasal spray combined with a mometasone nasal implant (1350 µg) experienced sustained olfactory improvement (p = 0.0470) versus placebo (Table 1) after 90 days of follow-up [25]. A first-in-human study with 30 patients reported a statistical improvement in the CCCRC test (Table 1) between baseline and 24 weeks with 0.1% tretinoin added to intranasal budesonide compared to the latter alone [26]. Poletti *et al*. compared the efficacy of a specific device to distribute steroid aerosol endonasally (AMSA®) versus a conventional nasal spray. The clinically relevant olfactory improvement was limited and this device showed no superiority over the conventional spray according to the Sniffin' Sticks test results (Table 1) [27]. Lastly, a prospective randomized open-label trial evaluated the efficacy of montelukast as an add-on treatment to INCS in postoperative CRSwNP patients (n = 72), compared to INCS alone. The mean change in BAST-24 and VAS scores after 1 year was similar between the two treatment groups (Table 1), so the addition of montelukast to INCS in the treatment of postoperative CRSwNP patients is not recommended [28].

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Discussion

Among the cardinal symptoms of CRSwNP, olfactory impairment is usually described by patients as one of the most bothersome, impacting severely on their QoL [5]. This is the first systematic review evaluating the three currently available therapeutic approaches (biologics, surgery, and conventional medical treatment) in CRSwNP patients. In general, very few studies directly compare the different therapeutic approaches. Overall, significant olfactory improvements have been detected with all assessed interventions. In terms of conventional medical treatment, better olfactory outcomes have been achieved in more than one study with the combination of OCS and INCS than with the latter alone [23, 24], but the evidence is very limited and inconclusive for other combinations [26-28]. Comparisons among the outcomes retrieved with different biologics when using the same measurement tool reveal dupilumab as the most beneficial in terms of olfactory recovery [1, 12, 17, 29, 30]. In all these studies, the comparator was placebo or the medical standard of care. These findings are supported by the network meta-analysis [2, 13-15], although they are based on indirect treatment comparisons, which means that samples may not be comparable and results may have a bias of sample selection. Thus, head-to-head comparisons between biologics with longer follow-up times and real-world evidence are required to draw more reliable conclusions. With respect to surgery, most included publications also reported a significant response to ESS and better olfactory function based on both subjective and objective measurements. However, there is some disagreement in this regard: Lind *et al.* stated that certain patients are less likely to benefit from surgery, and 7 – 10% of the patients may experience deterioration in their sense of smell after surgery [31].

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Although the outcomes of medical interventions (mostly corticosteroids) show an olfactory improvement, the results do not seem as clear as those obtained with surgery or biologics. According to De Conde *et al.* [22], CRSwNP subjects were significantly more likely to report complete resolution of smell following surgery compared to medical treatment. However, it is difficult to make a global comparison of the three evaluated interventions due to the heterogeneity of the olfactory tests applied and the population characteristics. In general terms, the methodological design of the studies assessing biologics or medical treatment is more robust, as most are RCTs with a large sample size, whereas studies analyzing surgery tend to be observational and include significantly fewer patients. Besides, some of the studies included in this review perform subgroup analyses within the CRSwNP population. These revealed significant improvements in olfaction for dupilumab regardless of prior sinonasal surgery or prior systemic corticosteroids use [1]. Furthermore, among patients with anosmia at baseline, the proportions of patients who regained some sense of smell (UPSIT >18) at week 24 with dupilumab were comparable in patients with and without N-ERD [30]. However, higher percentages of patients with N-ERD are anosmic and have more severe and difficult-to-treat disease, which might result in better outcomes in this subpopulation as compared to those without N-ERD.

It is important to emphasize that most studies to date only include information on olfactory outcomes expressed as objectively measured and/or patient-reported scores, and do not include data on the percentage of anosmic or hyposmic patients who recover their sense of smell, a variable that reflects the clinically relevant change. Only a few studies incorporate these qualitative criteria. According to these results, biological

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treatments, including dupilumab, seem to be the most effective intervention in terms of olfactory improvement. This suggests that the design of studies should include more qualitative parameters for measuring the recovery of the sense of smell.

The measurement of olfaction must be standardized, in order to establish common criteria for all studies that compare treatments in terms of efficacy or effectiveness. Nevertheless, the phenotyping of respiratory diseases with an underlying pathophysiology mechanism, such as T2 inflammation, is becoming the cornerstone of accurate patient management [32], helping patients to benefit from the best treatment option depending on the primary therapeutic goal. This classification is often omitted in current clinical practice, hindering the choice of the most suitable first-line therapeutic option that may achieve the desired outcomes.

A limitation of this work is the broadly-based research question, which gave rise to high heterogeneity between studies, including patient cohorts that differ in severity, number of previous surgeries, or type and location of polyps. Additionally, it should be considered that the severity of olfactory impairment may vary depending on the endotype, which has not been assessed in all studies. Likewise, in patients with the same endotype, the degree of olfactory improvement may vary according to the degree of olfactory impairment, which is not well defined in many publications. Therefore, these samples are not always easily comparable, but our results may guide the design of future studies. In contrast, a major strength of our work is that the studies selected are high quality and recent, and used validated measurement tools. Another asset of this review is that it brings together all the evidence on the effect of the three current therapeutic interventions in olfactory loss in CRSwNP patients.

In conclusion, this review of the literature reveals that treatments targeting CRSwNP, such as OCS, biologics, or ESS, improve not only other markers and symptoms of this disease but also the loss of smell. However, the currently available evidence is highly diverse due to the variability in outcome measurements, so establishing standardized criteria would be desirable. Further research with real-world data that includes results on clinically relevant changes measured by qualitative parameters is needed to gain in-depth knowledge on the optimal management of olfactory impairment.

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Conflict of interests

IA declares receiving consulting fees, honoraria for lectures, presentations, speakers bureaus, educational events, and expert testimony, as well as support for attending meetings and/or travel from Menarini, Metronic, Olympus, Salvat, Novartis, Sanofi, GSK, AstraZeneca, Galenus health, Viatris. BB declares receiving honoraria for lectures, presentations, speakers bureaus, educational events for Chiesi and Roxall, as well as support for attending meetings and/or travel from Sanofi, GSK, Allergopharma, Allergy and Roxall. CC declares receiving consulting feed form Forwardontics, honoraria for lectures, presentations, speakers bureaus, educational events from Sanofi, GSK, Mylan, Forwardontics, and Cinfa, and for expert testimony form Audifon, as well as support for attending meetings and/or travel from Sanofi, GSK, Mylan, Forwardontics, and Cinfa. MGF is an employee of Medical Satitstics Consulting, SL and declares no other conflicts of interest. JS declares receiving grants form Sanofi paid to the Fundación Jimenez Diaz, consulting fees from Sanofi, AbbVie, and Novartis, honoraria for lectures, presentations, speakers bureaus, or educational events form Sanofi, GSK, FAES Farma, as well as support for attending meetings and/or travel from Sanofi. JS also declares having an unpaid leadership or fiduciary role in the Spanish Society of Allergology and Clinical Immunology (SEAIC), the European Academy Of Allergy And Clinical Immunology (EAACI) and, the American Academy of Allergy, Asthma & Immunology (AAAAI).

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Table 1. Olfactory outcomes for each CRSwNP therapeutic intervention in the selected studies

Biologics			
Study	**Olfactory outcomes with non-subjective smell test**	**Olfactory outcomes with subjective test**	**Clinically relevant change[a]**
(Bachert *et al.*, 2016)[29]	**UPSIT:** LS mean difference (95% CI) for dupilumab vs. placebo at 16 weeks: 14.8 (10.9 to 18.7), *p*<0.001	N/A	N/A
(Bachert *et al.*, 2017)[16]	**SNIFFIN´ STICKS:** Mean difference for mepolizumab vs. placebo at 24 weeks: 0.7 (-0.5 to 1.9), *p*=0.233	**VAS:** Mean difference for mepolizumab vs. placebo at 24 weeks: -1.9 (-2.9 to –0.9), *p*<0.001	N/A
(Bachert *et al.*, 2019)[12]	**UPSIT:** SINUS 24 STUDY (24 weeks): LS mean change (*SD*) with placebo from baseline: 0.70 (0.71); LS mean change (*SD*) with dupilumab from baseline: 11.26(0.67); LS mean difference for dupilumab vs. placebo (95% CI): 10.56 (8.79 to 12.34), *p*<0.0001. SINUS 52 STUDY (52 weeks): LS mean change (*SD*) with placebo from baseline: -0.81 (0.71) LS mean change (*SD*) with dupilumab from baseline: 2.49 (0.79); LS mean difference for dupilumab vs. placebo (95% CI): 10.52 (8.98 to 12.07), *p*<0.0001)	**LIKERT:** SINUS 24 STUDY (24 weeks): LS mean change (*SD*) with placebo from baseline: -0.29 (0.07); LS mean change (*SD*) with dupilumab from baseline: - 1.41 (0.07); LS mean difference for dupilumab vs. placebo (95% CI): -1.12 (- 1.31 to -0.93), *p* <0.0001) SINUS 52 STUDY: LS mean change (*SD*) with placebo from baseline☹SD) -0.23 (0.08); LS mean change (*SD*) with dupilumab from baseline:-1.21 (0.06); LS mean difference for dupilumab vs. placebo (95% CI): -0.98 (-1.15 to -0.81), *p* <0.0001)	N/A
(Desrosiers *et al.*, 2021)[1]	**UPSIT:** LS mean difference (95% CI) for dupilumab vs. placebo and with/without prior SCS use: 10.53 (9.17 to 11.90)/ 10.61 (8.35 to 12.86); LS mean difference (95% CI) for dupilumab vs. placebo and with/without prior ESS: 10.57 (9.07 to 12.06)/ 10.45 (8.56 to 12.35)	N/A	379 (84.2%) patients with surgery and 172 (66.2%) without surgery were anosmic at baseline (UPSIT score ≤18). Anosmia was reduced to 234 (53.4%) patients with surgery and 95 (37.3%) patients without surgery at week 24 with dupilumab
(Gevaert *et al.*, 2020)[11]	**UPSIT:** POLYP 1 STUDY: LS mean difference for omalizumab vs. placebo at 24 weeks: 3.81 (1.38 to 6.24), *p* = 0.0024.	**LIKERT:** POLYP 1 STUDY: LS mean difference for omalizumab vs. placebo at 24 weeks: -0.33 (-0.60 to - 0.06), *p* = 0.0161.	N/A

	POLYP 2 STUDY: LS mean difference for omalizumab vs. placebo at 24 weeks: 3.86 (1.57 to 6.15), *p* = 0.0011	POLYP 2 STUDY: LS mean difference for omalizumab vs. placebo at 24 weeks: -0.45 (-0.73 to - 0.16), *p* = 0.0024	
(Gevaert *et al.*, 2022)[33]	**UPSIT:** Mean change in continued omalizumab group from baseline: 4.24 at week 24 and 4.13 at week 52; mean change in switch to omalizumab group from baseline:3.88 at week 52	N/A	N/A
(Han *et al.*, 2021)[34]	N/A	**VAS:** Mean change (95% CI) for mepolizumab vs. placebo after 49 – 52 weeks: -0.37 (-0.65 to -0.08), *p* = 0.02	N/A
(Mullol *et al.*, 2022)[17]	**UPSIT:** LS mean difference (95% CI) for dupilumab vs. placebo: 10.57 (9.40 to 11.74), *p* <0.0001 at week 24	**LIKERT:** LS mean difference (95% CI) for dupilumab vs. placebo: -1.04 (-1.17 to -0.91), *p* <0.0001 at week 24 **SNOT-22:** LS mean difference (95% CI) for dupilumab vs placebo: -1.97 (-2.19 to -1.75), *p* <0.0001 at week 24	**Pretreatment:** Normosmia:12 (1.7%) Hyposmia:147 (20.7%) Anosmia:551 (77.6%) **Post treatment:** Anosmia:28%
(Mullol *et al.*, 2021)[30]	**UPSIT:** LS mean difference (95% CI) for dupilumab vs. placebo in with/without NSAID-ERD groups: 10.17 (7.95 to 12.39), *p*<0.0001/ 10.69 (9.32 to 12.07), *p*<0.0001	**LIKERT:** LS mean difference(95% CI) for dupilumab vs. placebo in with/without NSAID-ERD groups: -1.01 (-1.23 to -0.79), *p*<0.0001/ -1.05 (-1.20 to -0.89), *p* <0.0001 **SNOT-22:** LS mean difference (95% CI) for dupilumab vs. placebo in with/without NSAID-ERD groups: -2.12 (-2.54 to -1.70), *p*<0.0001/ -1.92 (-2.18 to -1.66), *p* <0.0001	N/A
(Naclerio *et al.*, 2017) ABSTRACT[35]	**UPSIT:** LS mean difference (95% CI) for dupilumab vs. placebo at 16 weeks: 14.78 (10.90 to 18.65), *p* <0.0001	**LIKERT:** LS mean difference (95% CI) for dupilumab vs. placebo at 16 weeks: -1.28 (-1.73 to -0.84), *p* <0.0001 **SNOT-22:** LS mean difference for dupilumab vs. placebo at 16 weeks: -2.06, p<0.001	**Pretreatment:** Anosmia: 25 (83.3%) **Post treatment:** Anosmia: 3 (10.7%)
(Cai *et al.*, 2022)[13]	**UPSIT:** Mean difference (95% CI) omalizumab vs. placebo: 3.84 (2.19 to 5.50) at week 24; dupilumab vs .placebo: 10.54 (9.24 to 11.84) at week	N/A	N/A

	24;10.54 (8.82 to 12.26) at EOF; dupilumab vs. omalizumab: 6.70 (4.59 to 8.80) at week 24; dupilumab vs. mepolizumab: 9.24 (5.18 to 13.30) at EOF		
(Ohkyman *et al*., 2022)[14]	**UPSIT:** Mean difference from baseline (95% CI): dupilumab (10.96 [9.75 to 12.17]), omalizumab (3.75 [2.14 to 5.35]), mepolizumab (6.13 [4.07 to 8.19]), benralizumab (2.95 [1.02 to 4.88]). Mean difference (95%) dupilumab vs. omalizumab (7.21 [5.20 to 9.23]), dupilumab vs. mepolizumab (4.83 [2.43 to 7.22]), dupilumab vs. benralizumab (8.01 [5.73 to 10.29])	N/A	N/A
(Peters *et al*., 2021)[15]	**UPSIT:** Mean difference (95% CI) dupilumab vs. omalizumab at 24 weeks: 6.70 (4.67 to 8.73)	**LIKERT:** Mean difference (95% CI) dupilumab vs. omalizumab at 24 weeks: - 0.66 (-0.90 to -0.42)	N/A
(Tsetsos *et al*., 2020)[2]	**UPSIT:** Mean difference (95% CI) dupilumab vs. placebo: 1.22 (1.06 to 1.37), *p*<0.0001	**LIKERT:** DUPI mean difference (95% CI): -1.33 (-1.42 to -0.84), p <0.0001	N/A
(Wang *et al*.,2022)[36]	**UPSIT:** Mean difference (95% CI) benralizumab + mepolizumab vs. placebo (2 RCT, *n*=132): 2.09 (0.42 to 3.77), *p*=0.01	**VAS:** Mean difference (95% CI) benralizumab + mepolizumab vs. placebo (2 RCT, *n*=463): - 1.38 (-1.97 to -0.79), *p* <0.0001	N/A
Surgery			
Study	**Olfactory outcomes with non-subjective smell test**	**Olfactory outcomes with subjective test**	**Clinically relevant change[a]**
(Andrews *et al*., 2016)[18]	**UPSIT:** Pretreatment: mean (*SD*) 21.9 (± 10.4) Post treatment (6 months): mean (*SD*) 24.3 (±10.5), *p*=0.04	**VAS:** Pretreatment: mean (*SD*) 7.4 (±2.8) Post treatment (6 months): mean (*SD*) 5.0 (±3.4), *p*=0.01	**Pretreatment:** Normosmia:0% Hyposmia:60% Anosmia:0% **Post treatment:** Normosmia:0% Hyposmia:60% Anosmia:0%
(Arancibia *et al*., 2022)[37]	**BAST-24:** Pretreatment: Smell detection, % median (IQR) = 0 (0 – 5); Smell memory, % median (IQR) = 0 (0 – 5); Smell identification, % median (IQR) = 0 (0 – 0)	N/A	N/A

	Post treatment (12 years): Smell detection, % median (IQR): 65 (0 – 100), *p* <0.001; Smell memory, % median (IQR): 15 (0 – 46.2) *p*=0.031; Smell identification,% median (IQR): 30 (0 – 55) *p* <0.001		
(Baradaranfar *et al*., 2014)[38]	**CCCRC:** Pretreatment: mean ± *SD* in the surgical group: 2.23 ± 1.78 (range 0 to 6); mean ± *SD* in the medical group:2.16 ± 1.53 (range 0 to 4.5) Posttreatment (12 weeks): mean ± *SD* in the surgical group at 12 weeks: 5.8 ± 1.24.; mean ± *SD* in the medical group at 12 weeks: 3.48 ± 2.	**VAS:** Pretreatment: surgical group (Mean ± *SD*): 2.6 ± 2.23; medical group (Mean ± *SD*): 2.63 ± 1.9 Post treatment (12 weeks): surgical group (Mean ± *SD*): 6.8 ± 2.23; medical group (Mean ± *SD*): 4.7 ± 2.58	N/A
(Bardaranfar *et al*., 2014)[21]	**CCCRC:** Pretreatment: mean ± SEM in the Triamcinolone group: 1.10 ± 0.344; mean ± SEM in the control group: 1.33 ± 0.32 Post treatment (8 weeks): mean ± SEM in the Triamcinolone group: 7.00 ± 0.0; mean ± SEM in the control group: 6.37 ± 0.24	*N/A*	**Pretreatment:** Normosmia: 0% in Triamcinolone group; 0% in control group Hyposmia: 27% in triamcinolone group; 40% in control group Anosmia: 73% in triamcinolone group; 60% in control group **Post treatment:** Normosmia:100% in triamcinolone group; 77% in control group Hyposmia:0% in triamcinolone group; 23% in control group Anosmia:0% in Triamcinolone group; 0% in control group
(Beswick *et al*., 2021)[39]	**BSIT:** mean ± *SD* difference at 18 months: 0.8 ± 3.5	N/A	N/A
(Bogdanov *et al*., 2020)[40]	**SNIFFIN´ STICKS:** Globally at 1 month: the TDI score increased by (mean ± *SD*) 5.6 ± 4.9; at 3 months the TDI score increased by 4.6 ± 5.1	N/A	N/A

(Chen *et al*., 2016)[41]	N/A	**VAS:** Difference (mean ± *SD*) at 1 year: 6.00 ± 3.67 in the EESS group; 3.30 ± 3.44 in the FESS group, *p*= 0.015	N/A
(Dadgarnia *et al*., 2019)[42]	**UPSIT:** Pretreatment: Iran SIT score (mean ± *SD*) was 14.75 ± 4.39 (*p* = 0.001) Post treatment (3 months): Iran SIT score 3 months after surgery (mean ± *SD*) was 17.05 ± 4.7	N/A	N/A
(DeConde *et al*., 2015)[22]	N/A	**SNOT-22:** Mean (*SD*) difference in sense of smell/taste in global cohort at 18 months: −1.0 (1.8) (*p*<0.001); mean (*SD*) difference in sense of smell/taste in medical management cohort at 18 months: −0.5 (1.9) (*p* = 0.044); mean (*SD*) difference in sense of smell/taste in ESS cohort at 18 months: −1.1 (1.8) (*p*<0.001)	N/A
(Djukic *et al*., 2015)[43]	N/A	**VAS:** Pretreatment: mean (*SD*) score: 8.5 ± 2.3 Post treatment: mean (*SD*) score at 6 months:5.1 ± 3.8; mean (*SD*) score at 12 months: 5.3 ± 3.9	N/A
(Galletti *et al*., 2019)[44]	N/A	**VAS:** Improvement in smell score (mean ± *SD*) in group A (ESS with computed navigation system) after 1 year: 7.68 ± 1.53, and improvement in smell score (mean ± *SD*) in group B (conventional ESS) after 1 year: 7.37 ± 1.69 (*p* = 0.36)	N/A
(Haxel *et al*., 2017)[20]	**SNIFFIN´ STICKS:** Mean ± *SD* difference at 2 weeks: 1.3 ± 5.0, *p* = 0.224; mean ± *SD* difference at 6 months: 2.2 ± 4.2, *p* = 0.02	N/A	**Pretreatment:** Normosmia:17.1% Hyposmia:46.4% Anosmia:36.6% **Post treatment:** Normosmia: at 2 weeks: 29.3% and at 6 months: 36.6% Hyposmia: at 2 weeks: 51.2% and at 6 months: 46.4% Anosmia: at 2 weeks: 19.5% and at 6 months: 17.1%

(Haxel *et al*., 2022)[45]	**SNIFFIN´ STICKS:** Mean increase (*SD*) at 3 months in TDI score of 3.1 (8.1) (p = 0.012), ranging from - 24.3 to +27.4 (p <0.008). Mean (*SD*) increase at 3 months of 0.9 (2.7) (p = 0.026), 1.4 (3.6) (p = 0.011), and 0.8 (3.4) (p = 0.12) for T, D, and I, respectively.	N/A	**Pretreatment:** Normosmia:30% Hyposmia:43% Anosmia:28% **Post treatment:** Normosmia:45% Hyposmia:45% Anosmia:10%
(Hema *et al*., 2021)[46]	**CCCRC:** Pretreatment: mean (*SD*) olfaction composite score for the CRSwNP: 2.8 (1.9) patients (p<0.0001) Post treatment (6 months): mean (*SD*) olfaction composite score for the CRSwNP patients: 4.3 (1.4) (p<0.0001)	N/A	**Pretreatment:** Normosmia:10% Hyposmia:68% Anosmia:22% **Post treatment:** Normosmia:14% Hyposmia:80% Anosmia:6%
(Levy *et al*., 2016)[47]	**BSIT score:** Improvement in score at 6months in the CRSwNP patients: -3.64 (p = 0.001)	N/A	N/A
(Lind *et al*., 2016)[31]	**SNIFFIN´ STICKS:** Pretreatment: mean (*SD*) score: 6.9 (3.63) for the total cohort; 6.4 (3.6) for the CRSwNP group; 8.6 (3.1) for the CRSsNP group Post treatment: Mean (*SD*) score at 6 months: 7.9 (2.9) for the total cohort; 7.5 (3.0) for the CRSwNP group; 9.4 (1.7) for the CRSsNP group. Score change at 6 months: p = 0.002 for the total cohort; p = 0.003 for the CRSwNP group; p = 0.342 for the CRSsNP group	N/A	N/A
(Lötsch *et al*., 2021)[48]	**SNIFFIN´ STICKS:** Pretreatment: mean ± *SD* Sniffin´Sticks: 17.84 ± 9.66; range: 2 – 35.5 Post treatment (4 months): mean ± *SD* score: 22.8 ± 8.24; range: 5 – 41.75 Difference: p = 0.0006678	**VAS:** Pretreatment: mean ± *SD:* 1.88 ± 1.64; range: 0 – 7 Post treatment (4 months): mean ± *SD*: 3.48 ± 1.72; range: 0 – 7 Difference: p <0.0001	N/A
(Nguyen *et al*., 2015)[49]	**SNIFFIN´ STICKS:** Pretreatment: mean ± *SD* TI score: 9.02 ± 8.8 Post treatment (6 weeks): mean ± *SD* TI score: 13.95 ± 8.2	**VAS:** Pretreatment: mean ± *SD*: 7.80 ± 2.6 Post treatment (6 weeks): mean ± *SD:* 3.71 ± 3.4	N/A
(Nguyen *et al*., 2016)[50]	**SNIFFIN´ STICKS:** Pretreatment: mean ± *SD* score: 7.74 ± 2.81	N/A	**Pretreatment:** Normosmia:32.31% Hyposmia:23.08% Anosmia:44.62%

	Post treatment: mean ± *SD* score: 3.75 ± 3.56 (at 6 weeks); 3.46 ± 3.60 (at 7 months)		**Post treatment:** Normosmia: at 6weeks, 51.56%; at 7months, 67.21% Hyposmia: at 6weeks, 25.00%; at 7months, 18.03% Anosmia: at 6weeks, 23.44%; at 7months, 14.75%
(Paksoy *et al*., 2019)[51]	**SNIFFIN´ STICKS:** Pretreatment: mean ± *SD* TDI score: 14.1 ± 6.45 Post treatment (3 months): mean ± *SD* TDI score: 20.9 ± 5.00 Difference: *p*<0.001	N/A	**Pretreatment (*n*):** Normosmia:0 Hyposmia:11 Anosmia:19 **Post treatment (*n*):** Normosmia:1 Hyposmia:25 Anosmia:4 *N = 30
(Szaleniec *et al*., 2015)[52]	N/A	**LIKERT:** Pretreatment: median (min;max): 2 (0; 3) Post treatment: median (min;max) at 3-6 months: 1 (0;3); at 12 months: 1 (0;3)	**Pretreatment:** Normosmia:26% Hyposmia:37% Anosmia:37% **Post treatment:** Normosmia: at 6 months, 47%; at 12 months, 41% Hyposmia: at 6 months, 40%; at 12 months, 45% Anosmia: at 6 months, 13%; at 12 months, 9%
(Kohli *et al*., 2016)[19]	**SNIFFIN´ STICKS:** Mean difference (95% CI): 11.54 (6.03, 17.04); I2 = 98**%**	**VAS:** Mean difference 95% CI): - 3.31 (-4.44, -2.18); I2 = 97%	N/A
(Zhao *et al*., 2021)[53]	**SNIFFIN´ STICKS:** Mean difference (95% CI) for CRSwNP patients: 2.35 (1.17, 3.53); I2 = 93.7%; *p* = 0.000 **UPSIT:** Mean difference (95% CI) for CRSwNP patients: 5.52 (0.10, 10.94); I2 = 92.3%; *p* = 0.000	**VAS:** Mean difference (95% CI) for CRSwNP patients: - 2.26 (- 2.26, - 1.56); I2= 95.2%, *p* = 0.000	N/A
Medical treatment			
Study	**Olfactory outcomes with non-subjective smell test**	**Olfactory outcomes with subjective test**	**Clinically relevant change[a]**
(Alobid *et al*., 2014)[23]	**BAST-24 (%):** Pretreatment: smell detection: 30.7 ± 39.5%, identification: 7.1 ± 16.1%, forced choice: 13.8 ± 23.3%	N/A	N/A

	Post treatment: at week 2, smell detection: 60.9 ± 42.8%, identification: 20.4 ± 22.8%, and forced choice: 31.1 ± 30.8%; at week 12, smell detection: 45.2 ± 44.3%, identification: 15.7 ± 22.9%, and forced choice: 25.7 ± 30.9%		
(Antonio *et al.*, 2021)[26]	**CCCRC:** Pretreatment: median (25th percentile, 75th percentile): 1.25 (0, 4.25) in the treatment group Post treatment: median (25th percentile, 75th percentile): 3 (0, 5.5) at week 12; 5 (1.75, 5.75) at week 24 in the treatment group	N/A	N/A
(Kern *et al.*, 2018)[25]	N/A	**LIKERT:** Between groups mean difference (95% CI) from baseline at 90 days: - 0.46 (- 0.85 to - 0.06); $p = 0.0470$	N/A
(Papadakis *et al.*, 2021)[24]	**SNIFFIN´ STICKS:** Mean difference (95% CI) at 2 weeks: 2.1 (1.4 to 2.7), $p < 0.001$; at 12 weeks: 1.05 (0.2 to 1.8), $p = 0.01$; at 24 weeks: 1.32 (0.37 to 2.0), $p < 0.001$	**VAS:** Mean difference (95% CI) at 2 weeks: -2 (-2.49 to -1.6), $p < 0.001$; at 12 weeks: −1.4 (- 1.7 to - 1.08), $p<0.001$; at 24 weeks: -1.12 (-1.4 to -0.8), $p<0.001$	N/A
(Poletti *et al.*, 2017)[27]	**SNIFFIN´ STICKS:** TDI score improvement average at 2 weeks: 2.2 points using AMSA®, 2.6 points using nasal spray; decrease at 8 weeks (2 weeks of therapy + 6 weeks later): 1.8 point using AMSA®, 1.2 using nasal spray ($p = 0.005$)	N/A	N/A
(Van Gerven *et al.*, 2018)[28]	**BAST-24** Pretreatment: mean ± *SD* in INCS vs. INCS+montelukast: detection: 21.1 ± 34.7 vs. 7.0 ± 20.7, recognition: 14.0 ± 25.6 vs. 3.8 ± 16.6, identification: 8.7 ± 18.6 vs. 3.2 ± 16.5 Post treatment (1 year): N/A Significant improvement in smell detection ($p = 0.002$ for INCS and $p = 0.018$ for INCS + montelukast)and in recognition/memory ($p = 0.001$ and $p = 0.029$ for INCS), but not for forced-choice identification	**VAS:** Pretreatment: mean ± *SD* in INCS vs. INCS+montelukast: 2.0 ± 1.7 vs. 1.2 ± 1.7 Post treatment (1 year): N/A Significant improvement for the INCS group ($p<0.0001$) but not for the INCS + montelukast group ($p = 0.36$), with no difference between both treatment groups.	N/A

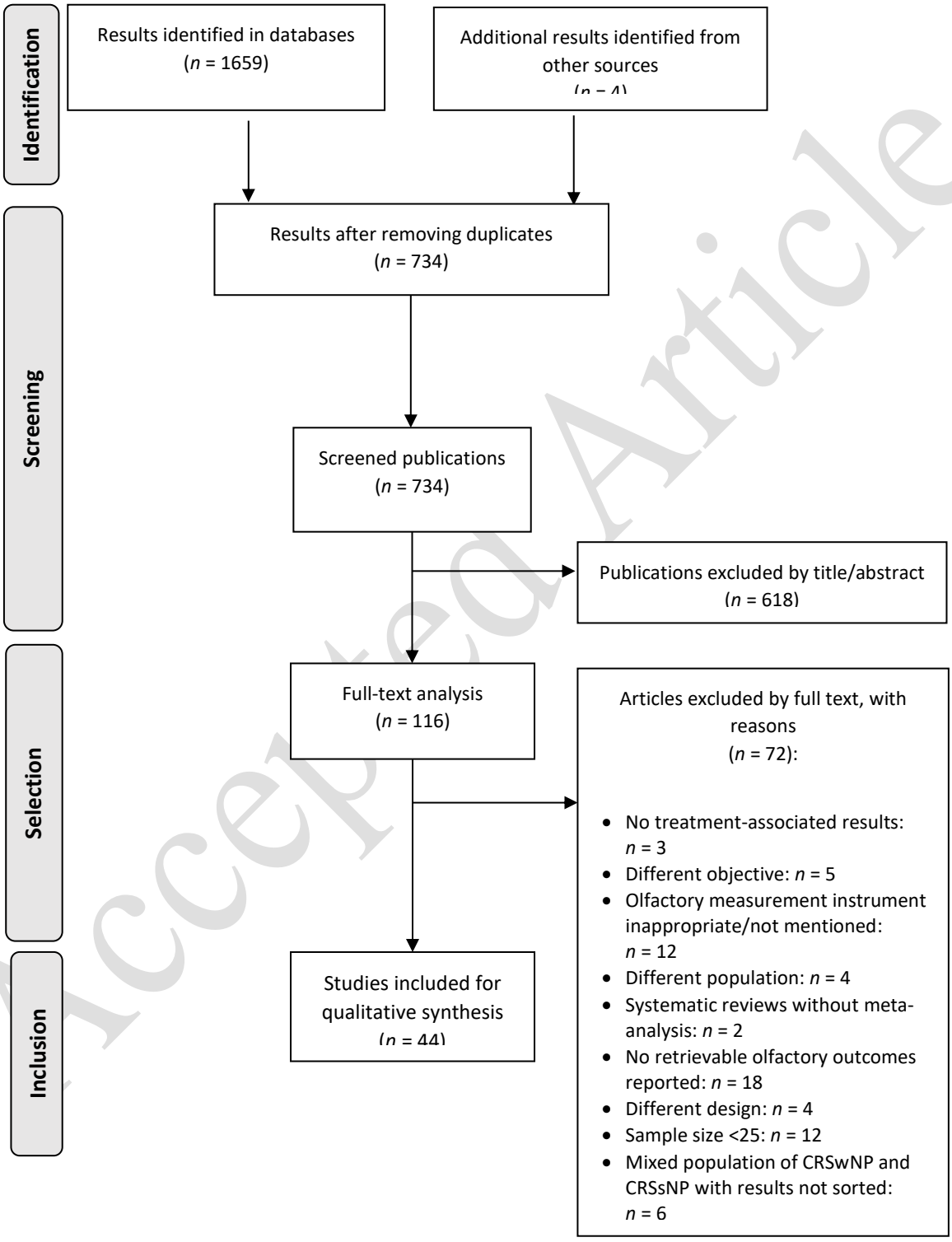
N/A, not available; EOF, end of follow-up; RCT, randomized controlled trial; TDI, threshold discrimination identification; ESS, endoscopic sinonasal surgery; EESS, extensive endoscopic sinonasal surgery; FESS, functional endoscopic sinonasal surgery; CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis

without nasal polyps; INCS, intranasal corticosteroids; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; LS, least square; IQR, interquartile range; CI, confidence interval; SCS, systemic corticosteroids; SD, standard deviation; SEM, standard error of the mean; BAST, Barcelona Smell Test; UPSIT, University of Pennsylvania Smell Identification Test; CCCRC, Connecticut Chemosensory Clinical Research Center; VAS, visual analogue scale; SNOT, Sinonasal Outcome Test

[a] Based on the olfactory status of patients (number and/or percentage of anosmic/hyposmic/normosmic patients) before and after the intervention

FIGURE LEGENDS

Figure 1. PRISMA diagram showing the selection flow of identified references.



CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyps