REVIEW

J Rhinol 2023;30(2):62-68 | https://doi.org/10.18787/jr.2023.00029 pISSN 1229-1498 / eISSN 2384-4361
www.j-rhinology.org

Effectiveness of Dupilumab Treatment to Treat Chronic Rhinosinusitis With Nasal Polyposis: A Systematic Review and Meta-Analysis

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Background and Objectives: Evidence bearing on the safety and efficacy of dupilumab treatment for chronic rhinosinusitis with nasal polyps (CRSwNP) has recently been presented by researchers from various institutions. Therefore, we compared the safety and efficacy of dupilumab treatment to those of endoscopic sinus surgery.

Methods: The PubMed, Scopus, Embase, Web of Science, and Cochrane databases were searched independently by two authors from the dates of their inception to December 2022. We retrieved the clinical results of CRSwNP patients after dupilumab administration, including changes in patient symptoms and the effects on the quality of life, and compared the results of dupilumab (treatment group) to those of endoscopic sinus surgery (control group).

Results: Eight articles (1,251 patients) were ultimately included. Dupilumab significantly improved nasal symptoms (nasal congestion) (mean difference [MD], -1.4433; 95% confidence interval [CI], -1.7233 to -1.1632; I^2=94.2%), the visual analog sinusitis score (MD, -5.0506; 95% CI, -5.4744 to -4.6267; I^2=84.0%), olfactory function (standardized MD, 1.2691; 95% CI, 1.1549 to 1.3833; I^2=18.4%), the quality of life (SNOT-22 score) (MD, -34.4941; 95% CI, -39.4187 to -29.5695; I^2=90.8%), the Lund-Mackay computed tomography score (MD, -7.2713; 95% CI, -8.9442 to -5.5984; I^2=87.7%), and the nasal polyp score (MD, -3.1021; 95% CI, -3.7066 to -2.4977; I^2=95.6%) at about 12 months after treatment compared to the pretreatment values. Compared to endoscopic sinus surgery, dupilumab similarly improved olfactory function (MD, 1.9849; 95% CI, -1.6190 to 5.5888; I^2=0.0%) but was less effective in terms of reducing the SNOT-22 score (MD, 3.8472; 95% CI, 1.9872 to 5.7073; I^2=96.7%) and reducing nasal congestion (MD, 0.6519; 95% CI, 0.5619 to 0.7420; I^2=97.7%).

Conclusion: Dupilumab reduced subjective symptom scores and improved the quality of life and objective measures of progression compared to the preoperative values.

Keywords: Biological products; Dupilumab; Antibodies, Monoclonal; Sinusitis; Nasal polyps.

INTRODUCTION

The prevalence of chronic rhinosinusitis with nasal polyps (CRSwNP) ranges from 2.1% to 8.4% worldwide [1-4]. CRSwNP has a poorer prognosis than CRS without polyps; many refractory CRSwNP cases exhibit marked eosinophil and mast cell infiltration into the nasal mucosa and polyp tissues [5]. The principal feature of eosinophilic-dominant CRSwNP is an inflammatory response induced by T-helper 2 (Th2) cells, as revealed by local and systemic increases in the levels of type 2 cytokines, including eosinophil cationic protein, eotaxin, interleukin (IL)-4, IL-5, and IL-13. These Th2 cytokines play

Received: April 3, 2023 **Revised:** April 25, 2023 **Accepted:** April 27, 2023

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important roles in the pathophysiology of CRSwNP [6]. Intranasal corticosteroids are often prescribed; in severe cases, short-term systemic steroids are also given [7]. Endoscopic sinus surgery (ESS) with or without polypectomy is recommended for patients who do not respond to drugs [5]. However, the underlying inflammatory process may not resolve after surgery; symptoms and polyps may recur, particularly when type 2 inflammation is severe [8]. Therefore, treatment that directly targets type 2 inflammation is desirable, since such an approach would minimize the side effects of systemic immunosuppression via selective immunomodulation and ultimately induce immune tolerance by restoring the balance of the immune system [9]. Dupilumab inhibits IL-4/IL-13 signaling and type 2 inflammation, and is currently approved as a maintenance treatment for adults with refractory CRSwNP [6].

Evidence bearing on the safety and efficacy of dupilumab in CRSwNP patients has recently been presented by researchers from various institutions. Therefore, this meta-analysis evaluated the effect of dupilumab on CRSwNP in terms of clinical findings, patient-reported symptom changes, and morbidity.

METHODS

Study selection

We extracted studies published in or before December 2022 from the PubMed, Scopus, Embase, Web of Science, and Cochrane databases using the search terms "nasal congestion," 'nasal obstruction," "dupilumab," "quality of life," "olfaction," "chronic sinusitis," "chronic rhinosinusitis," "nasal polyp," and "polyps." Two authors (JK and DHK) independently checked all abstracts. When the relevance was not clear from the abstract alone, the full text was checked. If the reviewers disagreed, the issue was solved by discussion with a third reviewer (SHH). The inclusion criteria were a comparison of dupilumab treatment outcomes to pretreatment status or the outcomes of a control (placebo) group and a comparison of dupilumab to ESS. Studies using biologics other than dupilumab were excluded, as were studies that lacked a clear presentation of quantifiable data. Fig. 1 summarizes the search strategy.

Data extraction and risk of bias assessment

Data were extracted using a standardized form [10,11]. We analyzed two types of outcomes [9,12-18]. Objective clinical markers included the endoscopic nasal polyp score (0–8; higher values correspond to poorer results), the Lund-Mackay computed tomography (LMCT) score (0–24; higher values indicate more opacification), the University of Pennsylvania Smell Identification Test results (0–40; higher values [35–40] reflect normal olfaction), and the results of other smell tests. Subjective clinical markers included the 22-item SinoNasal Outcome Test (SNOT-22) scores (0–110; higher values correspond to poorer outcomes), nasal congestion/obstruction

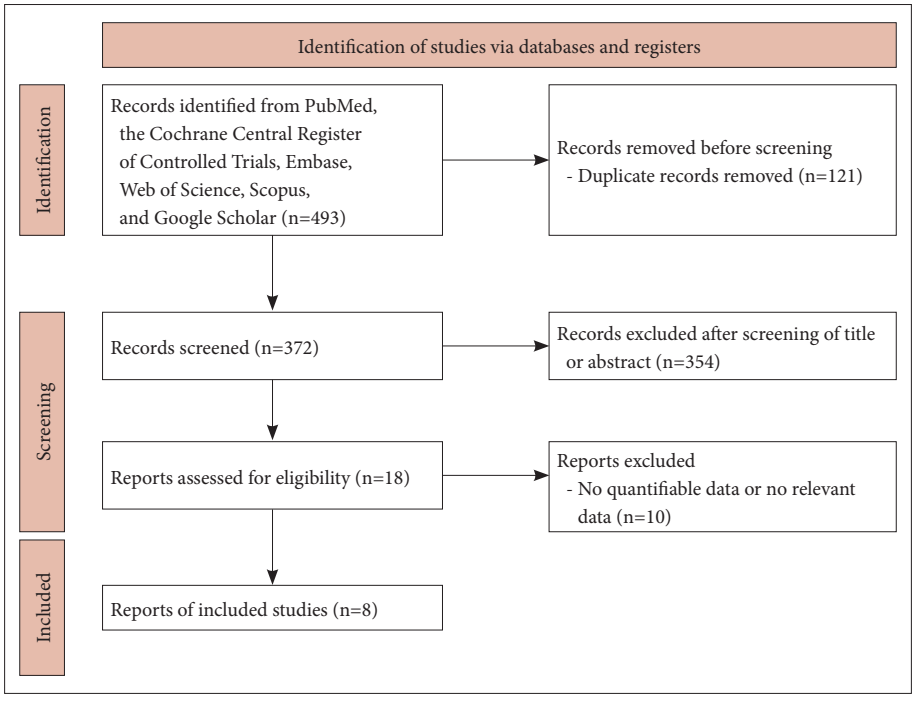

Fig. 1. Flow chart of the article retrieval and selection process.

symptoms (0=none, 1=mild, 2=moderate, 3=severe), and sinusitis symptom severity (visual analog scale; VAS) (0–10; higher scores indicate more severe symptoms). We also compared pre- and post-treatment or control and post-treatment ESS outcomes during the follow-up period (12–13 months). Furthermore, we extracted patient numbers, age, and sex, as well as the study design. For non-randomized controlled studies, the Newcastle-Ottawa Scale was used to assess the risk of bias. The quality assessment of randomized controlled trials employed the Cochrane Risk of Bias tool.

Statistical analysis

The meta-analysis employed R software ver. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). When the measured outcome was a continuous variable, the effect size was expressed using the mean difference (MD) and 95% confidence interval (CI), corresponding to the difference between the means of the treatment and control groups. The results of studies that used the same outcomes and measurement modes (the VAS nasal congestion score for sinusitis; and the SNOT-22, LMCT, and nasal polyp scores) were pooled and subjected to MD calculations. In the olfactory function test, the standardized mean difference (SMD) was calculated using various methods that evaluated the same outcome. In the clinical context of SMDs, an effect size of about 0.206 is considered small, 0.506 medium, and ≥0.806 both large and clinically significant. Heterogeneity was assessed using the Cochrane Q and I^2 tests. Funnel plots were drawn and the Egger test applied to seek potential publication bias. We used the trim-and-fill method of Duval and Tweedie to evaluate publication bias based on the summed effect size.

RESULTS

Eight studies (1,251 patients) met the inclusion criteria, and the characteristics of the studies included in the meta-analysis are listed in Supplementary Table 1 (in the online-only Data Supplement). The bias assessment results are shown in Supplementary Tables 2 and 3 (in the online-only Data Supplement).

Changes in CRS-related outcomes after dupilumab treatment

Dupilumab reduced LMCT score compared to baseline at 3–4 months (MD, -9.2000; 95% CI, -11.7557 to -6.6443; I^2 not applicable) and 6–8 months (MD, -6.8723; 95% CI, -8.6181 to -5.1265; I^2=88.8%) (Supplementary Fig. 1 in the online-only Data Supplement). The difference between the two periods was significant (p=0.1405) (Table 1). Dupilumab reduced baseline nasal congestion at 3–4 months (MD, -1.0000; 95% CI, -1.3542 to -0.6458; I^2 not applicable), 6–8 months (MD, -1.3849; 95% CI, -1.7195 to -1.0503; I^2=93.1%), and 12–13 months (MD, -1.7814; 95% CI, -2.5751 to -0.9876; I^2=97.8%) (Supplementary Fig. 2 in the online-only Data Supplement). The differences were significant at both 3 and 12 months (p=0.1189) (Table 1). Dupilumab reduced the nasal polyp score at 3–4 months (MD, -2.6903; 95% CI, -4.1582 to -1.2225; I^2=91.7%), 6–8 months (MD, -2.9647; 95% CI, -3.8076 to -2.1218; I^2=96.1%), and 12–13 months (MD, -3.7891; 95% CI, -5.4599 to -2.1183; I^2=97.0%) (Supplementary Fig. 3 in the online-only Data Supplement). The 3- and 12-month differences varied significantly (p=0.6002) (Table 1). Dupilumab improved olfactory function compared to baseline at 3–4 months (SMD, 1.9022; 95% CI, 1.2857 to 2.5187; I^2 not applicable), 6–8 months (SMD, 1.2167; 95% CI, 1.0905 to 1.3429; I^2=0.0%), and 12–13 months (SMD, 1.4139; 95% CI, 1.1156 to 1.7123; I^2=59.8%) (Supplementary Fig. 4 in the online-only Data Supplement). The 3- and 12-month values differed significantly (p=0.0602) (Table 1). Dupilumab improved the SNOT-22 score from baseline to 3–4 months (MD, -31.4118; 95% CI, -36.2351 to -26.5886; I^2=0.0%), 6–8 months (MD, -32.5001; 95% CI, -38.6271 to -26.3731; I^2=89.7%), and 12–13 months (MD, -41.5717; 95% CI, -56.1916 to -26.9518; I^2=96.4%) (Supplementary Fig. 5 in the online-only Data Supplement). The differences between the 3- and 12-month values were significant (p=0.4331) (Table 1). Dupilumab improved the sinusitis VAS score compared to baseline at 3–4 months (MD, -4.9519; 95% CI, -5.9546 to -3.9492; I^2=56.4%), 6–8 months (MD, -4.8422; 95% CI, -5.4014 to -4.2831; I^2=86.8%), and 12–13 months (MD, -5.8090; 95% CI, -6.5847 to -5.0333; I^2=62.1%) (Supplementary Fig. 6 in the online-only Data Supplement). The differences between the 3- and 12-month values were significant (p=0.1299) (Table 1).

We explored whether ESS (the current standard treatment) was better than biologic treatment. ESS significantly reduced the disease-specific quality of life SNOT-22 score and the olfactory function and nasal congestion scores from baseline to 6–8 and 12–13 months postoperatively (Supplementary Figs. 7-9 in the online-only Data Supplement). Compared to the ESS group, dupilumab treatment was associated with poorer outcomes, as revealed by the postoperative disease-specific SNOT-22 quality of life score (6–8 months: MD, 4.2021; 95% CI, 1.5954 to 6.8089; I^2=98.9%; 12–13 months: MD, 2.7431; 95% CI, -1.5734 to 7.0596; I^2=51.0%) and the nasal congestion score (6–8 months: MD, 0.6051; 95% CI, 0.5169 to 0.6933; I^2=97.6%; 12–13 months: MD, 0.7500; 95% CI, 0.7116 to 0.7884; I^2 not applicable) (Table 2); however, the difference in olfactory function was not significant (MD, 1.9849; 95% CI, -1.6190 to 5.5888; I^2=0.0%). Dupilumab may be less effective than ESS in terms of improving nasal congestion and quality of life. However, only two studies featured sham-operated groups, and the results must thus be interpreted with caution.

Table 1. Subgroup analyses of changes from baseline over time

	Total	3–4 Months	6–8 Months	12–13 Months	p-value
LMCT score	MD=-7.2713; 95% CI=-8.9442 to -5.5984; I^2=87.7%	n=1; MD=-9.2000; 95% CI=-11.7557 to -6.6443; I^2=NA	n=4; MD=-6.8723; 95% CI=-8.6181 to -5.1265; I^2=88.8%	No data	0.1405
Nasal congestion score	MD=-1.4433; 95% CI=-1.7233 to -1.1632; I^2=94.2%	n=1; MD=-1.0000; 95% CI=-1.3542 to -0.6458; I^2=NA	n=5; MD=-1.3849; 95% CI=-1.7195 to -1.0503; I^2=93.1%	n=2; MD=-1.7814; 95% CI=-2.5751 to -0.9876; I^2=97.8%	0.1189
Nasal polyp score	MD=-3.1021; 95% CI=-3.7066 to -2.4977; I^2=95.6%	n=2; MD=-2.6903; 95% CI=-4.1582 to -1.2225; I^2=91.7%	n=8; MD=-2.9647; 95% CI=-3.8076 to -2.1218; I^2=96.1%	n=3; MD=-3.7891; 95% CI=-5.4599 to -2.1183; I^2=97.0%	0.6002
Olfactory function	SMD=1.2691; 95% CI=1.1549 to 1.3833; I^2=18.4%	n=1; SMD=1.9022; 95% CI=1.2857 to 2.5187; I^2=NA	n=5; SMD=1.2167; 95% CI=1.0905 to 1.3429; I^2=0.0%	n=2; SMD=1.4139; 95% CI=1.1156 to 1.7123; I^2=59.8%	0.0602
SNOT-22	MD=-34.4941; 95% CI=-39.4187 to -29.5695; I^2=90.8%	n=2; MD=-31.4118; 95% CI=-36.2351 to -26.5886; I^2=0.0%	n=7; MD=-32.5001; 95% CI=-38.6271 to -26.3731; I^2=89.7%	n=3; MD=-41.5717; 95% CI=-56.1916 to -26.9518; I^2=96.4%	0.4331
VAS for sinusitis	MD=-5.0506; 95% CI=-5.4744 to -4.6267; I^2=84.0%	n=2; MD=-4.9519; 95% CI=-5.9546 to -3.9492; I^2=56.4%	n=6; MD=-4.8422; 95% CI=-5.4014 to -4.2831; I^2=86.8%	n=2; MD=-5.8090; 95% CI=-6.5847 to -5.0333; I^2=62.1%	0.1299

LMCT, Lund-Mackay computed tomography; MD, mean difference; CI, confidence interval; SMD, standardized mean difference; NA, not available; SNOT-22, 22 item SinoNasal Outcome Test; VAS, visual analog scale

Table 2. Subgroup analyses of changes from baseline in the dupilumab and ESS groups over time

	Total	6–8 Months	12–13 Months	p-value
Nasal congestion score	MD=0.6519; 95% CI=0.5619 to 0.7420; I^2=97.7%	n=2; MD=0.6051; 95% CI=0.5169 to 0.6933; I^2=97.6%	n=1; MD=0.7500; 95% CI=0.7116 to 0.7884; I^2=NA	0.0032
Olfactory function	MD=1.9849; 95% CI=-1.6190 to 5.5888; I^2=0.0%	n=2; MD=1.9849; 95% CI=-1.6190 to 5.5888; I^2=0.0%	No data	-
SNOT-22	MD=3.8472; 95% CI=1.9872 to 5.7073; I^2=96.7%	n=2; MD=4.2021; 95% CI=1.5954 to 6.8089; I^2=98.9%	n=2; MD=2.7431; 95% CI=-1.5734 to 7.0596; I^2=51.0%	0.5707

ESS, endoscopic sinus surgery; MD, mean difference; CI, confidence interval; NA, not available; SNOT-22, 22 item SinoNasal Outcome Test

Risk of bias assessment

There was no evident publication bias in terms of the nasal polyp score (p=0.05959), SNOT-22 score (p=0.07339), or the sinusitis VAS score (p=0.9539) (Supplementary Fig. 10 in the online-only Data Supplement). Publication bias in terms of the nasal congestion score, the LMCT, and olfactory function was not assessed because the number of trials included was too small to allow for funnel plot evaluation or advanced regression-based assessments.

DISCUSSION

In this meta-analysis, we evaluated the efficacy of dupilumab in CRSwNP patients and compared the effects to those of ESS. Dupilumab improved the nasal polyp and LMCT scores, as well as nose-related quality of life indicators, including olfactory function, the SNOT-22 score, and the sinusitis VAS score. Compared to ESS, which is the current standard of care for patients with intractable CRSwNP, the improvements in olfactory function afforded by dupilumab and ESS were similar, but ESS led to greater improvements in the SNOT-22 score and nasal congestion.

The classification of CRS by the endotype rather than the phenotype has recently become gradually systematized, and the treatment strategies have been optimized [5,19]. With the exceptions of some Asian cases, most patients with severe CRSwNP exhibit a type 2-dominant endotype [20,21]. The initial treatment is nasal saline irrigation and intranasal corticosteroid administration [5,22]. ESS is recommended when there is no improvement despite appropriate medical treatment. However, the polyp recurrence rate after surgery is quite high (40%–60%) [23,24]. Polyps recur after surgical removal if the underlying cause of inflammation is not appropriately addressed [7]. Treatment must consider the underlying pathophysiology; anti-immunoglobulin E (IgE; omalizumab), anti-IL-4/IL-13 (dupilumab), and anti-IL-5 (mepolizumab) antibodies have thus been developed. Several biologics targeting type 2 inflammation, including anti-IL-5 receptor α (benralizumab) monoclonal antibodies, have been commercialized, and others are under development [25]. Dupilumab was the first such drug to receive approval from the Food and Drug Administration for use in CRSwNP patients, and more clinical trial data are thus available than is the case for other biologics. The efficacy and side-effects of dupilumab inform the use of biologics to target type 2 inflammation-dominant CRSwNP. After the large, randomized controlled trials of Bachert et al. [9], various clinical studies have shown that dupilumab exerts significant effects on CRSwNP without major side effects. Dupilumab is a good treatment option for CRSwNP patients with various underlying diseases.

However, special considerations arise when employing biologics, including dupilumab. As mentioned above, patients with severe CRSwNP often exhibit a type 2-dominant endotype, but mixed-type or neutrophil-dominant cases also exist. Therefore, the standard definition of type 2 inflammation (tissue eosinophil level ≥10/high-power field, blood eosinophil level ≥250 cells/mm^3, or total IgE level ≥100 kU/L) of the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [5] may require correction because of drug reactions. Studies on patients with asthma and atopic dermatitis prescribed biologics earlier than CRSwNP cases found that assays of type 2 inflammatory biomarkers displayed certain limitations in terms of determining individual responses to biologics, and prognoses [26,27]. A follow-up study after dupilumab discontinuation reported polyp recurrence [9]. A cost–benefit analysis suggested that the annual drug cost of

US $36,000 drug cost was excessive [28,29]. Although there are few relevant studies, we found that dupilumab cannot completely replace ESS. For patients with contraindications to or concerns about general anesthesia, dupilumab may be the first choice. Otherwise, the drug may be appropriate only when nasal polyps recur after surgery.

Although we present evidence supporting the use of dupilumab in patients with CRSwNP and compare the effects of the drug to ESS, our analysis has certain limitations. First, although all recent clinical studies on dupilumab were included, the number of studies was small and the follow-up periods were relatively short; therefore, the results should be generalized only with caution. Second, neither the treatment nor maintenance period was standardized. The effects of drug cessation and periodic administration should be explored to reveal the duration of drug efficacy and enable standardization of the dose and the intervals between maintenance treatment. Third, the efficacy of combination therapies other than dupilumab and intranasal steroids should be evaluated.

In future studies, it would be necessary to subjectively and objectively compare the effects of biologic agents other than dupilumab and ESS.

CONCLUSION

Dupilumab effectively treats type 2 inflammation in patients with refractory CRSwNP. However, it is not yet clear whether dupilumab treatment can replace ESS. Nonetheless, dupilumab treatment could be considered in patients exhibiting nasal polyp recurrence after surgery.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.18787/jr.2023.00029.

Ethics Statement

An ethics statement is not applicable because this study was based exclusively on published literature.

Availability of Data and Material

The raw data of individual articles used in this meta-analysis are included in the main text or supplementary data.

Conflicts of Interest

Do Hyun Kim and Se Hwan Hwang who are on the editorial board of the *Journal of Rhinology* were not involved in the editorial evaluation or decision to publish this article. Jiyeon Kim has declared no conflicts of interest.

Author Contributions

Conceptualization: Do Hyun Kim, Se Hwan Hwang. **Data curation:** Jiyeon Kim. **Formal analysis:** Do Hyun Kim, Se Hwan Hwang. **Funding acquisition:** Do Hyun Kim, Se Hwan Hwang. **Methodology:** Do Hyun Kim, Se Hwan Hwang. **Project administration:** Do Hyun Kim, Se Hwan Hwang. **Supervision:** Do Hyun Kim, Se Hwan Hwang. **Validation:** Jiyeon Kim. **Writing—original draft:** Jiyeon Kim. **Writing—review & editing:** all authors.

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Funding Statement

This work was supported by the National Research Foundation of Korea (NRF) (2022R1F1A1066232, 2019M3A9H2032424, 2019M3E5D5064110), Ministry of Trade, Industry & Energy (MOTIE, Korea) (20012378), and the Institute of Clinical Medicine Research of Bucheon St. Mary's Hospital, Research Fund (2022). The sponsors had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Supplementary Table 1. Summary of the studies included in the meta-analysis

Study author (year)	Sample size	Age (mean, range, or standard deviation)/ Sex (male:female)	Study design	Comparison	Outcome measure analyzed
Bachert (2016) [12]	60	Dupilumab group: 47.4 (9.8) years/18:12 Placebo 49.3 (9.1) years/16:14	Randomized controlled	Dupilumab group (16 weeks) vs. Placebo group	Clinical symptomatic markers
Bachert (2019) [9]	276	LIBERTY NP SINUS-24 (24 weeks treatment) Dupilumab group: 52 (39–61) years/88:55 Placebo: 50 (41–60) years/70:63	Randomized controlled	Dupilumab group (24 weeks) vs. Placebo group	Clinical symptomatic markers
	298	LIBERTY NP SINUS-52 (52 weeks treatment) Dupilumab group: 53 (42–63) years/87:58 Placebo: 53 (44–61) years/95:58		Dupilumab group (52 weeks) vs. Placebo group	
Dharmarajan (2022) [14]	108	52.39±15.81 years/NA	Cohort study	LIBERTY NP SINUS-24 or LIBERTY NP SINUS-52	Clinical symptomatic markers
Bertlich (2022) [13]	75	NA/49:26	Cohort study	LIBERTY NP SINUS-52	Clinical symptomatic markers
Haxel (2022) [16]	49		Cohort study		Clinical symptomatic markers
Miglani (2023) [15]	295	52.0 (42–63) years/184:111	Cohort study	Dupilumab group (24 weeks)/ Dupilumab group (52 weeks) vs. ESS group	Clinical symptomatic markers
Torretta (2022) [17]	80	51.58 (23–78)/47:33	Observational study		Clinical symptomatic markers
Matsuyama (2023) [18]	10	60.1±9.77:3	Case series		Clinical symptomatic markers

NA, not availalbe; ESS, endoscopic sinus surgery

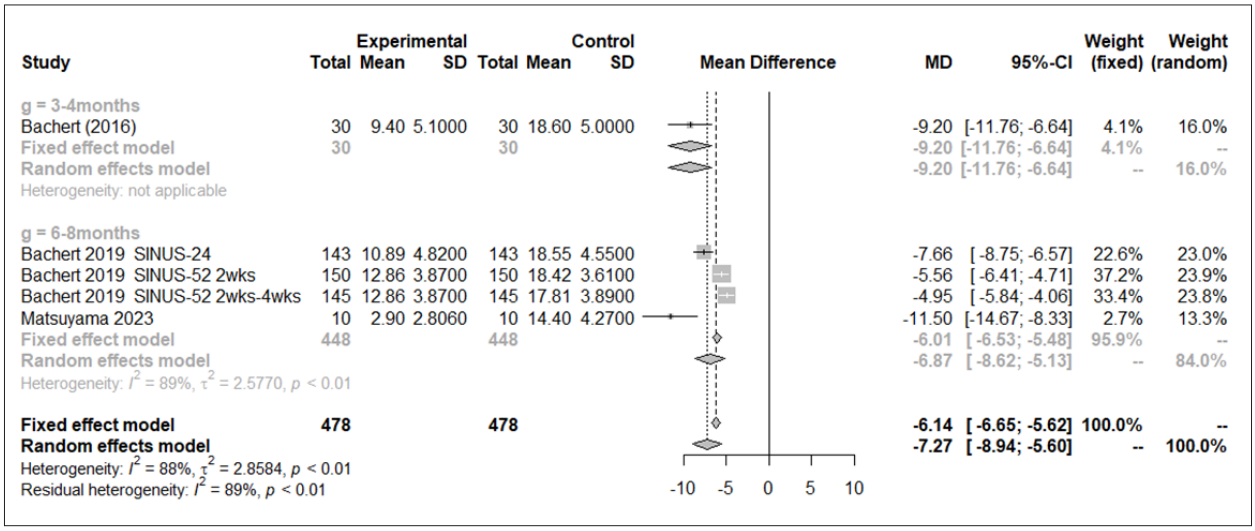
Supplementary Table 2. Quality assessment of non-randomized studies

Study author (year)	Selection*				Comparability†		Exposure‡			Newcastle-Ottawa Scale score
	1	2	3	4	5A	5B	6	7	8	
Dharmarajan (2022) [14]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
Bertlich (2022) [13]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Haxel (2022) [16]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Miglani (2023) [15]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9
Torretta (2022) [17]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Matsuyama (2023) [18]	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	6

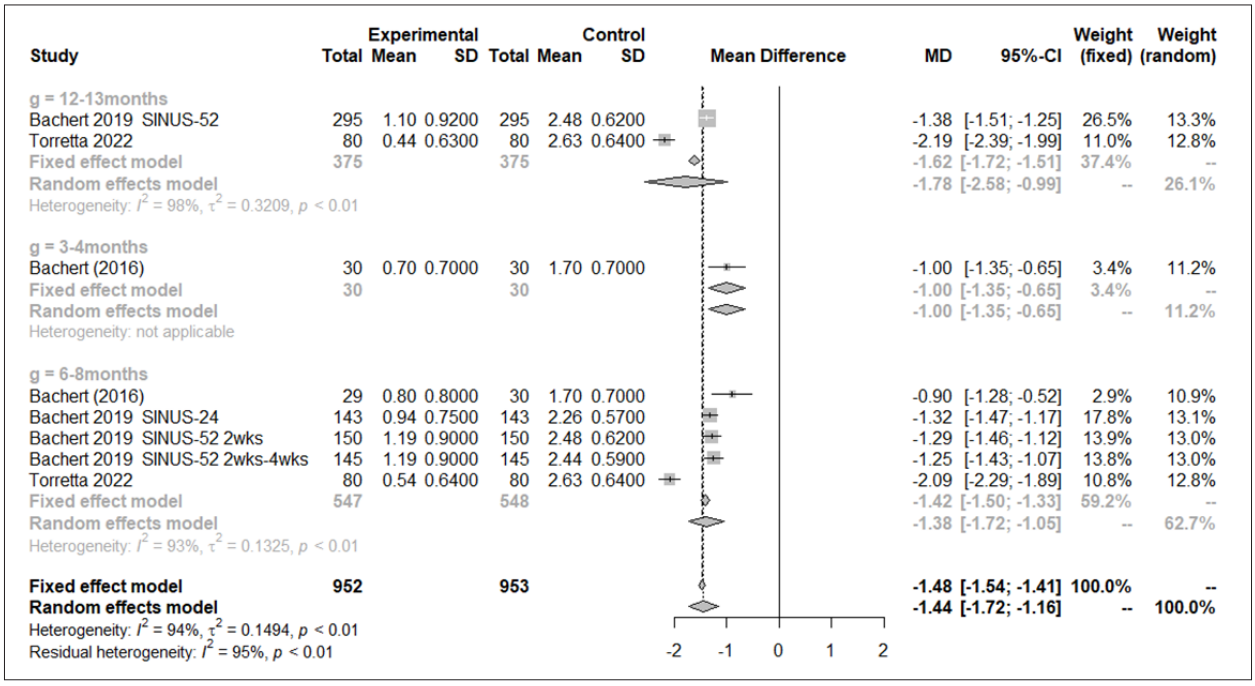
A star rating system was used to indicate the quality of a study, with a maximum rating of nine stars. A study could be awarded a maximum of one star for each numbered item within selection and exposure categories. *selection (4 items): adequacy of case definition; representativeness of cases; selection of controls; definition of controls; †comparability (1 item): comparability of cases and controls on the basis of design or analysis; ‡exposure (3 items): ascertainment of exposure; same method of ascertainment used for cases and controls; and non-response rate (same rate for both groups)

Supplementary Table 3. Quality assessment of randomized controlled trials

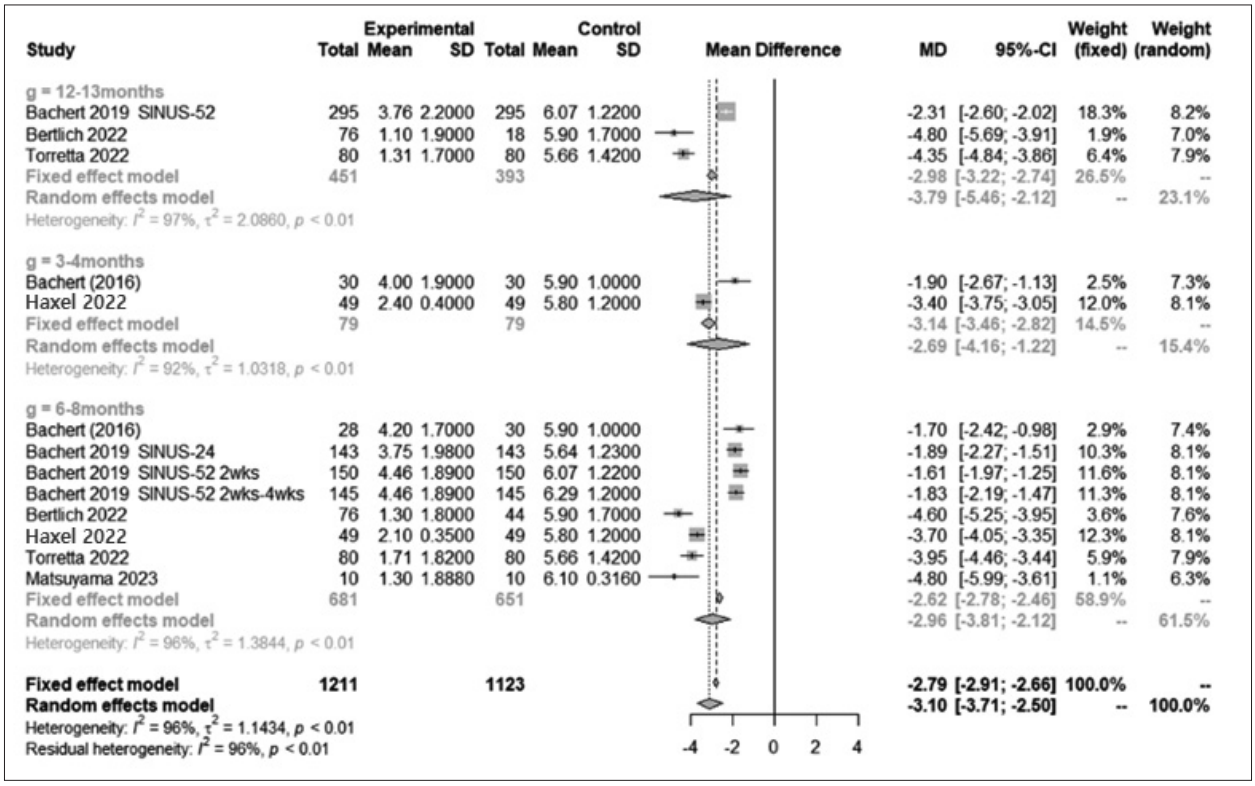
Study author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective reporting	Risk of Bias of randomized studies
Bachert (2016) [12]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Bachert (2019) [9]	Yes	Yes	Yes	Yes	Yes	Yes	Low



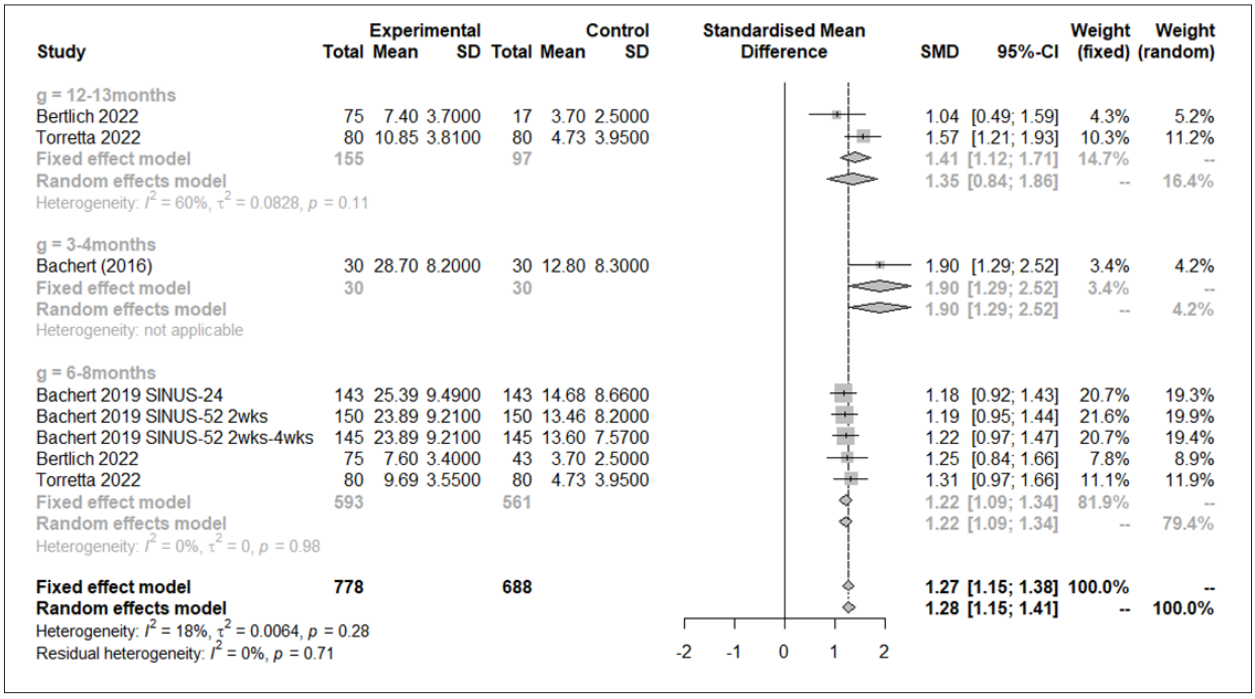
Supplementary Fig. 1. Changes in LMCT scores from baseline (dupilumab). The mean post-treatment differences in the LMCT scores at 3, 6, and 12 months of treatment [9,12,18]. Totals: numbers of participants per group. LMCT, Lund-Mackay computed tomography score; SD, standard deviation; MD, mean difference; CI, confidence interval.



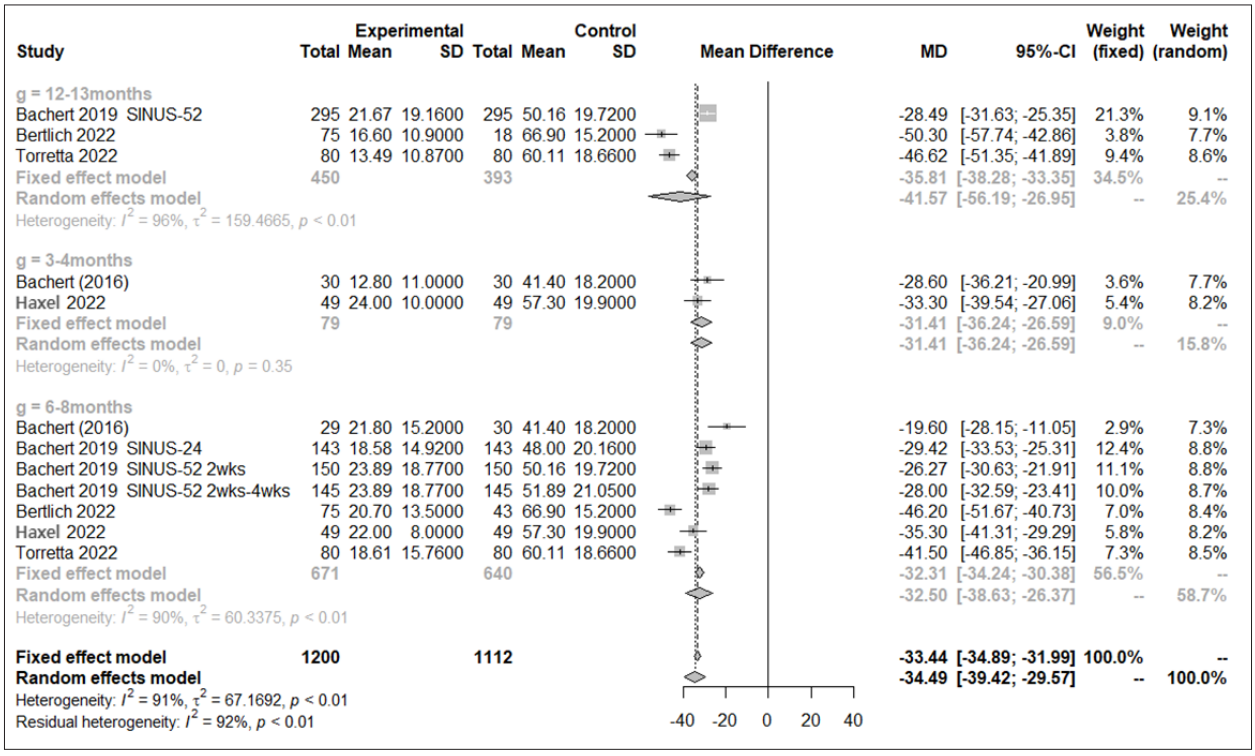
Supplementary Fig. 2. Changes in nasal congestion scores from baseline (dupilumab). The mean post-treatment differences in the nasal congestion scores at 3, 6, and 12 months of treatment [9,12,17]. Totals: numbers of participants per group; SD, standard deviation; MD, mean difference; CI, confidence interval.



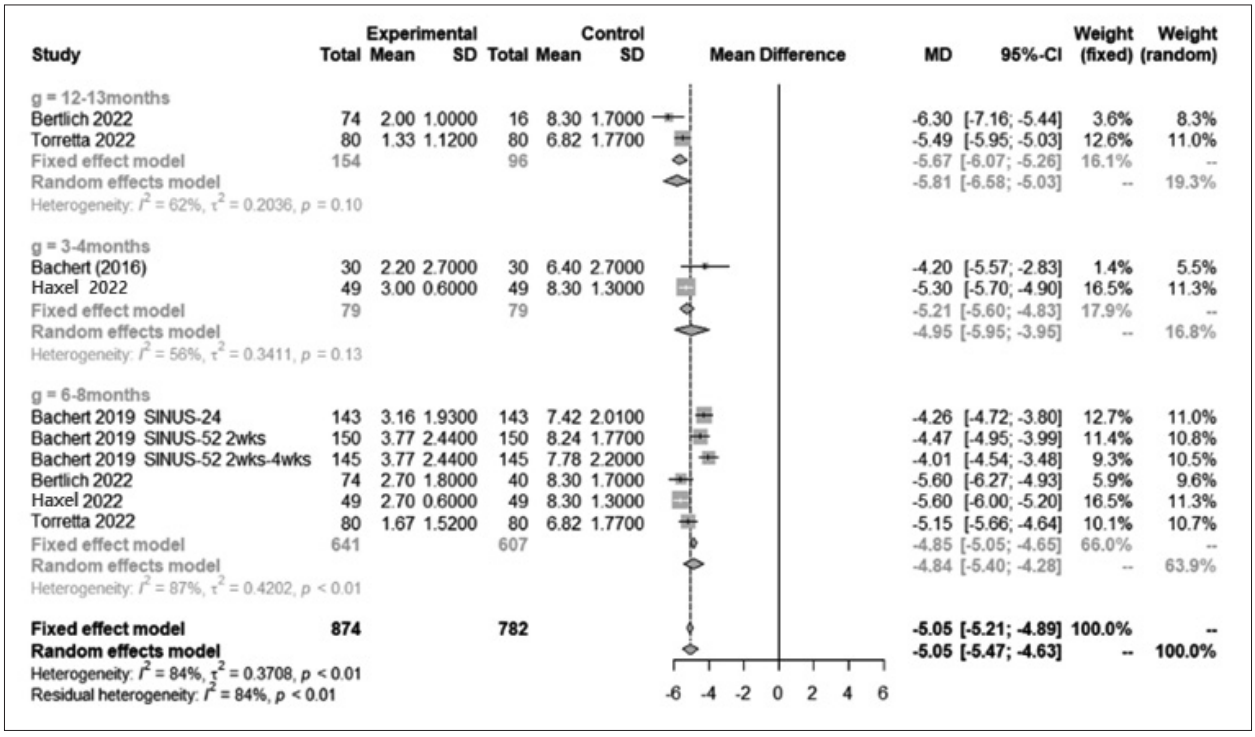
Supplementary Fig. 3. Changes in nasal polyp scores from baseline (dupilumab). The mean post-treatment differences in the nasal polyp scores at 3, 6, and 12 months of treatment [9,12,13,16-18]. Totals: numbers of participants per group; SD, standard deviation; MD, mean difference; CI, confidence interval.



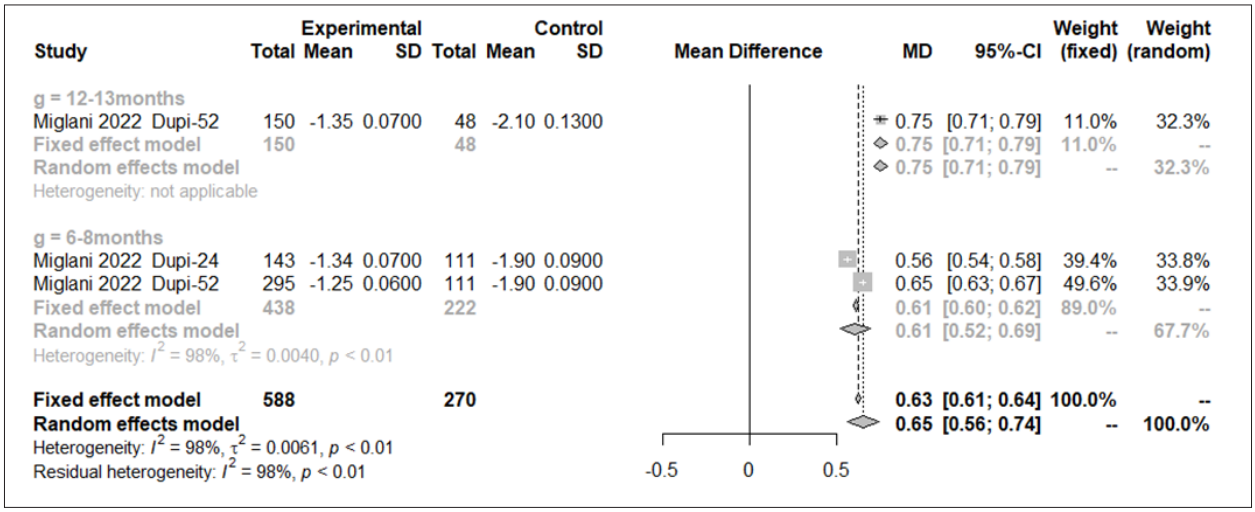
Supplementary Fig. 4. Changes in olfactory function test scores from baseline (dupilumab). The mean post-treatment differences in the olfactory function test scores at 3, 6, and 12 months of treatment [9,12,13,17]. Totals: numbers of participants per group; SD, standard deviation; SMD, standardized mean difference; CI, confidence interval.



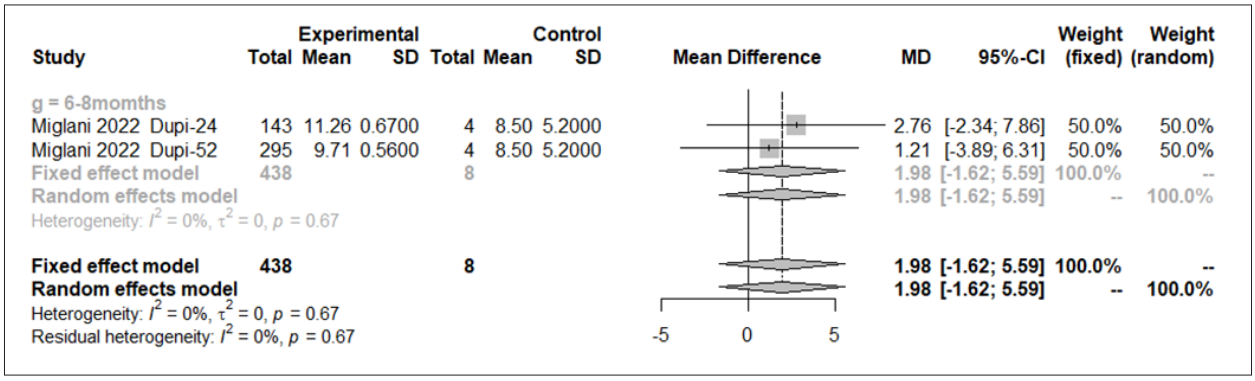
Supplementary Fig. 5. Changes in SNOT-22 scores from baseline (dupilumab). The mean post-treatment differences in the SNOT-22 scores at 3, 6, and 12 months of treatment [9,12,13,16,17]. Totals: numbers of participants per group. SNOT-22, 22-item SinoNasal Outcome Test; SD, standard deviation; MD, mean difference; CI, confidence interval.



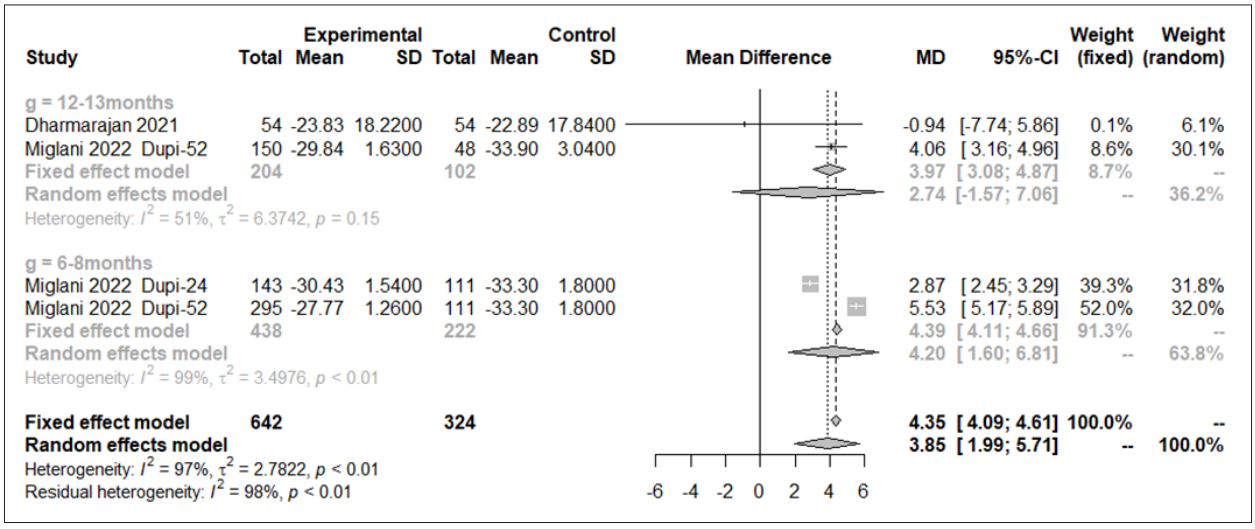
Supplementary Fig. 6. Changes in sinusitis VAS scores from baseline (dupilumab). The mean post-treatment differences in the sinusitis VAS scores at 3, 6, and 12 months of treatment [9,12,13,16,17]. Totals: numbers of participants per group. VAS, visual analog scale; SD, standard deviation; MD, mean difference; CI, confidence interval.



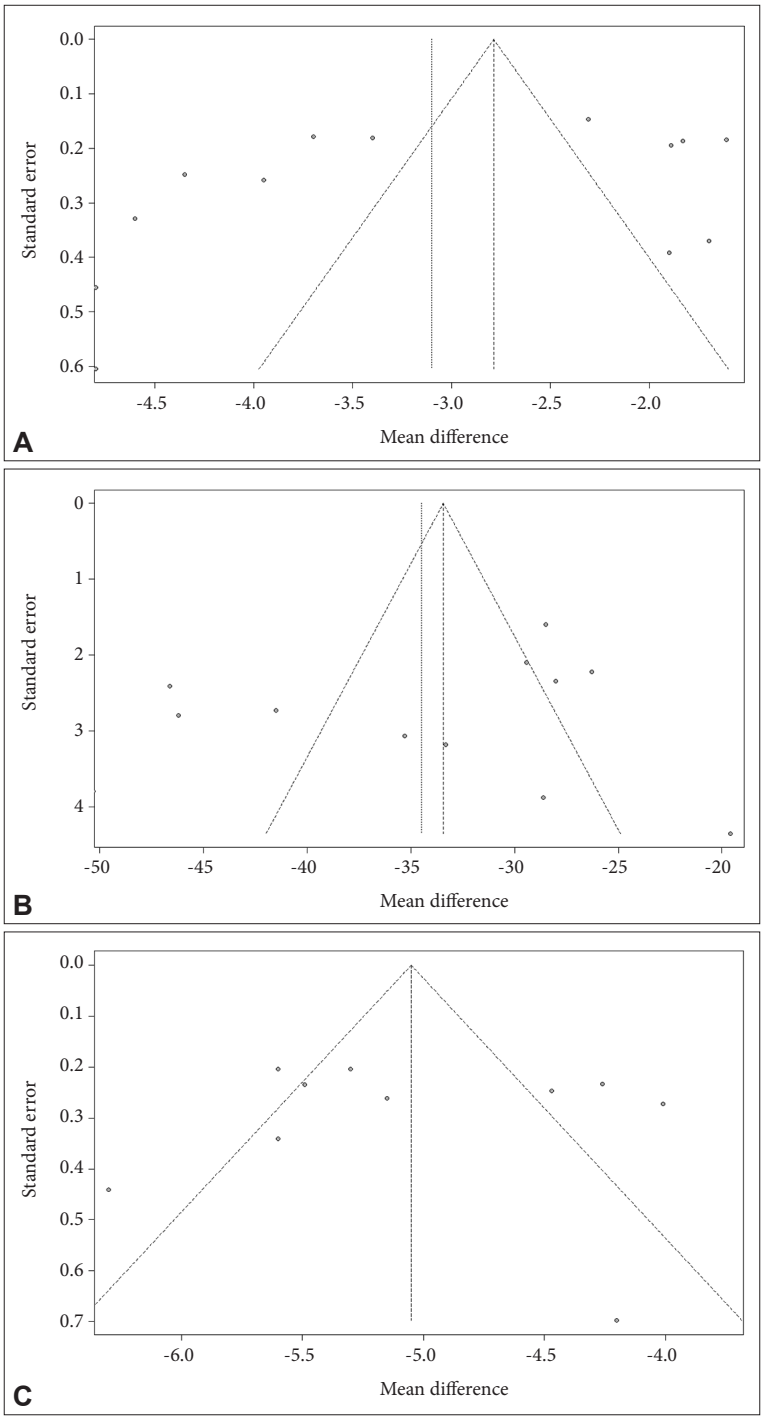
Supplementary Fig. 7. Changes in nasal congestion scores from baseline in the dupilumab and ESS groups. The mean post-treatment differences at 6 and 12 months [15]. ESS, endoscopic sinus surgery; SD, standard deviation; MD, mean difference; CI, confidence interval.



Supplementary Fig. 8. Changes in olfactory function test results from baseline in the dupilumab and ESS groups. The mean post-treatment differences at 6 and 12 months [15]. ESS, endoscopic sinus surgery; SD, standard deviation; MD, mean difference; CI, confidence interval.



Supplementary Fig. 9. Changes in SNOT-22 scores from baseline in the dupilumab and ESS groups. The mean post-treatment differences at 6 and 12 months [14,15]. SNOT-22, 22-item SinoNasal Outcome Test; ESS, endoscopic sinus surgery; SD, standard deviation; MD, mean difference; CI, confidence interval.



Supplementary Fig. 10. Funnel plot of the changes in the nasal polyp score (A), SNOT-22 score (B), and sinusitis VAS score (C) after treatment (dupilumab). SNOT-22, 22-item SinoNasal Outcome Test; VAS, visual analog scale.