Olfactory outcomes following biological therapy in chronic rhinosinusitis: a systematic review and meta-analysis

Dhruv Patel[1], James S. Morris[2], Vikas Acharya[3], Peter Andrews[3]

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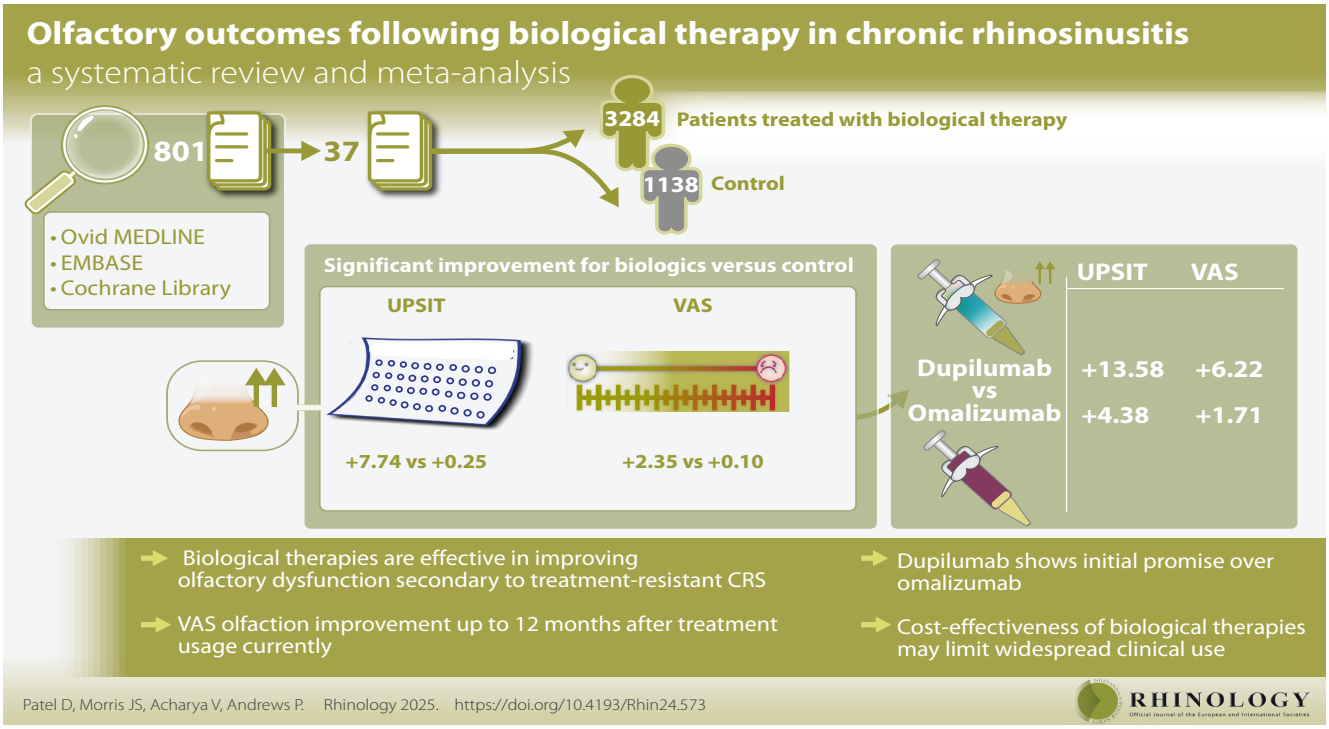

Abstract

Background: Anosmia is a common, debilitating, and often treatment-resistant symptom of CRS. Biological therapies are a novel and promising treatment for severe and uncontrolled CRS, however, the impact of biological therapy specifically on olfactory dysfunction has not yet been evaluated through systematic review.

Methodology: Systematic searches of Ovid MEDLINE, EMBASE and Cochrane Library were performed on 25/05/2024, assessing olfactory outcomes following treatment with biologics. Random-effects meta-analyses were conducted to generate restricted maximum-likelihood estimates for the absolute improvement in each outcome of interest.

Results: Systematic searches yielded 801 papers, of which 37 studies comprising of 3284 patients treated with biologics and 1138 controls. In the RCT-only analysis, biologics conferred significant improvements versus control in UPSIT and VAS olfaction (measured as a 0-10 Likert scale). Across all papers, Dupilumab showed significant improvements versus Omalizumab in UPSIT and VAS.

Conclusions: Biological therapies are effective in improving olfactory dysfunction secondary to treatment-resistant CRS, with VAS olfaction gains being demonstrated up to 12 months after treatment. Dupilumab shows initial promise over omalizumab; however, cost-effectiveness of biological therapies may limit widespread clinical usage currently.

Key words: biological treatment, chronic rhinosinusitis, olfaction disorders, smell

Introduction

Chronic rhinosinusitis

Chronic Rhinosinusitis (CRS) is a common pathology affecting up to 11% of UK adults [1], characterised by inflammation of the nose and paranasal sinuses [2]. CRS significantly impacts health-related quality of life (HRQoL) through frequent exacerbations and poor symptomatic control [3,4], and can complicate into intracranial infection or visual impairment.

Clinically, CRS is sub-categorised into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Within European cohorts, CRSwNP is associated with type-2 inflammation with local eosinophilic infiltration and production of eosinophil cationic protein, IL-4, IL-5, IL-13 and local IgE [6]. Conversely, CRSsNP is driven by type-1 inflammation associated with IFN-γ signalling and activity of TH1 cells, natural killer cells, and antigen-presenting cells [7]. Overlap between phenotypic and inflammatory patterns exists, and thus endotyping is likely to better define patient subgroups using measurable molecular biomarkers [8].

'Biologics' or 'biological therapy' refer to drugs produced by a biological process such as monoclonal antibodies. A range of biologics have now been developed to target specific receptors in the type-2 inflammatory pathway principally affected in CRSwNP. Biologics are developing a significant evidence base for their efficacy in improving HRQoL in severe and uncontrolled CRS [13-15], reflected in the recommendations in the 2023 European Position Paper on Rhinosinusitis and Nasal Polyps [12]. However, to date, the impact of biological therapy specifically on olfactory dysfunction caused by CRS has not been evaluated through systematic review [17,18].

Anosmia in CRS

CRS is a world-leading cause of olfactory dysfunction [19,20], with anosmia present in 67-75% of cases [21]. Anosmia specifically is the most debilitating symptom of CRS [1], as severity correlates with the risk of developing major depressive disorders [22]. Anosmia also has a well-proven, strong and significant association with risk of mortality [23-29]; a finding which is not replicated in impairments in vision or hearing. Possible mechanisms include decreased ability to enjoy food causing decreased appetite and chronic malnourishment, or an inability to sense 'danger signals' such as smoke, natural gas, or malodorous foods, increasing risk of cooking accidents, fires, gas leaks, and consumption of toxins in spoiled food [30].

Olfactory dysfunction can be hard for patients to identify and thus clinical testing is essential. Psychophysical olfactory tests are widely used, and generally assess three domains; Threshold, Detection, and Identification (TDI). Threshold involves assessing the lowest-identifiable concentration of a given odour, detection requires attempts at odour discrimination amongst multiple odours, and identification assesses ability to identify specific odours. Commonly used psychophysical tests include the University of Pennsylvania Smell Identification Test (UPSIT) [32], assessing identification, and Sniffin' Sticks [33], assessing all three domains. Despite showing cultural variability [34], both are well-validated in European cohorts with high test-retest reliability [32,35,36]. Visual analogue scale (VAS) olfaction is also widely used as a quick and repeatable subjective anosmia score, involving self-assessment of anosmia severity from 0-10 [37,38].

Given the prevalence of olfactory dysfunction in CRS, the significant morbidity and mortality anosmia causes, and the relative paucity of level-one evidence, our primary aims were to evaluate the olfactory outcomes of CRS patients following biological treatment. Our secondary aims were to compare the olfactory outcomes of different biologics, to determine the most commonly reported adverse effects, and to identify factors which significantly affect the degree of improvements in olfactory outcomes following treatment with biologics.

Materials and methods

Protocol and registration

This systematic review and meta-analysis was designed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [39] and was registered prospectively with PROSPERO (CRD42024541645). The review adhered to the PRISMA reporting guidelines [40], and the meta-analysis conducted with close attention to the MOOSE reporting checklist.

Systematic searches

A PICOS chart was designed prior to systematic search, with notable exclusion criteria including secondary CRS caused by known aetiologies, such as vasculitides, granulomatous disease, cystic fibrosis, or immunodeficiency as these represent different pathological processes. In Table 1, full inclusion and exclusion criteria are described.

Systematic searches were performed on April 25th 2024 on MEDLINE via Ovid, Embase, CENTRAL and the Cochrane Database of Systematic Reviews (CDSR), with expert librarian support. Key search terms focused around three concepts: chronic rhinosinusitis, biological therapy, and anosmia (Appendix 1 shows full details of the search strategy).

Data extraction

Outcome data was extracted in duplicate by JM and DP and recorded onto a standardised database designed according to the STARD 2015 checklist. Outcomes of interest included study characteristics and improvements in the following parameters

Table 1. PICOS inclusion and exclusion criteria for study selection.

Domain	Inclusion criteria	Exclusion criteria
Population	Clinical study conducted on human populations with Chronic Rhinosinusitis (CRS) with or without Polyps related to Olfactory dysfunction regardless of age, gender or ethnicity.	Populations with Chronic Rhinosinusitis without relation to Olfactory dysfunction Patients with CRS caused by known aetiologies such as vasculitides, granulomatous diseases, cystic fibrosis or immunodeficiency
Intervention	Patients treated with biologics for CRS, including but not limited to dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, lebrikizumab, tralokinumab	Patients treated with biologics for indications outside of CRS
Comparison	A non-exposed control group including alternative treatment or placebo	Control groups which included administration of biologics
Outcome	1.Validated psychophysical Olfaction scoring systems including "Sniffin' Sticks" (TDI) or UPSIT. 2. Health-related QoL measured by validated disease-specific scoring systems such as SNOT-22, RSOM-31 or others. 3. Disease severity and extent through validated objective and subjective symptom scores such as VAS, peak Nasal Inspiratory Airflow, Lund-Kennedy, Lund-Mackay, DIP or others. 4. Short-term, medium-term and long-term reported adverse events and length of follow-up. 5. Epidemiological data surrounding population in which biologics were administered including previous surgeries and length of olfactory dysfunction.	Studies where no outcome measures are directly related to efficacy of biologics on olfactory or clinical outcomes in patients with CRS.
Study Type	Full-text primary studies written in English or with full-text English translation available	Case reports, abstracts, reviews. Studies without full-text English translation. Animal studies.

following a course of biologic immunotherapy: Sniffin' Sticks [33], UPSIT [32], SNOT score [9], NOSE score [41], subjective olfaction (assessed using either a visual analogue scale or a binary metric such as present or absent anosmia), Nasal Polyp Score (NPS), Lund-Mackay score [42], Lund-Kennedy Score [43] and peak nasal inspiratory flow rate (NPIF). Data regarding patient-reported adverse reaction to biologics were also extracted. Where data were reported in terms of medians, it was assumed to be normally distributed in order to impute mean values. Authors were not contacted to request unpublished data.

Assessment of the risk of bias

The overall risk of bias in the included studies was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [44] and The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)[45] assessment tools. The risk of publication bias in our estimates of each of the main outcomes was assessed using Egger's tests [42] and visual inspection of funnel plots.

Statistical analysis

Where reported, the mean change in each outcome was recorded directly into the data extraction spreadsheet. Where missing, it was calculated from the before and after values. The standard deviation therein was imputed using the standard deviations in these values established methods [47,48] outlined in the Cochrane Handbook section 6.5.2.8. [38]. A correlation coefficient of 0.9 was selected on the assumption that greater variance in the before and after values would almost always result in greater variance in the difference between them, whilst avoiding non-real values for standard deviation when the individual standard deviations were equal, as was the case for SSIT-16 scores in the biologics cohort of De Corso [49]. A sensitivity analysis was conducted using correlation coefficients of 1.0, 0.9, 0.8, 0.7, 0.6 and 0.5 which demonstrated this imputation to not impact the results of any of our meta-analyses of RCTs (the difference between the changes in Lund-Mackay scores across all included papers in the biologic and control cohorts lost significance when the correlation coefficient was set to 0.5, but was otherwise significant for all other values tested). Where SD itself was not reported, it was calculated from the 95% confidence interval or interquartile range whilst assuming that data was normally distributed. In place of these measures of spread, the SYNAPSE RCT [50] reported range, from which the standard deviation was estimated using the rule of thumb method [51]. For each outcome of interest, we generated restricted maximum-likelihood estimates for the overall change following treatment with either biologics or a placebo, using a random-effects meta-analysis model [52-54]. Between-study heterogeneity was evaluated using the Cochran's Q statistic with a threshold of significance of α=0.05. Subgroup analyses were conducted for the studies fulfilling each of the following criteria in turn: assessed dupilumab

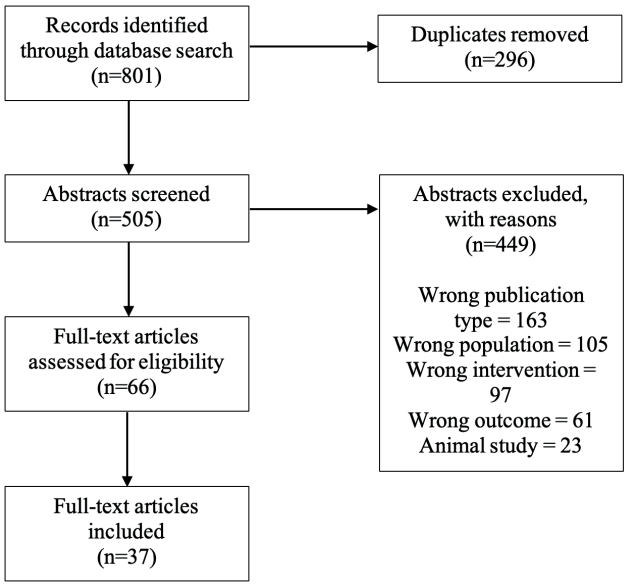

Figure 1. PRISMA diagram.

only; assessed omalizumab only; undertaken in upper-income countries only; undertaken, at least in part, in lower-middle or upper-middle income countries (both according to the World Bank Classification for the 2023/24 fiscal year) [55].

For each outcome of interest, the risk of confounding was assessed via univariate meta-regressions [56] using the following study-level covariates: sex ratio, mean age, mean follow-up, mean duration of biologic therapy and publication year. We planned to do the same for mean duration of CRS, mean delay since last sinus surgery and mean number of previous surgeries; however, fewer than four RCTs assessing each outcome of interest reported these covariates so these did not undergo meta-regression. To avoid inflating the type-I error rate, the Šidák correction [57] was applied to α=0.05 to generate an adjusted-significance threshold of 0.00183 for the 25 regressions. Were a significant correlation to be found, the residual plots would have been visually inspected to determine whether the regressions fulfilled the homoscedasticity assumption. All statistics are presented as mean [95% confidence interval], unless otherwise stated.

Results

Study characteristics

Systematic searches yielded a total of 801 papers of which 296 were duplicates. Thus, 505 abstracts were screened, of which 58 were post-hoc analyses of randomised controlled trials (RCTs) and so were coded as wrong publication type and excluded in favour of the original trial data published on clinicaltrials.gov. 66 full-text articles were assessed for eligibility, and after full text-screening a total of 37 individual studies [49,50,58-92], comprising 3,284 CRS patients taking biologics and 1,138 controls, were included in our analyses (Table S2 contains detailed study characteristics). Our principal analysis was concerned with the 12 RCTs [50,60,69,70,80-86,90], which comprised 981 CRS patients taking biologics and 957 controls. In Figure 1 all details are presented. Of the participants included from all 37 papers, 60.6% were male (n=2679) and the mean age was 51.76 years. Where reported, the mean duration of CRS was 12.4 years (7 papers, 844 participants) [50,67,70,87,90-92], the mean time delay since previous surgery was 63.4 months (6 papers, 1223 participants) [50,59,60,78,87,91] and participants had undergone 2.0 previous surgeries (15 papers, 2172 participants)[49,50,59,60,62,66,72,75,78,79,87-91]. 43.2% of papers employed a multi-centre design (n=16) [49,50,60,61,62,64,68,69,70,78,81-83,85,86,92], leaving a total of 575 different centres in 30 different countries in our final analysis. 94.6% of included papers (n=35) [49,59,58-68,69-79,81-92] were published after 1st January 2021 and 32.4% were RCTs (n=12) [50,60,69,70,80-86,90].

The number of studies assessing each biologic drug were as follows: dupilumab: 24 [49,58,59,62-65,67,68,71-79,83,85-87,89,91]; omalizumab: 8 [61,66,69,80-82,84,88]; mepolizumab: 4 [50,61,66,70]; benralizumab: 4 [60,61,66,90]; reslizumab: 1 [61]; strapokibart: 1 [92]. 43.2% of papers (n=16) [50,58,60,69,70,73,77,80-86,90,92] included a separate control cohort, while the other 56.8% (n=21) [49,59,61-68,71,72,74-76,78,79,87-89,91] only assessed the change in olfactory function in patients taking biologic immunotherapies. Patients were followed up for a median duration of 6 months (IQR: 5.025-12) across all included studies but 5 months (IQR: 4.5-7.5) across included RCTs.

Main findings: outcomes from RCTs

Data availability allowed for meta-analyses of six outcomes amongst the included RCTs: UPSIT, VAS olfaction, SNOT-22, bilateral NPS, Lund-Mackay Score and NPIF. Patients treated with biologic immunotherapy demonstrated significantly greater improvements in olfactory function after a median follow-up duration of 5 months (IQR:4.5-7.5) across included RCTs: the REML for the improvement in UPSIT was 7.74 [4.49-11.0] following biologics, compared to 0.25 [-0.37-0.86] in the control cohort (test of group difference: χ^2 =19.65, p<0.01, Figure 2). Subjective olfactory function demonstrated similar improvements following biologics: VAS olfaction (0-10 scale) decreased 2.35 [0.68-4.02] in the biologics cohort, compared to only 0.10 [-0.35-0.54] in the control cohort (test of group difference: χ^2 =6.52, p =0.01, Figure 3). CRS-related quality of life measures were also significantly improved by the addition of biologic therapies: SNOT-22 scores decreased 24.98 [21.41-28.55] in the biologics cohort versus 8.98 [7.65-10.32] in the control cohort (test of group difference: χ^2 =67.65, p<0.01, Figure 4). While the NPS (0-8 scale) showed good improvements with biologics (decreased by 1.57 points [0.75-2.39] compared to 0.12 points [-0.12-0.36], test of group difference: χ^2 =11.10, p <0.01, Figure 5), the relative improvement in the Lund-Mackay score with

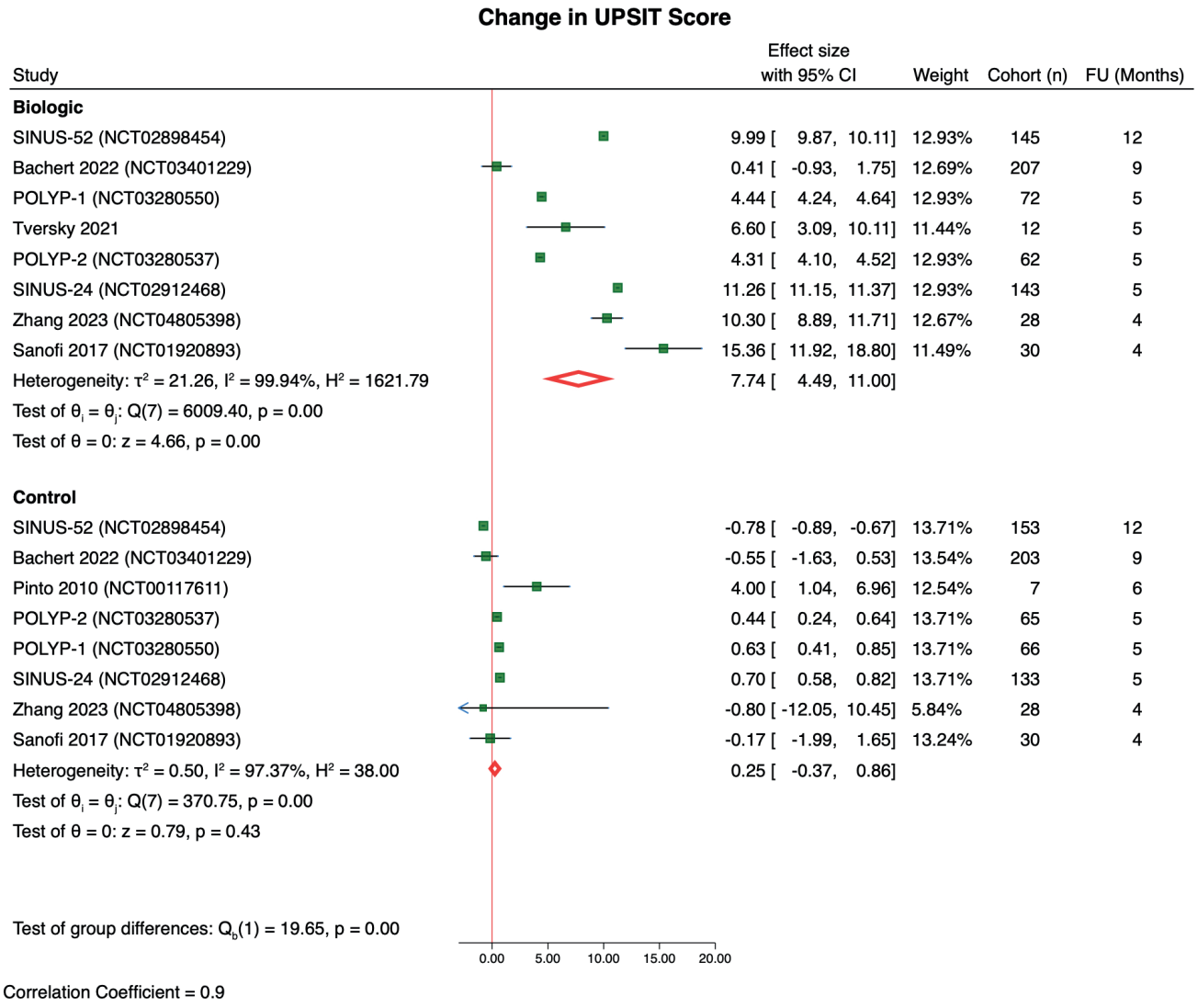

Figure 2. Forest plot for the change in UPSIT score within the biologic and control cohorts of included RCTs.

biologics failed to reach statistical significance: the Lund-Mackay score decreased by 6.95 [5.18-8.72] in the biologics cohort compared to 2.63 [-1.54-6.81] in the control cohort (test of group difference: $\chi 2 = 3.48$, p=0.06, Figure 6). Finally, the NPIF was found to increase by 43.90 ml/min [15.72-72.09] in the biologics cohort compared to 19.30 ml/min [13.21-25.39] in the controls (test of group difference: $\chi 2 = 2.80$, p =0.09, Figure 7). With the exception of the NPIF measurements reported in the control cohorts, the reported changes in each outcome of interest suffered from a high degree of heterogeneity therein (p <0.01).

Outcomes from non-randomised studies

When the meta-analysis was conducted to include non-RCTs, data availability allowed for SSIT-16 to be additionally analysed. Both the SSIT-16 and UPSIT scores demonstrated significantly greater improvements in the biologic cohort compared to the control cohort: the REML for the improvement in SSIT-16 was 5.85 [4.74-6.96] following biologics, compared to 0.79 [0.16-1.41] in the control cohort (test of group difference: $\chi 2 = 60.56$, p<0.01, Figure S1), while the REML for the improvement in UPSIT following biologics was 8.91 [5.15-12.68], compared to 0.25 [-0.37-0.86] in the control cohort (test of group difference: $\chi 2 = 19.83$, p<0.01, Figure S2). Subjective olfactory function showed similar improvements following biologics when assessed using all included papers, with VAS olfaction decreasing 4.14 [2.87-5.41] points in the biologic cohort, compared to 0.16 [0.3-0.62] points in the control cohort (test of group difference: $\chi 2 = 33.32$, p<0.01, Figure S3). The SNOT-22 score decreased by 35.40 [30.97-39.84] following biologics compared to 10.78 [7.77-13.79] in the control cohort (test of group difference: $\chi 2 = 81.03$, p<0.01, Figure S4). Finally, all three markers of disease activity assessed demonstrated significantly greater improvements following treatment with biologics: NPS decreased 3.21 [2.58-3.84] compared to 0.02 [-0.27-0.31] (test of group difference: $\chi 2 = 81.18$, p<0.01,

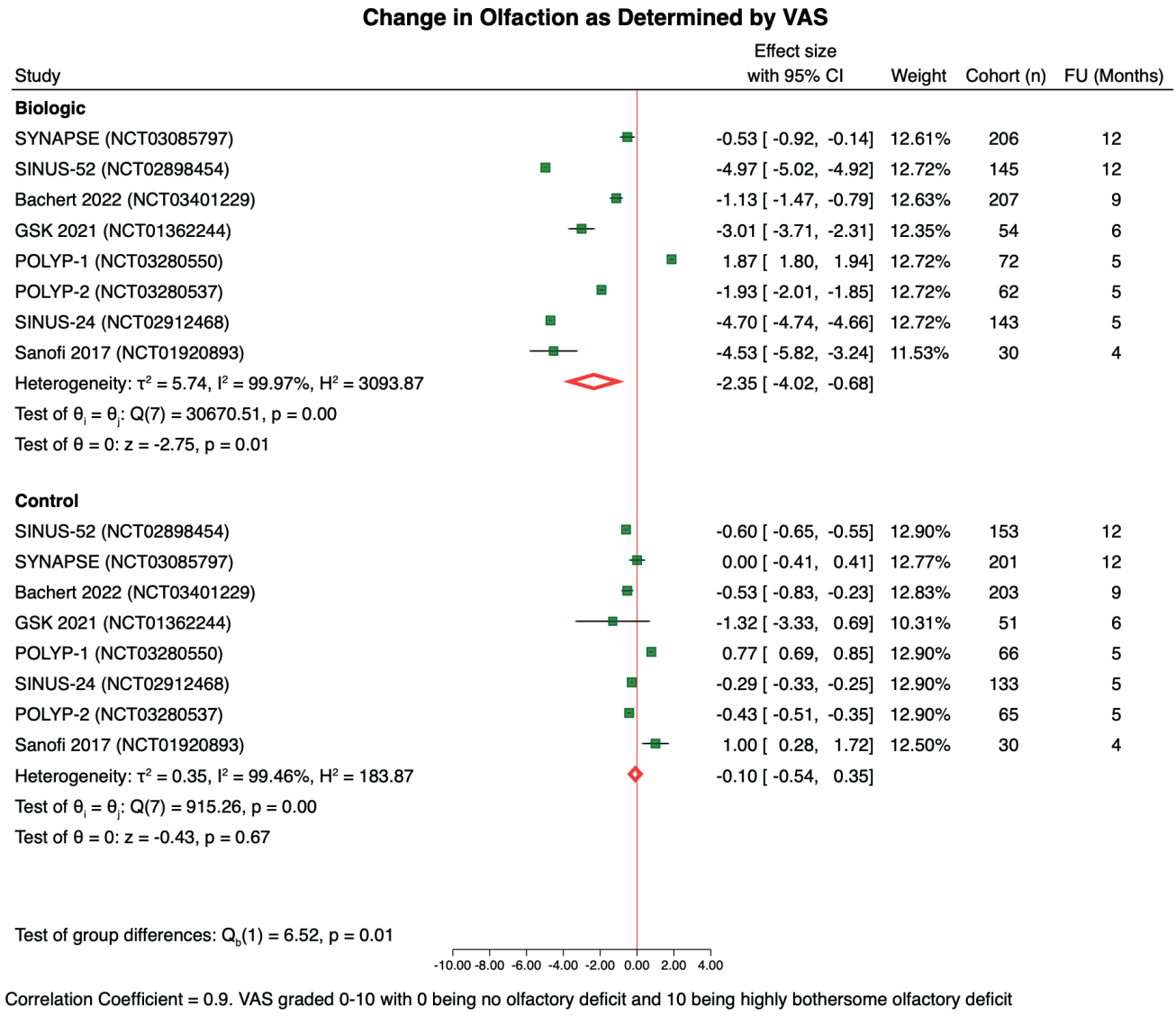

Figure 3. Forest plot for the change in VAS olfaction within the biologic and control cohorts of included RCTs.

Figure S5); Lund-Mackay score decreased 8.97 [6.34-11.60] compared to 3.82 [-0.42-8.06] (test of group difference: χ^2 =4.09, p=0.04, Figure S6); NPIF increased 57.99ml/min [43.04-72.94] compared to 19.30 [13.21-25.39] without biologic immunotherapy (test of group difference: χ^2 =22.08, p<0.01, Figure S7). With the exception of NPIF and SSIT-16 scores in the control cohorts, all outcomes demonstrated significant between-study heterogeneity in both the biologic and control cohorts when assessed using all included papers (p<0.01).

Outcomes with dupilumab versus omalizumab

Data availability across all papers also allowed direct comparison between outcomes following treatment with dupilumab or with omalizumab. Dupilumab was found to confer superior improvements in UPSIT, VAS olfaction and NPS compared to omalizumab. Conversely, no significant difference in the change in SNOT-22 score was demonstrated between the two therapies. Following treatment with dupilumab, UPSIT increased by 13.53 points [9.38-17.68] compared to 4.38 points [4.23-4.52] following omalizumab therapy (test of group difference: χ^2 =18.69, p<0.01, Figure S8); VAS olfaction improved 6.22 points [5.36-7.09] and 1.71 points [-1.33-4.75], respectively, (test of group difference: χ^2 =7.83, p=0.01, Figure S9); NPS decreased by 3.89 points [3.36-4.42] and 1.50 points [0.37-2.63], respectively, (test of group difference: χ^2 =14.03, p<0.01, Figure S10); SNOT-22 decreased by 38.38 points [34.94-41.82] and 33.72 points [13.16-54.27], respectively (test of group difference: χ^2 =0.19, p=0.66, Figure S11).

Meta-regressions of RCTs

Meta-regressions for the RCT-only meta-analyses demonstrated that the change in UPSIT, SNOT-22, VAS olfaction, NPS and Lund-Mackay scores were not significantly correlated with the

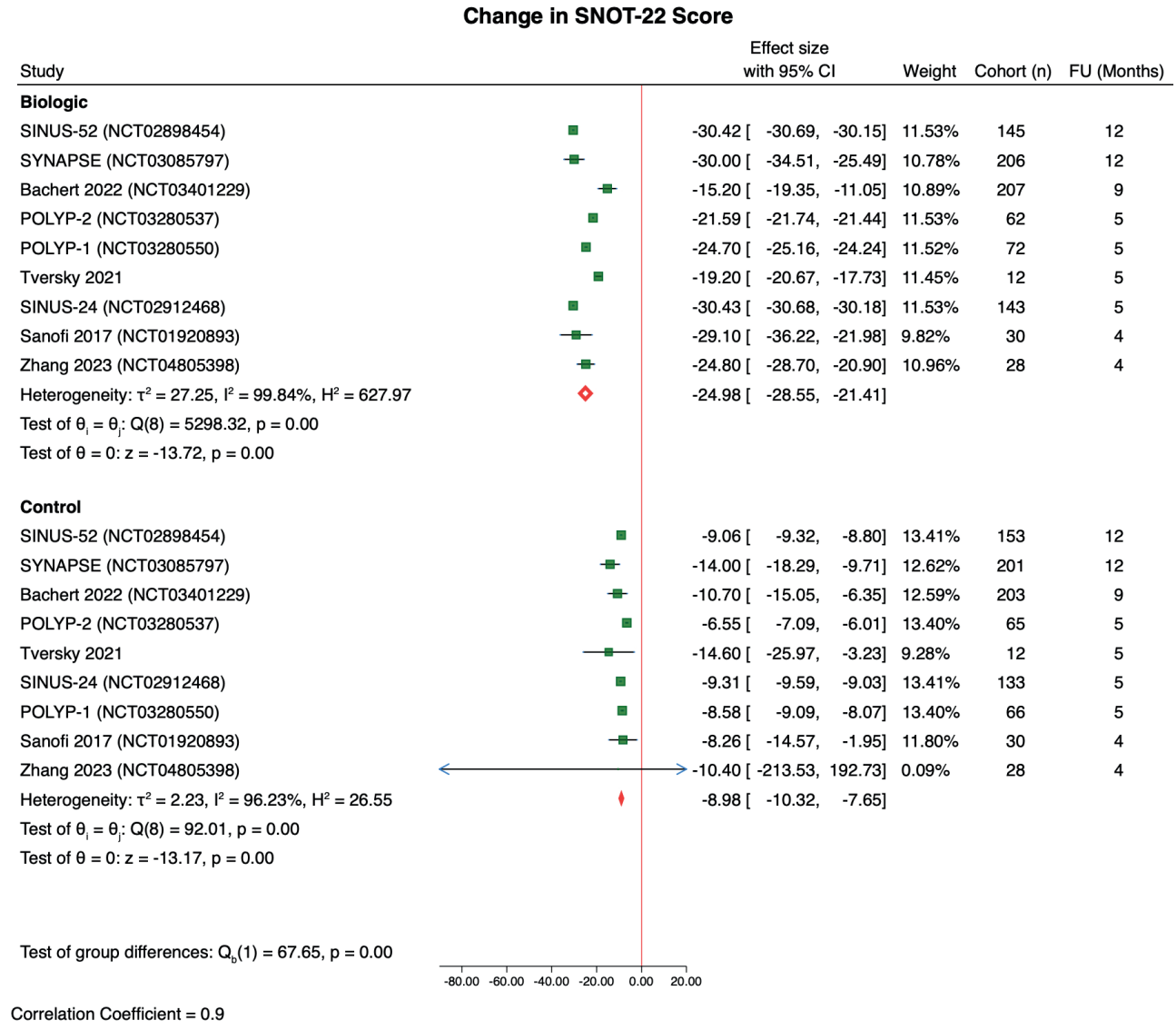

Figure 4. Forest plot for the change in SNOT-22 score within the biologic and control cohorts of included RCTs.

sex ratio, mean age of participants, mean follow-up duration, duration of biological treatment or the year of publication of included RCTs.

Meta-regressions of non-randomised studies

However, meta-regressions for meta-analyses across all papers demonstrated that 66.3% of the variance in improvements in UPSIT scores reported by included studies could be accounted for by the variance in the sex ratio of their biologic cohorts, with each 1% increase in the proportion of females conferring a 1.01% increase in the improvement in UPSIT score (p=0.0002, Figure S12). Similarly, 34.5% of the variance in the decreases in VAS olfaction following biologic therapy could be accounted for by variance in the duration of follow-up in included studies; VAS olfaction decreased a further 0.59 points for each additional month of follow-up (p=0.0003, Figure S13). Finally, 34.4% of the variance in the NPS scores reported could be accounted for by the variance in the year of publication, with the degree of improvement in NPS score improving a further 0.61 points per year between 2017 to 2024 (p=0.0002, Figure S14). No other correlations were found.

Reported side effects

Reporting of adverse reactions to biologics was highly variable amongst the included papers but was most reliably assessed by the RCTs. Of the 37 included studies, 29 assessed for side effects [49,50,59,60,63,65-72,74-83,85,86,88,90-92] and, of these, 6 papers [66,75,76,79,80,88] reported that their participants had suffered no adverse reactions to biologics. Amongst the 2,749 patients treated with biologics and assessed for adverse reactions, there were 44 cases of hypereosinophilic disorders, 41 cases of pruritus or rash, 23 cases of conjunctivitis and 26 cases of arthralgia. 5 deaths in total were

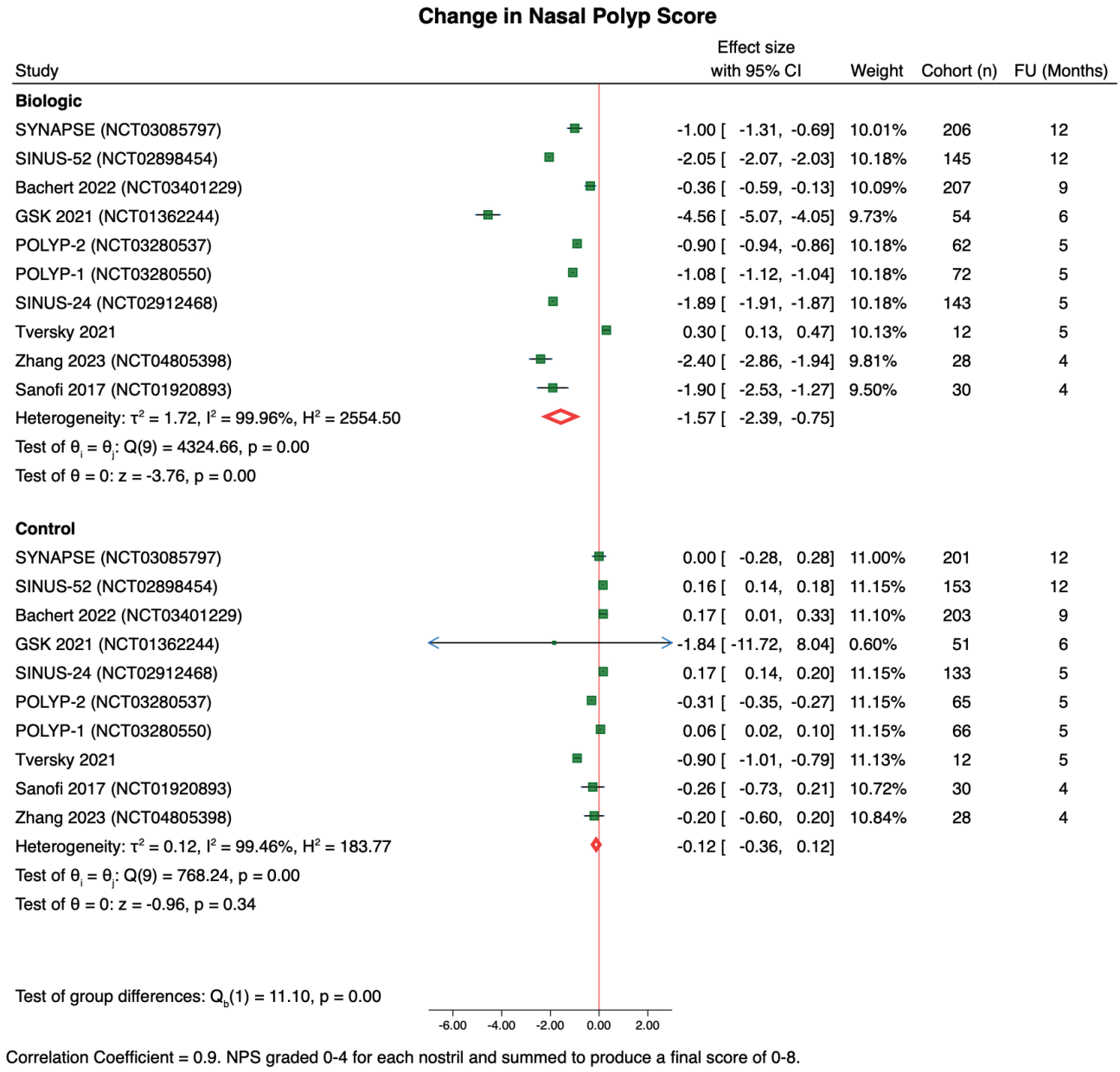

Figure 5. Forest plot for the change in NPS within the biologic and control cohorts of included RCTs.

reported: 1 in the SINUS-52 trial [86] and a further 3 in another non-randomised trial [91], though the latter deaths were reported to have been unrelated to treatment with biologics. Additionally, one patient from another RCT [69] was reported to have developed fatal chronic lymphocytic leukaemia one year after treatment with omalizumab.

Risk of bias

All but one randomised study included in this analysis was deemed to be at low overall risk of bias [50,60,69,70,81-83,85,86,90,92] (Figure S15). The baseline characteristics of the participants in the remaining paper [80] were found to suffer from statistically significant differences between cohorts, suggesting that there may have been an error in the randomisation process. Of the 25 non-randomised studies [49,58,59,61-68,71-79,84,87-89,91], 7 were deemed to be at low overall risk [65,67,68,75,77,78,91] and 19 at moderate overall risk of bias in their results [49,58,59,61-64,66,71-74,76,79,84,87-89] (Figure S16). 10 studies [61,62,66,71,74,76,84,87-89] at moderate risk failed to utilise appropriate analytical methods to account for the effect of potential confounding factors whilst 13 were at risk of bias from participants' awareness of which intervention they were receiving [61,62,66,71,74,76,84,87-89]. For six of the seven outcomes assessed through meta-analysis, excluding the change in the Lund-Mackay score, the Egger's test statistic demonstrated a low risk of publication bias for the included studies (p>0.05 for each, Figure S17). The improvements in Lund-Mackay score reported

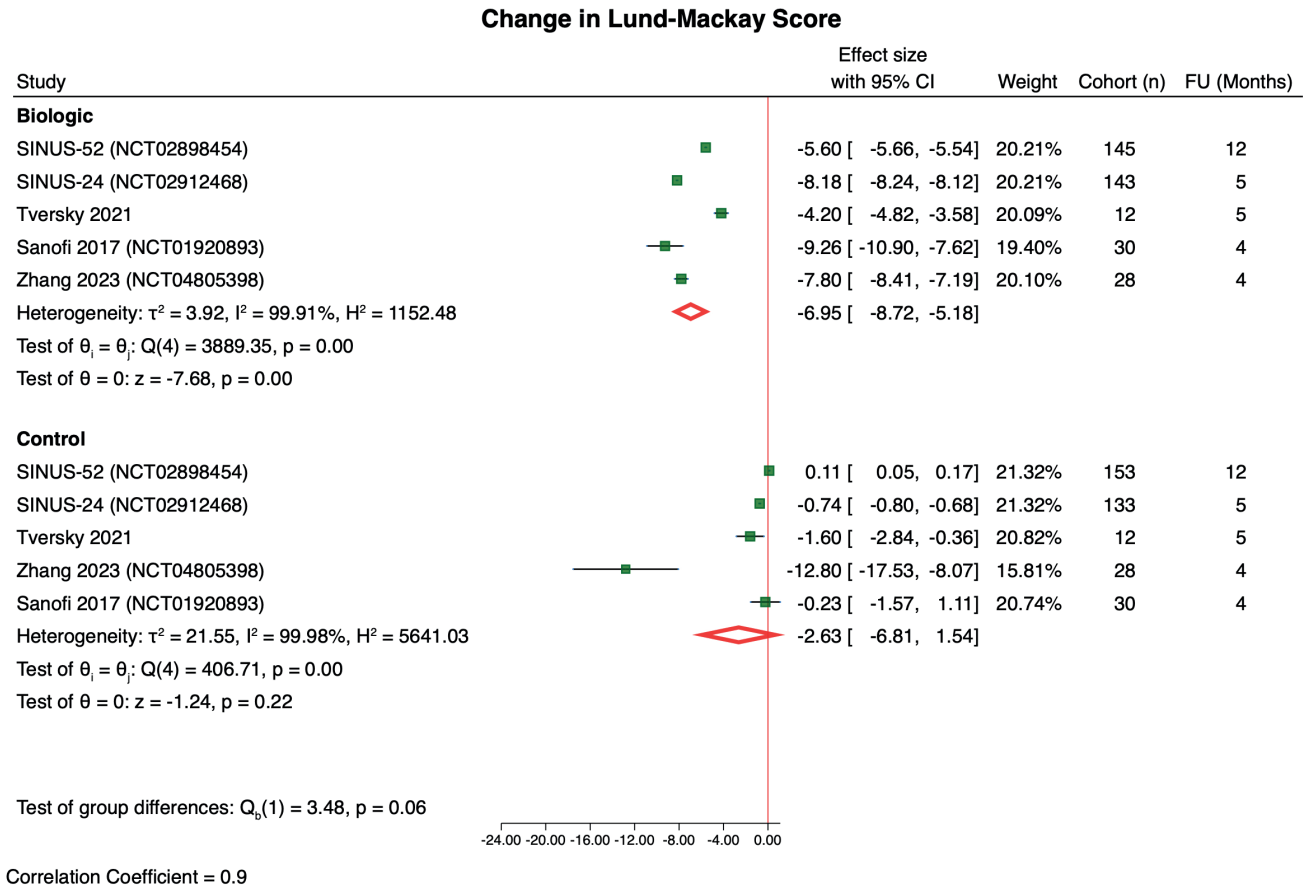

Figure 6. Forest plot for the change in Lund-Mackay score within the biologic and control cohorts of included RCTs.

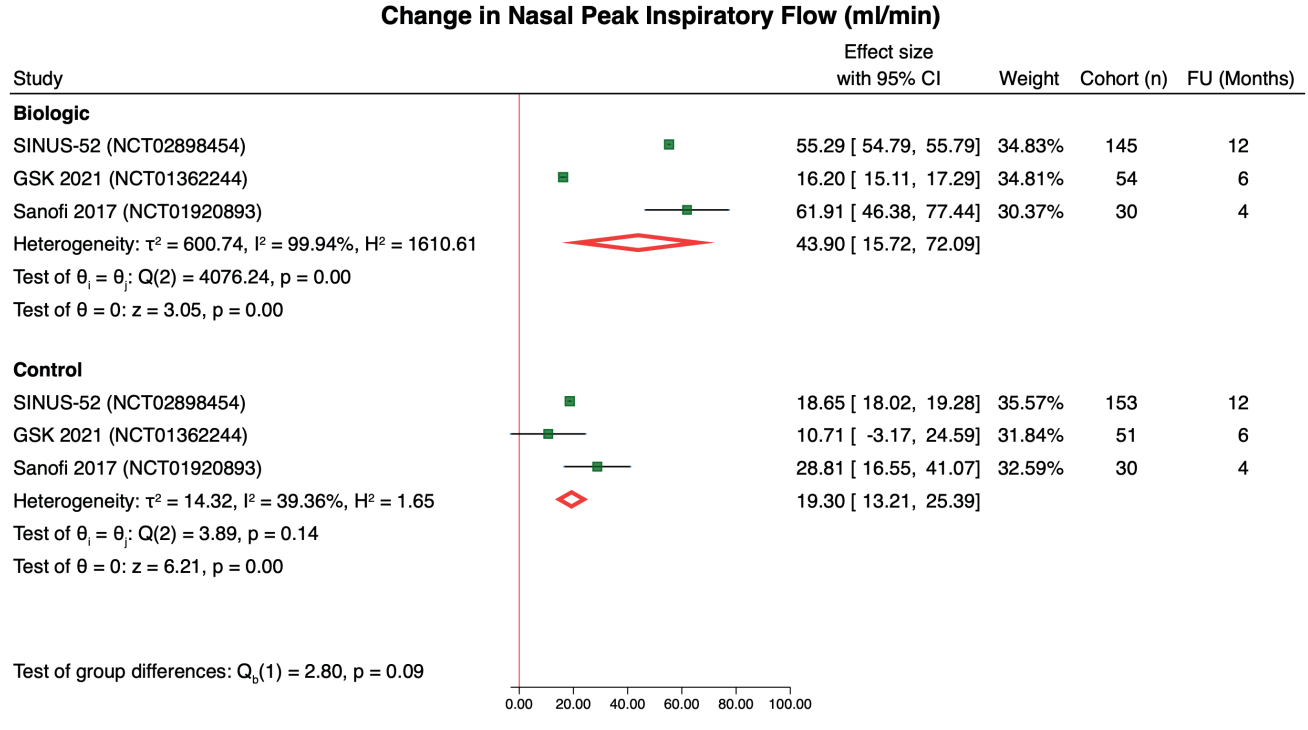

Figure 7. Forest plot for the change in NPIF within the biologic and control cohorts of included RCTs.

in 8 individual papers [58,75,83,85,86,89,90,92] was found to be at high risk of publication bias (t=-3.60, p=0.011, n=8) and the funnel plot exhibits a clear bias towards publishing studies which reported greater improvements in Lund-Mackay score. However, we acknowledge that these interpretations of both the Egger's test and funnel plots may not be valid, firstly, given the significant heterogeneity in this analysis [93], and secondly, due to the inclusion of fewer than 10 individual study arms [38].

Discussion

Biologics significantly improve olfactory dysfunction secondary to treatment-resistant CRS. Despite the cultural variability of psychophysical olfactory tests [34], UPSIT, VAS olfaction and SSIT-16 all show significant improvements after biological therapy through the range of 30 included countries when conducting meta-analyses across both RCTs and non-RCTs. Currently, the EPOS update in 2023 lists smell loss as a criteria for eligibility for biological therapy [13], and our findings support the efficacy of biologics in treating refractory anosmia, with an average patient in our cohort having prevailing anosmia after 12.4 years of disease burden, optimised medical management, initial FESS, and revision FESS. Revision FESS currently represents "end-stage" management for CRS, and displays a major complication rate of 0.46% relating to skull base, orbital, or haemorrhagic complications [95,96]. In contrast, biologics are effective in treating FESS-resistant CRS, and, to date, display a similar or better safety profile, representing a significant opportunity to improve the HRQoL, morbidity and mortality of patients with anosmia from CRS.

Of the biologics available, dupilumab shows initial promise as most effective for anosmia, demonstrating significant improvements in both VAS Olfaction and UPSIT over omalizumab, although there was insufficient data availability to compare the two across RCTs only. All papers exclusively assessed CRSwNP, driven by type-2 inflammation, which displays significant heterogeneity through distinct endotypes, which can independently predict the magnitude of dupilumab response [100]. Differences in underlying endotype prevalence or associated comorbidities across cohorts may partially explain dupilumab's relative efficacy, such as when considering the high concurrent prevalence of asthma in included cohorts, which dupilumab is well-recognised to be effective against. Future endotype-matched research may help untangle endotype-specific efficacies of individual biological therapies, including potentially effective biological therapies for type-1 inflammation.

VAS Olfaction demonstrated continuing improvements for each additional month of follow-up in the meta-regressions across all papers, up to a maximum of 12 months of follow-up in the longest studies. The median length of follow-up for included RCTs was 5 months, but given this association, we would recommend further RCTs to consider increasing their length of follow-up to at least 12 months to fully capture potential subjective patient-focused anosmia improvements. Notably, reliability of UPSIT analysis across all papers is improved through meta-regression demonstrating that improvements in UPSIT score were positively correlated to proportion of females in treatment groups, with females being known to have superior olfactory function and UPSIT scores [94].

While UPSIT, VAS olfaction and SSIT-16 all showed significant improvements, these findings must be interpreted with some caution, as the RCT-only analysis did not demonstrate significance with SSIT-16, and further RCTs incorporating Sniffin' Sticks would help discern significance from these findings. All papers included utilised only the identification component of the full TDI Sniffin' Sticks' test, which is the most widely used, researched, and modified of all three subtests [97], potentially due to relative ease-of-use and speed. However, both identification and discrimination rely on and measure cerebral interpretation of smell, thereby displaying variability based on cognitive ability, such as lower scores in young children [98,99]. In contrast, threshold measures the peripheral, or end-organ component of olfaction, and does not demonstrate the same cognitive age-related variability [98]. Use of threshold testing in future RCTs may therefore be a more accurate and sensitive measure of olfactory mucosa olfaction and subsequent olfactory mucosa restoration following biologics.

Currently, biological therapy is not as cost-effective in the management of CRS as FESS [4], although this may change as their patents begin to expire. Looking forwards, dupilumab's patent is set to expire in September 2032, but cost-efficiency gains may be on the horizon for omalizumab, which has come off patent in Europe earlier in March 2024, potentially paving the way for more regular clinical use. Smell was evaluated using different tests with a different time interval for each biologic. None of the RCTs primarily aimed to assess the sense of smell. Furthermore, although all these RCTs included patients with severe CRSwNP, they used different enrolment criteria and varied methods to assess baseline disease characteristics. Variability in inclusion criteria also extended to use of diagnostic modalities such as blood tests and cross-sectional imaging, and also prior treatment such as intranasal corticosteroids and previous nasal polyp surgery. This limits meaningful head-to-head comparison between RCTs relating to differences in observed olfaction improvements. As expected, the differences in eligibility criteria also led to differing baseline populations across the trials. For example, the prevalence of comorbid asthma, which is associated with more severe loss of smell, was higher in SYNAPSE [50] than in the SINUS [85,86], POLYP [81,82], and OSTRO [60] trials, and baseline eosinophilia was also higher in SINUS [85,86], SYNAPSE [85,86], and OSTRO [60] than

in POLYP [81,82].

Conclusion

Currently, biological therapy is not as cost-effective in the management of CRS as FESS (4), although this may change as their patents begin to expire. Looking forwards, dupilumab is set to expire in September 2032, but cost-efficiency gains may be on the horizon for omalizumab, which has come off patent in Europe earlier this year in March 2024, potentially paving the way for more regular clinical use.

Consent for publication

Not applicable.

Availability of data and materials

All data extracted from the included papers is publicly available from the original journals.

Conflict of interest

The authors have no conflicts of interest to declare.

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Authors' contributions

DP, JSM, VA and PA were involved in the acquisition, analysis and interpretation of data. Systematic screening and data extraction were conducted in parallel by JSM and DP. All statistical analyses were conducted by JSM. All figures were produced by JSM. DP, JSM, VA and PA were involved in the drafts and revisions during the writing process, in the final approval of the article before submission to Rhinology and are all accountable for all aspects of this work in ensuring that any questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved.

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Dhruv Patel
Luton and Dunstable Hospital
Bedfordshire Hospitals
NHS Foundation Trust
Luton
UK

E-mail: dhruv.patel14@nhs.net

Dhruv Patel[1], James S. Morris[2], Vikas Acharya[3], Peter Andrews[3]

[1] Luton and Dunstable Hospital, Bedfordshire Hospitals NHS Foundation Trust, Luton, UK

[2] University Hospital of Wales, Cardiff and Vale Health Board, Cardiff, Wales, UK

[3] Royal National ENT and Eastman Dental Hospitals, University College London Hospitals NHS Foundation Trust, London, UK

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SUPPLEMENTARY MATERIAL

Appendix 1. Detailed search strategies.

Database:	Ovid MEDLINE(R) ALL <1946 to April 25, 2024>	Results per line:	Number of results:
Date:	26/04/2024		
1	rhinitis/ or rhinosinusitis/ or exp sinusitis/	31106	**203**
2	(sinusitis or rhinosinusitis or rhinitis or CRSwNP or CRSsNP).ti,ab,kw,kf.	60315	
3	1 or 2	68236	
4	antibodies, monoclonal/ or exp antibodies, monoclonal, humanized/	263417	
5	biological therapy/ or immunomodulation/ or immunotherapy/ or immunosuppression therapy/	115046	
6	((biologic* adj3 (therap* or factor* or intervention* or drug*)) or monoclonal antibod* or mAb or mAbs or cytokine* or immunotherapy or immunomodulation or monoclonal antibod*).ti,ab,kw,kf.	860732	
7	(Dupilumab or Omalizumab or Mepolizumab or Benralizumab or reslizumab or lebrikizumab or tralokinumab).ti,ab,kw,kf.	7670	
8	4 or 5 or 6 or 7	1038890	
9	(olfact* or smell or anosmia or hyposmia).ti,ab,kw,kf.	71240	
10	olfaction disorders/ or anosmia/	6309	
11	Smell/	18711	
12	(SNOT-22 RSOM-31 or UPSIT or "Sniffin' Sticks" or "Sniffin Sticks").ti,ab,kw,kf.	1606	
13	9 or 10 or 11 or 12	75973	
14	3 and 8 and 13	234	
15	editorial/	688611	
16	news/	224384	
17	exp historical article/	410414	
18	anecdotes as topic/	4747	
19	case reports/	2398491	
20	(letter or comment*).ti.	198991	
21	(abstract or comment or letter).pt.	1762988	
22	15 or 16 or 17 or 18 or 19 or 20 or 21	5072522	
23	14 not 22	221	
24	limit 23 to english language	203	

Appendix 1B. Detailed search strategies.

Database:	Embase <1974 to 2024 Week 16>	Results per line:	Number of results:
Date:	26/04/2024		
1	exp rhinitis/	114971	
2	(sinusitis or rhinosinusitis or rhinitis or CRSwNP or CRSsNP).ti,ab,kw,kf.	84079	
3	1 or 2	144260	
4	exp monoclonal antibody/	808815	
5	biological therapy/ or immunosuppressive treatment/ or immunotherapy/	362824	
6	((biologic* adj3 (therap* or factor* or intervention* or drug*)) or monoclonal antibod* or mAb or mAbs or cytokine* or immunotherapy or immunomodulation or monoclonal antibod*).ti,ab,kw,kf.	1210746	
7	(Dupilumab or Omalizumab or Mepolizumab or Benralizumab or reslizumab or lebrikizumab or tralokinumab).ti,ab,kw,kf.	14630	
8	4 or 5 or 6 or 7	1917590	
9	(olfact* or smell or anosmia or hyposmia).ti,ab,kw,kf.	86796	
10	smelling/ or orthonasal olfaction/ or retronasal olfaction/	14141	
11	smelling disorder/ or anosmia/ or hyposmia/	19223	
12	(SNOT-22 RSOM-31 or UPSIT or "Sniffin' Sticks" or "Sniffin Sticks").ti,ab,kw,kf.	2470	
13	9 or 10 or 11 or 12	96144	
14	3 and 8 and 13	607	
15	letter/ or case report/ or case study/	4065433	
16	(letter or comment*).ti.	244053	
17	(abstract or letter or editorial or note).pt.	8213972	
18	15 or 16 or 17	10623557	
19	14 not 18	375	
20	limit 19 to english language	360	

Appendix 1C. Detailed search strategies.

Database:	Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR)	Results per line:	Number of results:
Date:	26/04/2024		
#1	MeSH descriptor: [Rhinitis] explode all trees	5079	**CENTRAL: 126 CDSR: 1**
#2	MeSH descriptor: [Sinusitis] explode all trees	1517	
#3	(sinusitis or rhinosinusitis or rhinitis or CRSwNP or CRSsNP):ti,ab,kw	14999	
#4	{OR #1-#3}	14999	
#5	MeSH descriptor: [Antibodies, Monoclonal] explode all trees	21642	
#6	MeSH descriptor: [Biological Therapy] this term only	98	
#7	MeSH descriptor: [Immunomodulation] explode all trees	12679	
#8	MeSH descriptor: [Immunotherapy] explode all trees	12072	
#9	MeSH descriptor: [Immunosuppression Therapy] explode all trees	2960	
#10	((biologic* NEAR/3 (therap* or factor* or intervention* or drug*)) or monoclonal antibod* or mAb or mAbs or cytokine* or immunotherapy or immunomodulation or monoclonal antibod*):ti,ab,kw	62424	
#11	(Dupilumab or Omalizumab or Mepolizumab or Benralizumab or reslizumab or lebrikizumab or tralokinumab):ti,ab,kw	3300	
#12	{OR #5-#11}	79657	
#13	(olfact* or smell or anosmia or hyposmia):ti,ab,kw	3725	
#14	MeSH descriptor: [Olfaction Disorders] explode all trees	267	
#15	MeSH descriptor: [Smell] explode all trees	481	
#16	(SNOT-22 RSOM-31 or UPSIT or "Sniffin' Sticks" or "Sniffin Sticks"):ti,ab,kw	287	
#17	{OR #13-#16}	3734	
#18	#4 and #12 and #17	127	
#19	#18 in Cochrane Reviews	1	
#20	#18 in Trials	126	

Table S2. Summary of main findings from meta-analysis of RCTs.

Outcome	Biologic Cohort		Cohort Control		Test of Group Difference
	No. Papers (No. Pts)	Change (95% CI)	No. Papers (No. Pts)	Change (95% CI)	
UPSIT	8 (699)	+7.74 [4.49 – 11.00]	8 (685)	+0.25 [-0.37 – 0.86]	χ^2 =19.65, p<0.01
VAS Olfaction (0-10 Likert Scale)	8 (919)	-2.35 [-0.68 – -4.02]	8 (902)	-0.10 [-0.54 – 0.35]	χ^2 =6.52, p =0.01
SNOT-22	9 (905)	-24.98 [-21.41 – -28.55]	9 (891)	-8.98 [-7.65 – -10.32]	χ^2 =67.65, p<0.01
Bilateral NPS (0-8)	10 (959)	-1.57 [-0.75 – -2.39]	10 (942)	- 0.12 [-0.36 – 0.12]	χ^2 =11.10, p <0.01
NPIF (ml/min)	3 (229)	+43.90 [15.72 – 72.09]	3 (234)	+19.30 [13.21 – 25.39]	χ^2 =2.80, p =0.09
Lund-Mackay Score	5 (358)	+6.95 [5.18 – 8.72]	5 (356)	+2.63 [-1.54 – 6.81]	χ^2 =3.48, p=0.06

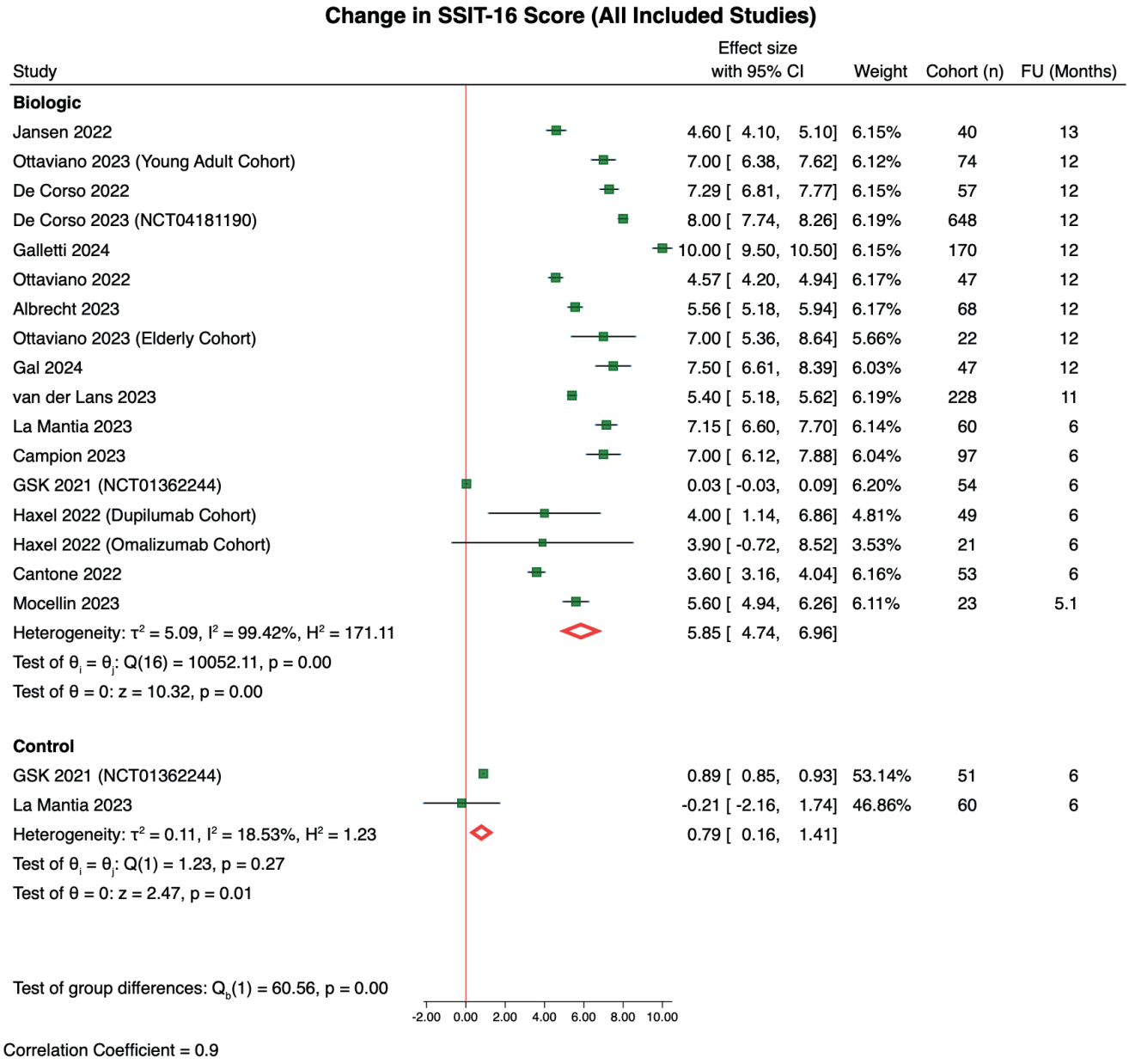

Figure S1. Forest plot for the change in SSIT-16 score within the biologic and control cohorts across all included studies (RCTs and non-RCTs).

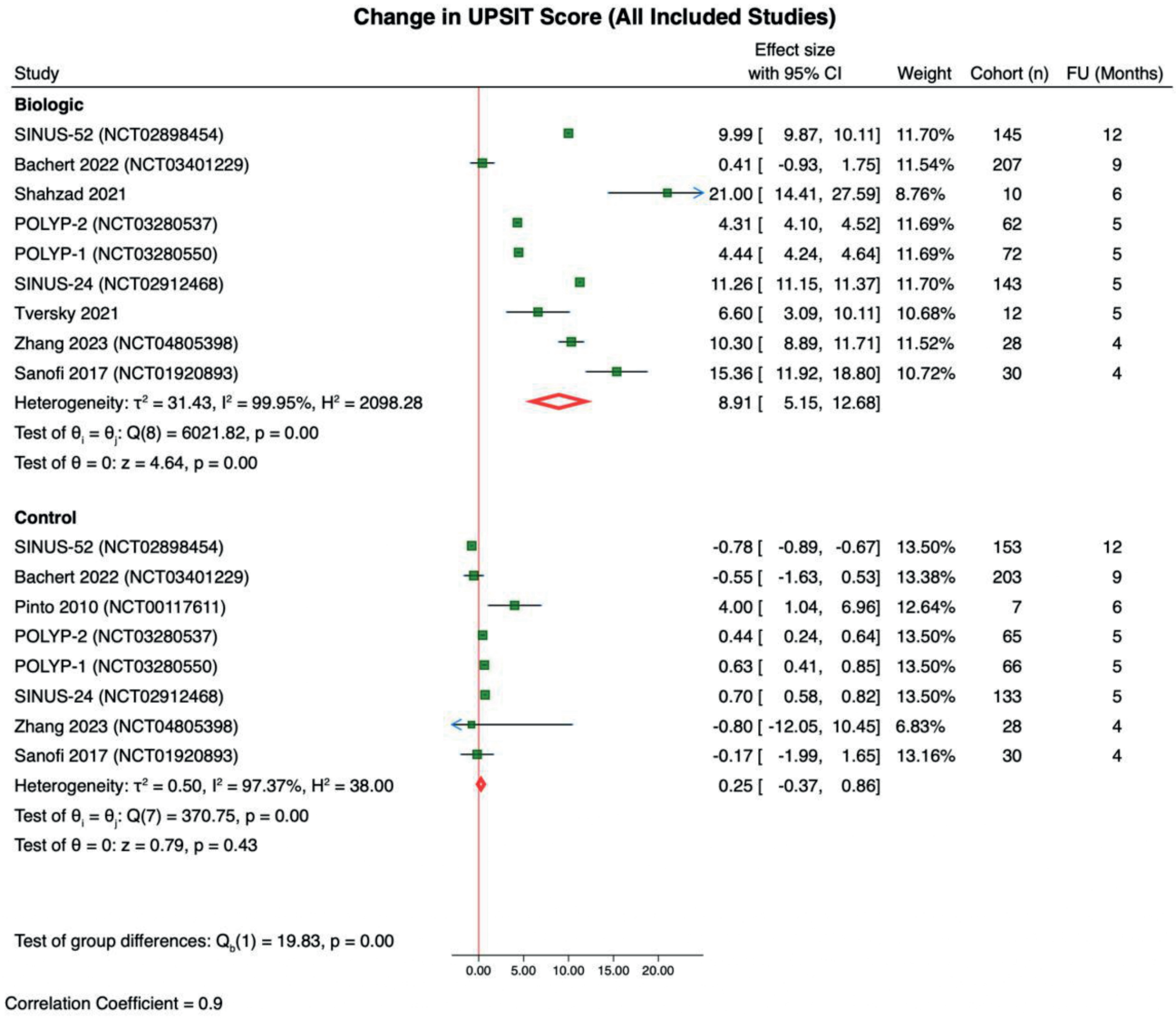

Figure S2. Forest plot for the change in UPSIT score within the biologic and control cohorts across all included studies (RCTs and non-RCTs).

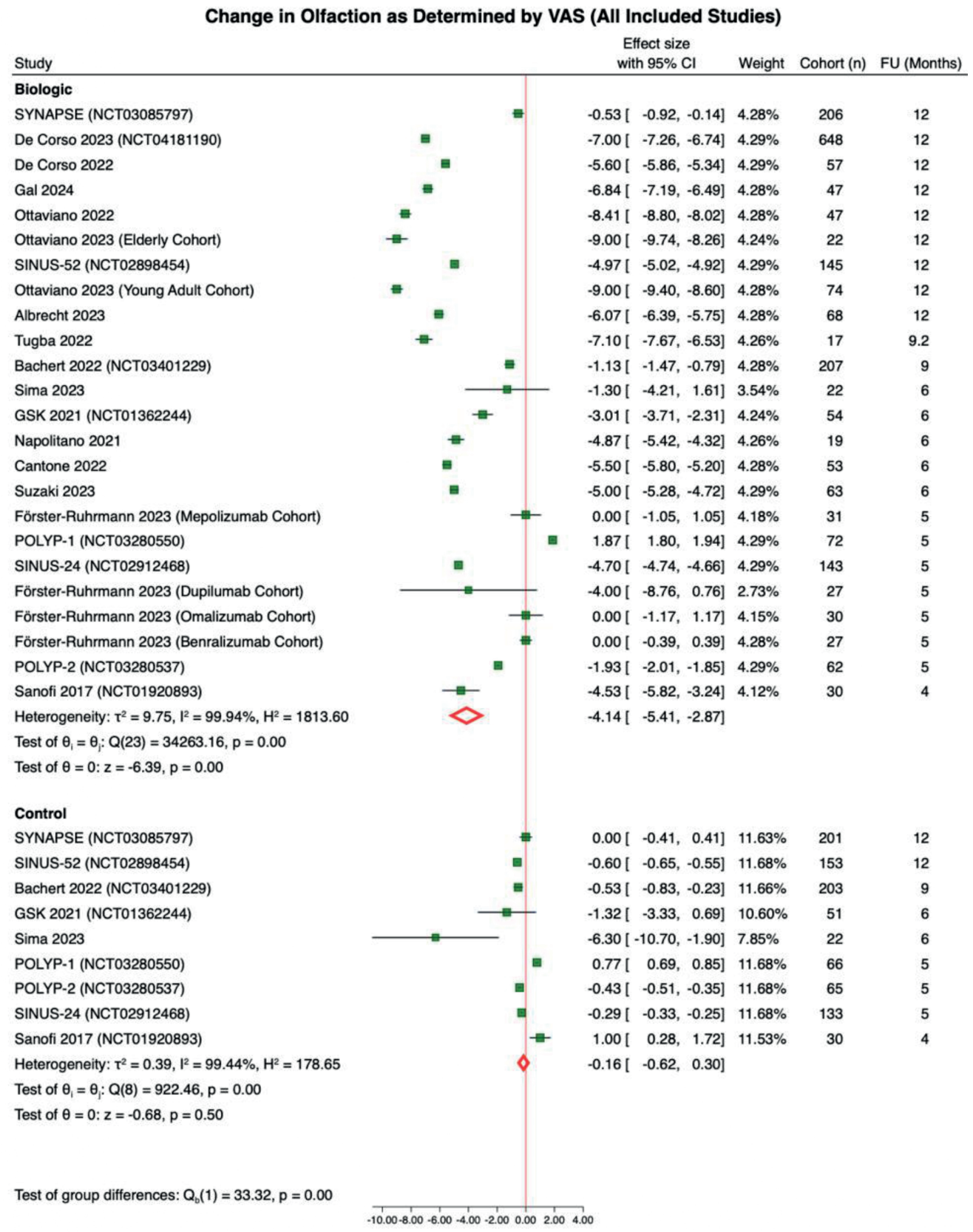

Figure S3. Forest plot for the change in VAS score within the biologic and control cohorts across all included studies (RCTs and non-RCTs).

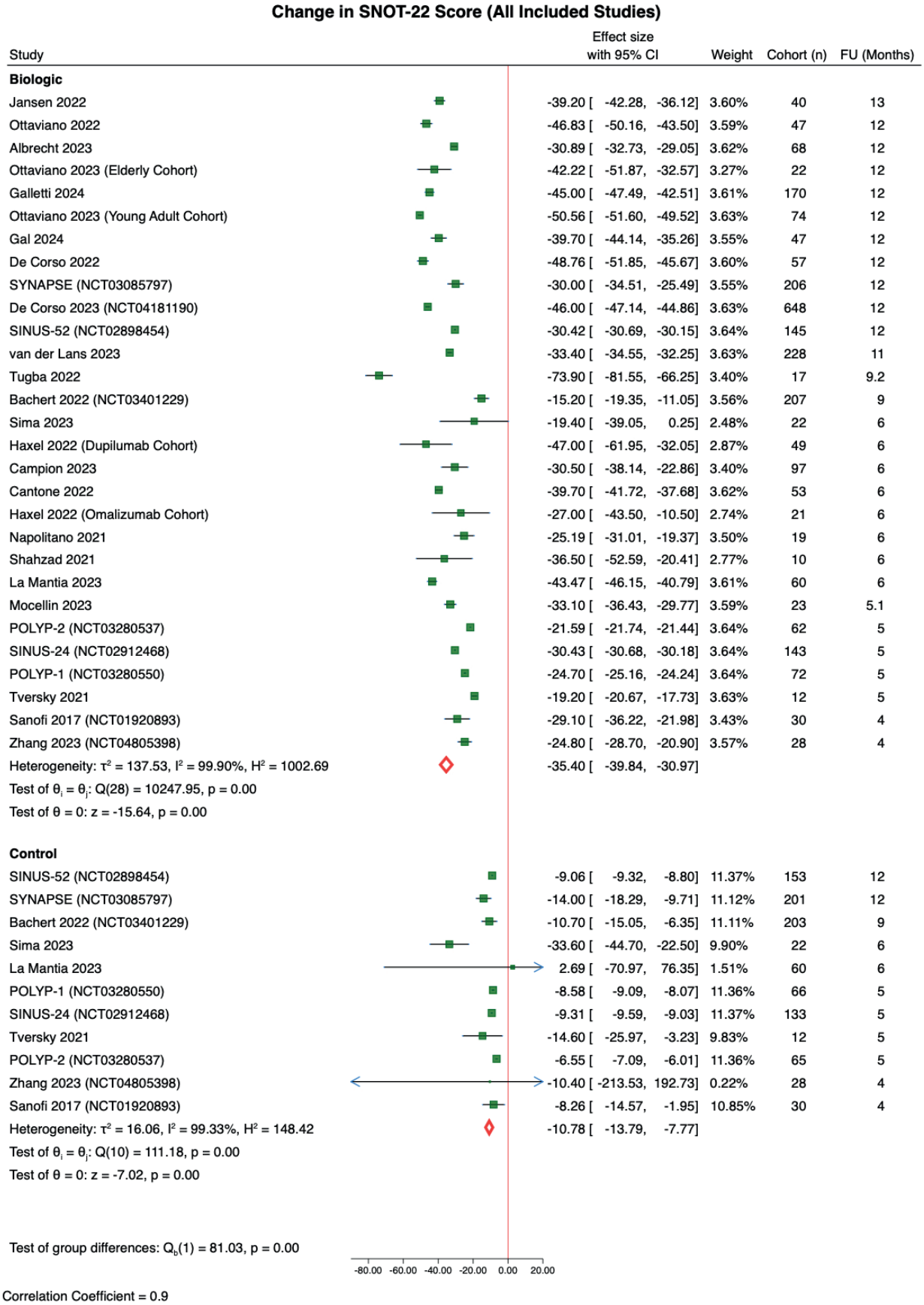

Figure S4. Forest plot for the change in SNOT-22 score within the biologic and control cohorts across all included studies (RCTs and non-RCTs).

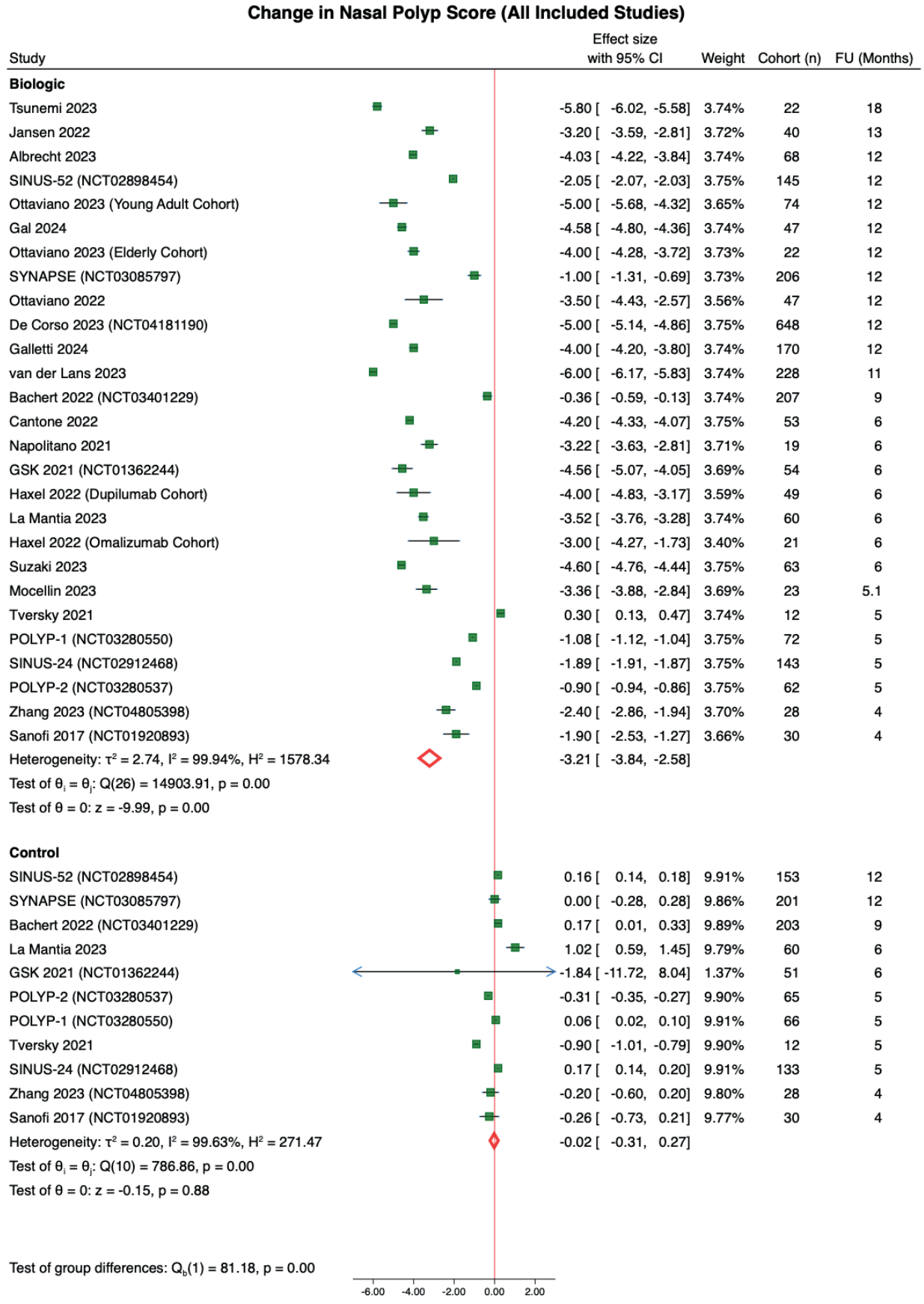

Figure S5. Forest plot for the change in NPS score within the biologic and control cohorts across all included studies (RCTs and non-RCTs).

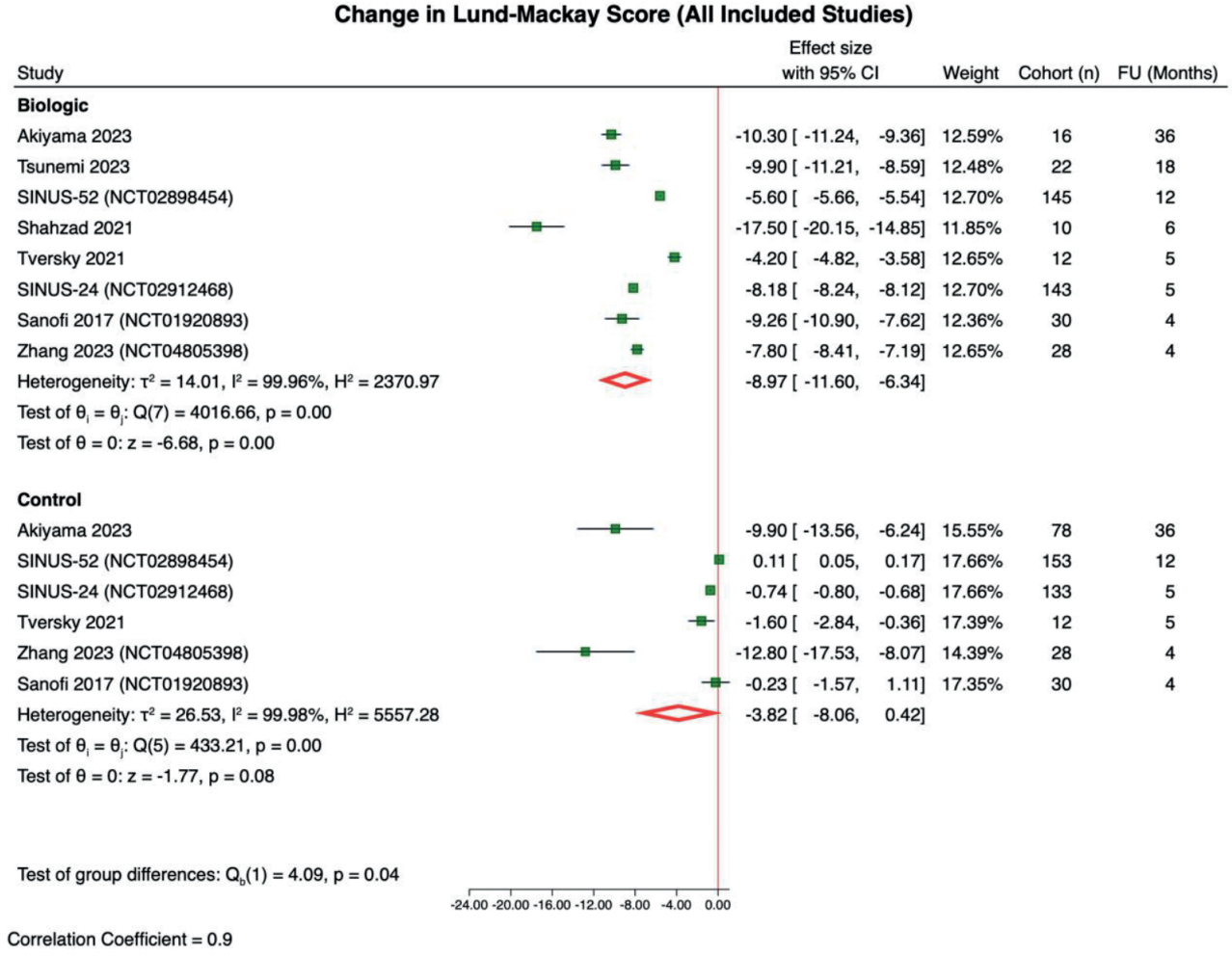

Figure S6. Forest plot for the change in Lund-Mackay score within the biologic and control cohorts across all included studies (RCTs and non-RCTs).

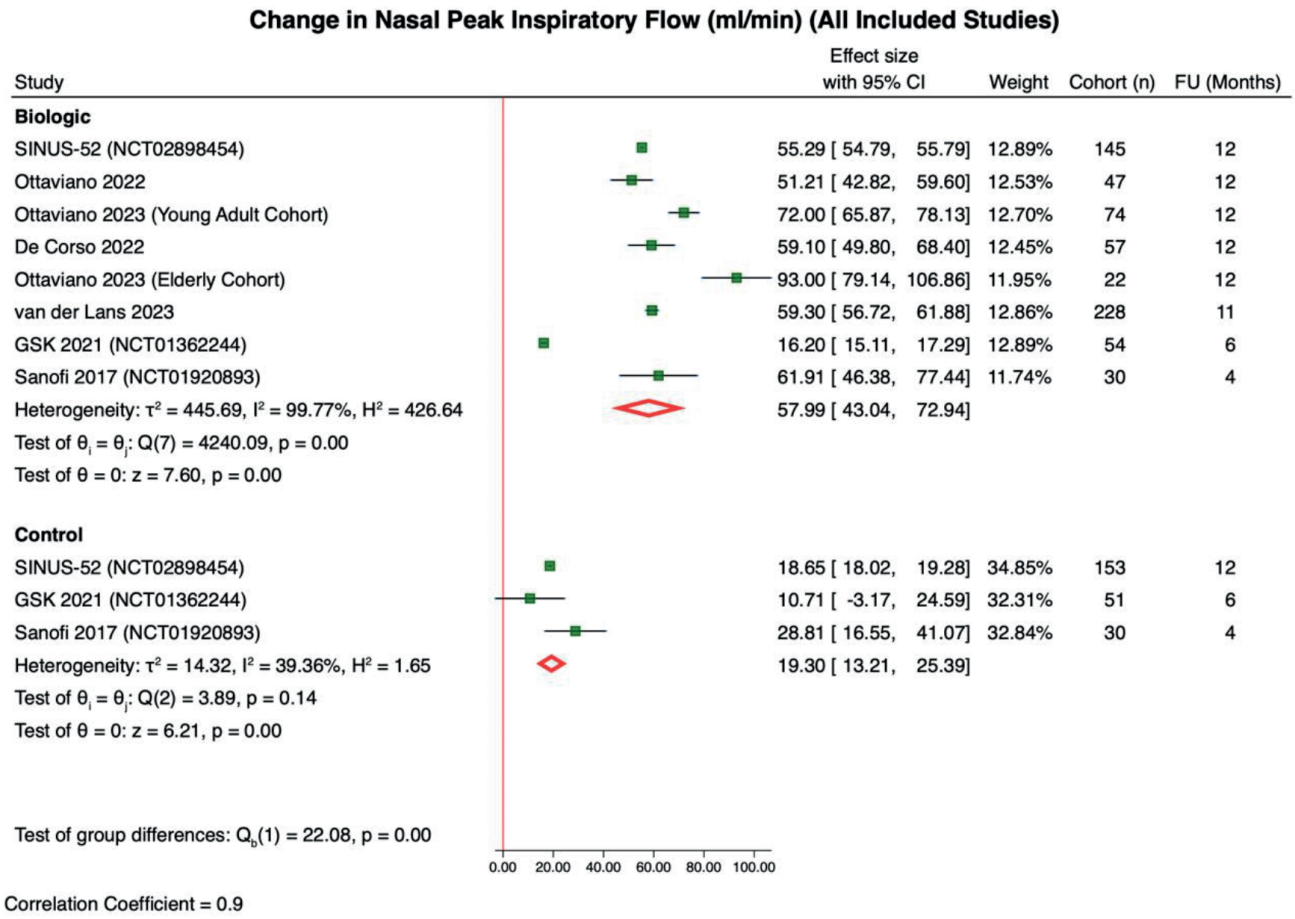

Figure S7. Forest plot for the change in NPIF score within the biologic and control cohorts across all included studies (RCTs and non-RCTs).

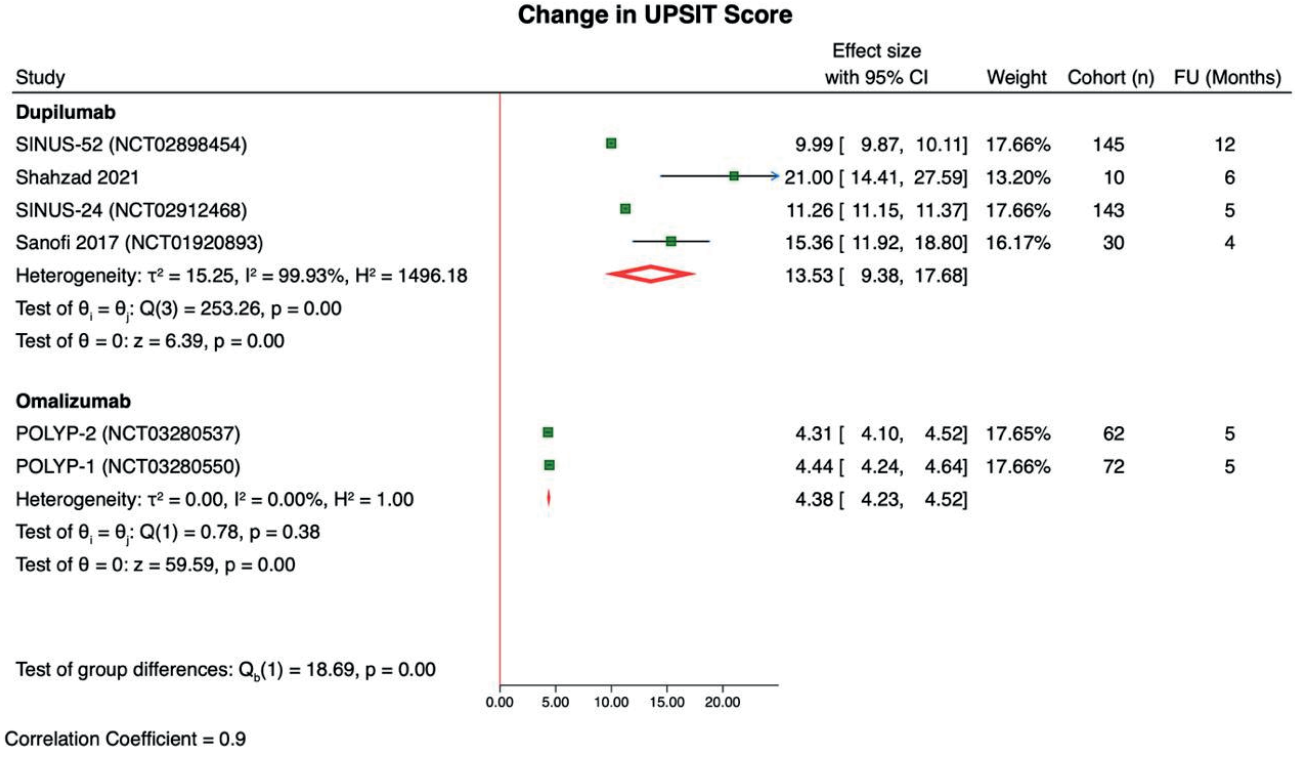

Figure S8. Forest plot for the change in UPSIT score comparing Dupilumab vs Omalizumab across all studies.

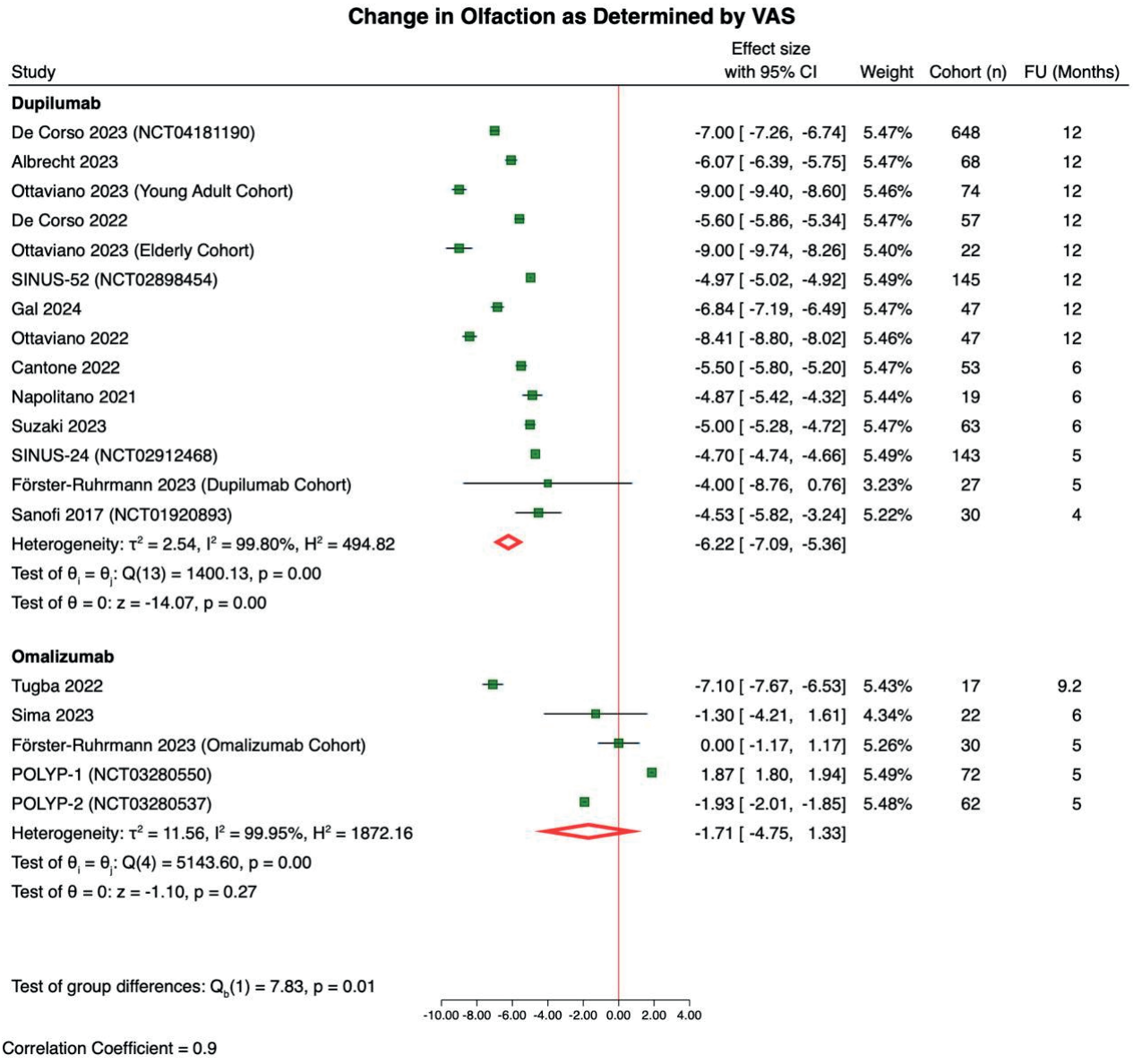

Figure S9. Forest plot for the change in VAS score comparing Dupilumab vs Omalizumab across all studies.

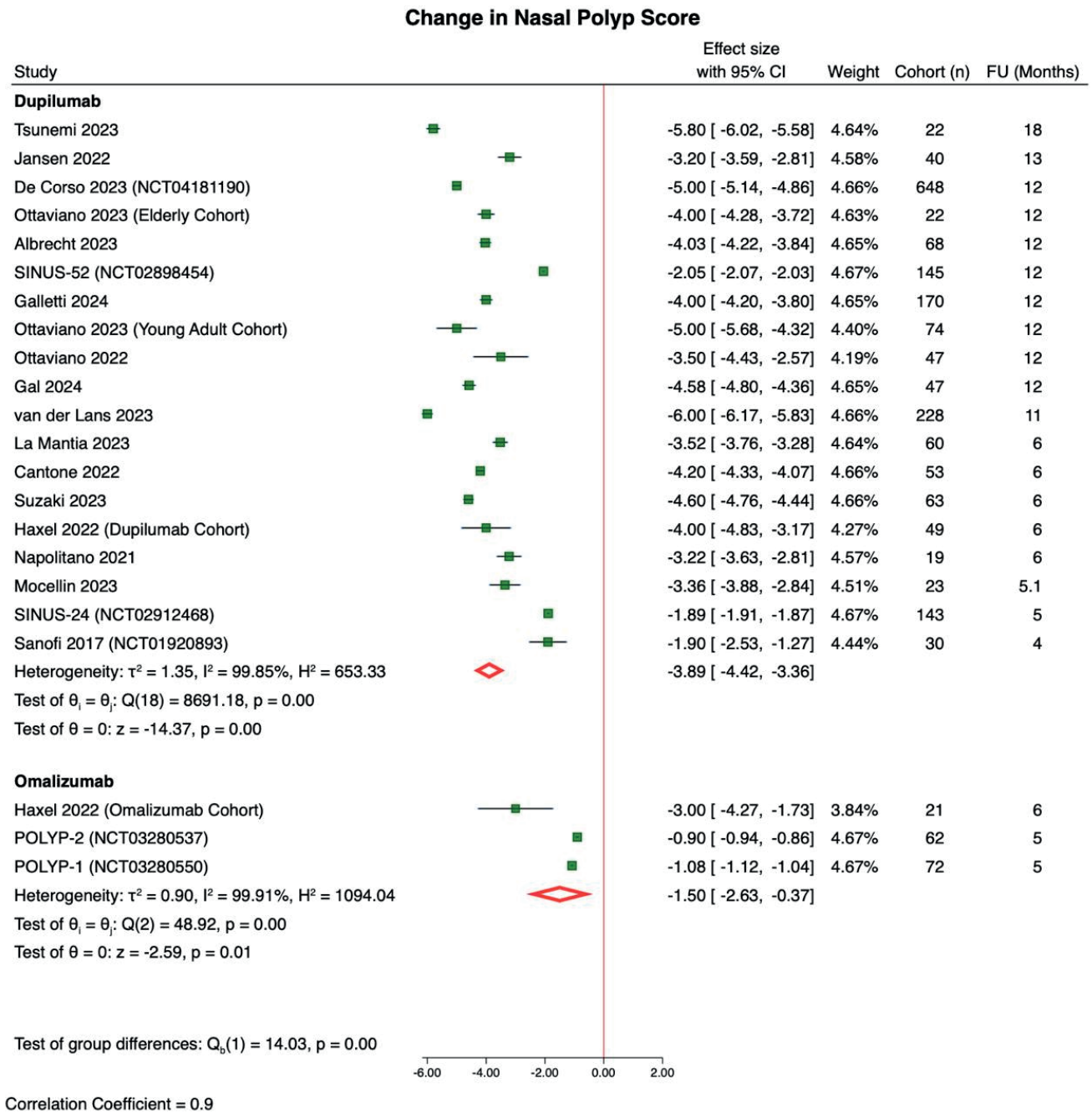

Figure S10. Forest plot for the change in nasal polyp score comparing Dupilumab vs Omalizumab across all studies.

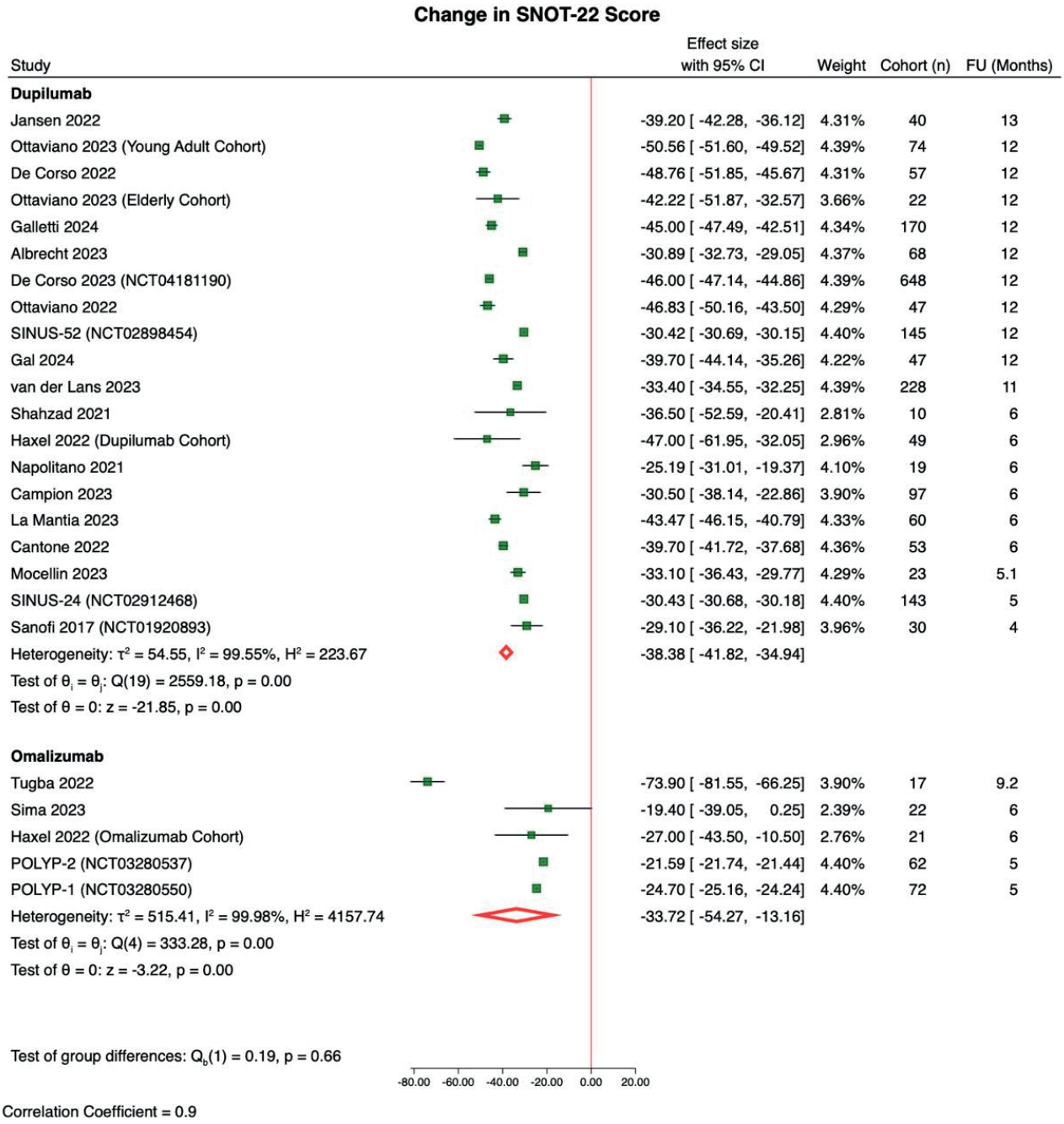

Figure S11. Forest plot for the change in SNOT-22 score comparing Dupilumab vs Omalizumab across all studies.

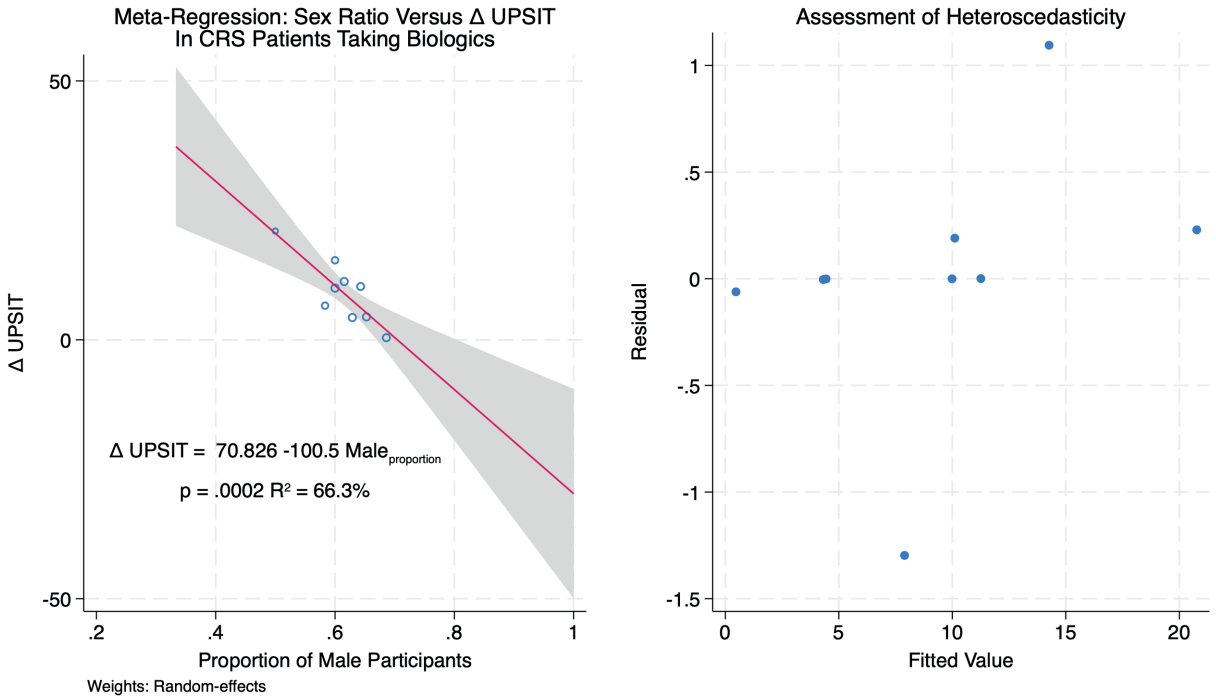

Figure S12. Meta regression for the change in UPSIT score in the biologic cohort of included RCTs against the sex ratio of the cohort.

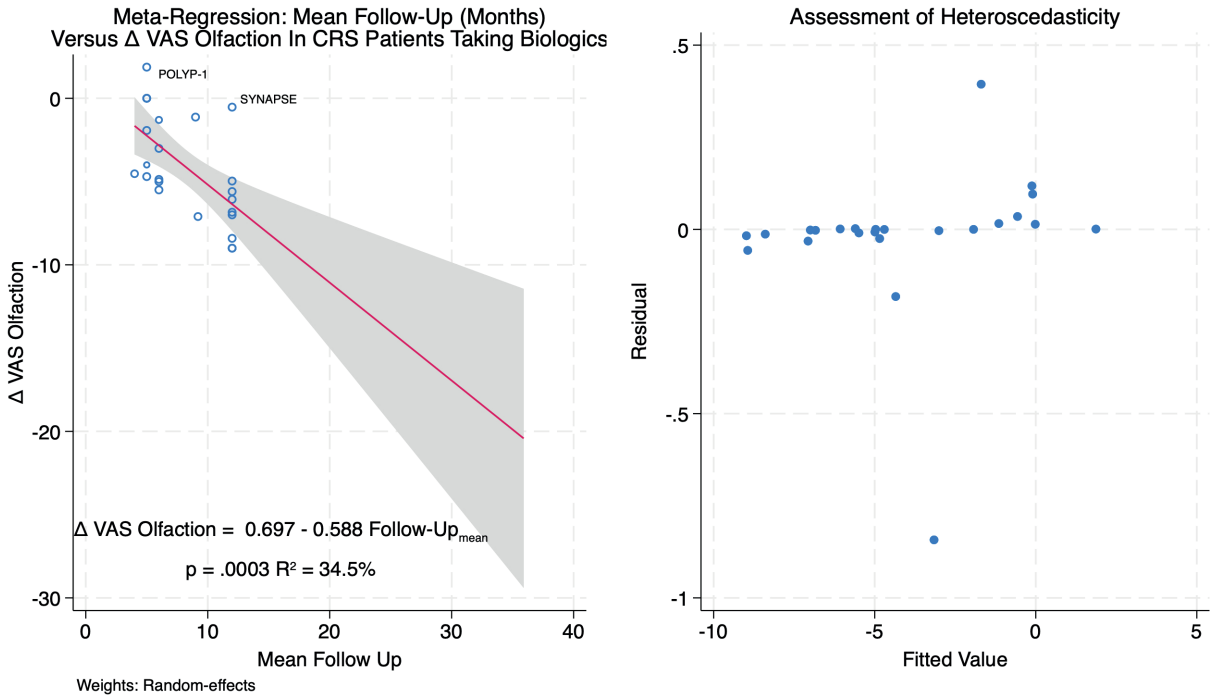

Figure S13. Meta regression for the change in VAS olfaction in the biologic cohort of included RCTs against the mean duration of follow up.

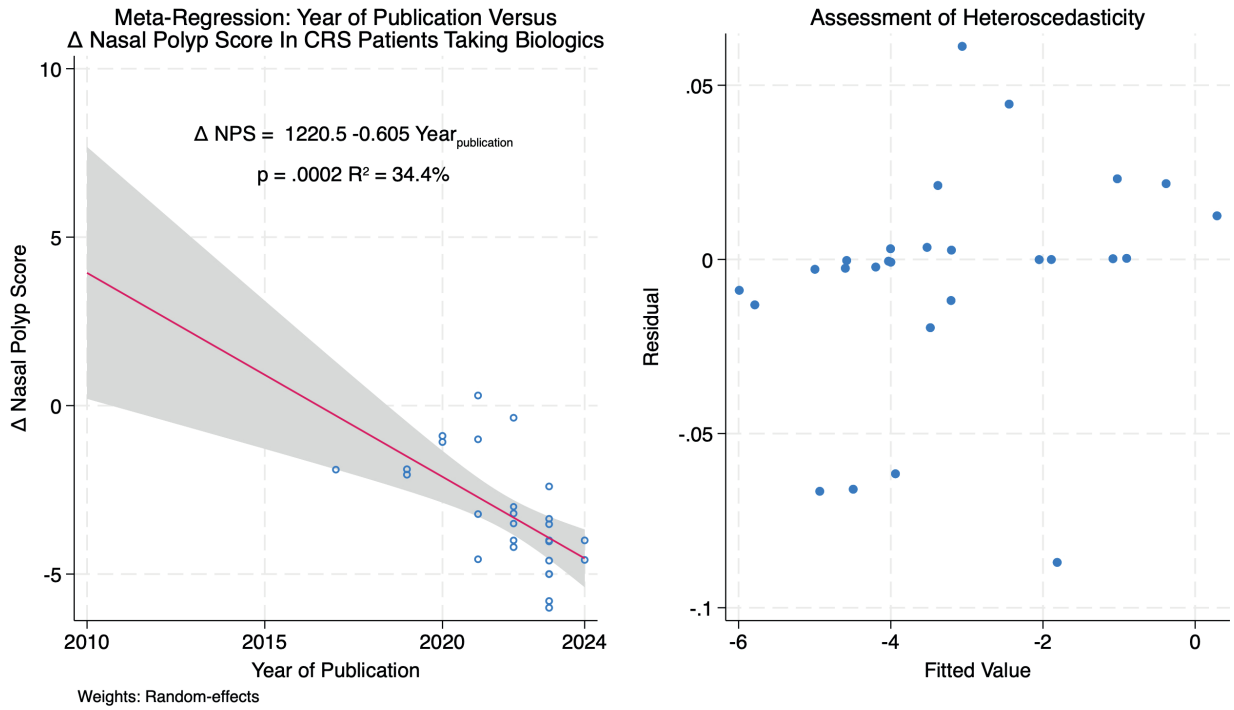

Figure S14. Meta regression for the change in nasal polyp score in the biologic cohort of included RCTs against the year of publication.

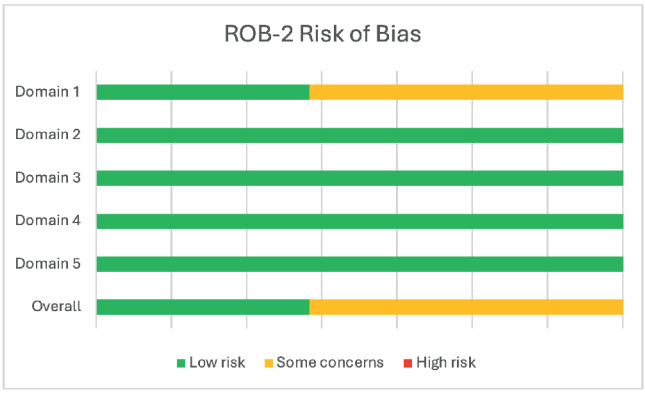

Figure S15. The risk of bias assessment for the included randomised studies.

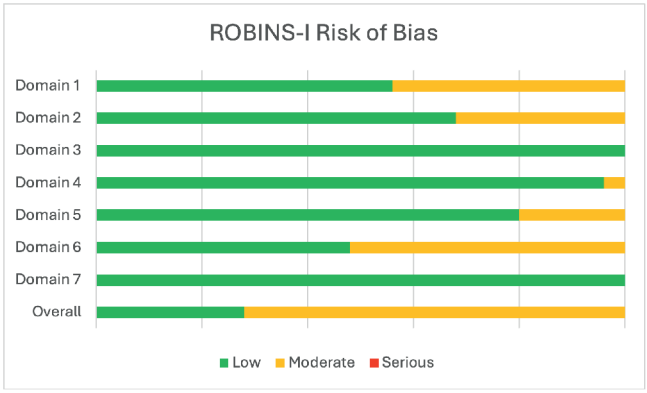

Figure S16. The risk of bias assessment for the included non-randomised studies.

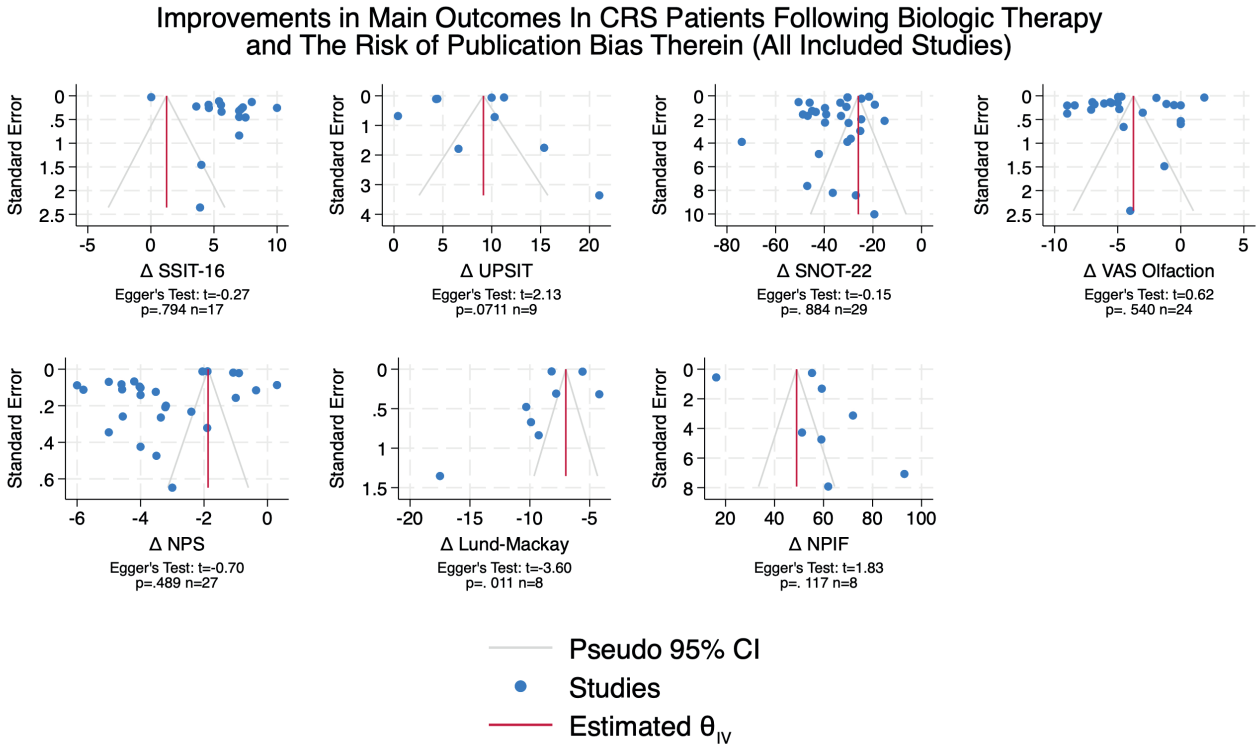

Figure S17. Funnel plots for the change in SSIT-16, UPSIT score, SNOT-22 score, VAS olfaction, nasal polyp score, Lung-Mackay score and nasal peak inspiratory flow rate for the biologic cohorts of included RCTs against the standard errors therein.