

Factors associated with olfactory recovery under biologic therapy in chronic rhinosinusitis with nasal polyps: the BIOPPOSE prospective multicentre cohort

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Research Article

Keywords: Chronic rhinosinusitis with nasal polyps, Olfaction disorders, Biological therapy, Dupilumab, Glucocorticoids, Prognosis

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11001342/v1>

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Additional Declarations: No competing interests reported.

Abstract

Purpose

Olfactory loss is a leading reason for initiating biologic therapy in chronic rhinosinusitis with nasal polyps (CRSwNP), yet 24–30% remain anosmic under dupilumab in the pivotal trials. We aimed to identify factors associated with olfactory recovery at 12 months.

Methods

In the BIOPOSE phase IV prospective multicentre cohort (15 French centres), adults initiating dupilumab or mepolizumab with an evaluable 12-month olfactory visual analogue scale (VAS) were analysed. Recovery was defined a priori as a 12-month VAS $\leq 20/100$ or a reduction of ≥ 50 points. Each factor was entered in a separate logistic model adjusted for age, sex and smoking status, with Firth's penalisation when near-separation occurred.

Results

Of 427 patients analysed, 116 had an evaluable 12-month outcome; 70 recovered (60.3%; 95% CI 51.2 to 68.8). A prior olfactory response to systemic corticosteroids was more frequent in recoverers (63.3% vs 8.3%) and remained associated after adjustment (adjusted odds ratio 9.65, 95% CI 1.48 to 62.86; $p = 0.018$; $n = 42$). Dupilumab rather than mepolizumab was likewise associated with recovery (82.9% vs 60.9%; adjusted odds ratio 3.82, 95% CI 1.55 to 9.41; $p = 0.004$). No other factor, including prior surgery and baseline eosinophils, showed a detectable association.

Conclusion

A prior olfactory response to systemic corticosteroids and dupilumab initiation were associated with olfactory recovery. Both estimates remain fragile – the corticosteroid subgroup was small and confounding by indication cannot be excluded – and warrant prospective confirmation before a corticosteroid test can guide counselling and biologic choice.

Trial registration

ClinicalTrials.gov NCT05228041

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disease of the upper airways driven by type 2 inflammation. Olfactory loss is one of its most frequent and most disabling symptoms, reported in 64% of patients with nasal polyps in a large real-life series [1], and it substantially impairs quality of life and general health [2]. Olfactory impairment is a major indication for initiating biologic therapy, in accordance with EPOS/EUFOREA criteria and, in France, with the marketing authorisation and reimbursement conditions [3–5].

Biologic agents — dupilumab (anti-IL-4R α) and mepolizumab (anti-IL-5) — have demonstrated significant improvements in disease control, endoscopic scores and quality of life in severe uncontrolled CRSwNP, whether used alone or in combination with surgery [6, 7]. Nevertheless, 24% to 30% of patients remained anosmic after 24 weeks of dupilumab in the pivotal trials [6].

Several structural and inflammatory factors are known to influence olfactory function in CRSwNP, including comorbid asthma, smoking, elevated total IgE and tissue eosinophilia [8, 9]. Under biologic therapy, and particularly under dupilumab, olfactory recovery appears to be driven by resolution of type 2 inflammation rather than by mere polyp volume reduction [10]. A prior responsiveness to systemic corticosteroids has been proposed as a positive prognostic marker for olfactory recovery [11, 12], whereas a history of repeated endoscopic sinus surgery has been associated with poorer olfactory outcomes even after biologic initiation [13].

Despite these insights, the prognostic factors for olfactory recovery under biologic therapy remain poorly defined. The aim of this study was to identify clinical, inflammatory and surgical factors associated with olfactory recovery at 12 months in patients with severe uncontrolled CRSwNP treated with biologic therapy, using data from the BIOPOSE (BIOlogics in severe nasal POLyposis SurvEy) prospective multicentre cohort.

Methods

Study design and population

BIOPOSE is a phase IV, real-life, observational, prospective cohort study conducted across 15 tertiary care centres in France (NCT05228041); its protocol has been published in full [14]. Patients treated with biologic therapy for severe uncontrolled CRSwNP were enrolled between August 2021 and December 2022. Pseudonymised data were collected at baseline (M0), 3 months (M3), 6 months (M6) and 12 months (M12). The study conformed to the Declaration of Helsinki, the French Public Health Code and European Union Good Clinical Practice guidelines. Reporting followed the STROBE statement for observational studies.

Inclusion, non-inclusion and exclusion criteria

Adults (≥ 18 years) with severe uncontrolled CRSwNP who had initiated biologic therapy (dupilumab or mepolizumab) within the marketing authorisation and reimbursement conditions were eligible. Patients were not included if they had an alternative aetiology of anosmia (post-traumatic, neurodegenerative or post-infectious causes unrelated to CRSwNP), a documented SARS-CoV-2 infection with olfactory impairment within the preceding three months, current pregnancy or breastfeeding, or a baseline olfactory VAS $\leq 20/100$, that is, normal olfaction at enrolment – a criterion that applied to 39 of the patients assessed for eligibility. Patients already enrolled were subsequently excluded if they received oral corticosteroids or underwent sinus surgery between two consecutive study visits (M0–M6 or M6–M12). The present analysis was further restricted to patients with an evaluable 12-month outcome, requiring an olfactory visual analogue scale (VAS) at both M0 and M12, or a 12-month VAS $\leq 20/100$.

Data collection

The following variables were collected: demographic and clinical data (age, sex, disease duration, comorbid asthma, smoking status, number and type of prior endoscopic sinus surgeries); inflammatory and biological parameters (blood eosinophil count, total IgE, biologic agent received); imaging data (Lund-Mackay score); olfactory VAS scores at baseline and 12 months; and a prior olfactory response to systemic corticosteroids, recorded prospectively at baseline as days of subjective improvement after an oral corticosteroid course and dichotomised as any improvement versus none (primary candidate predictor). The Global Initiative for Asthma (GINA) 2021 asthma-treatment step at baseline was additionally analysed as an exploratory covariate.

Outcome measures

The primary outcome was olfactory recovery at 12 months, defined as an olfactory VAS $\leq 20/100$ or a reduction of ≥ 50 points from baseline. Secondary analyses examined candidate prognostic factors in univariate and adjusted models.

Statistical analysis

Continuous variables were described using means and standard deviations, or medians and interquartile ranges, and categorical variables using frequencies and percentages. Recoverers and non-recoverers were compared using Student's t-test or the Mann-Whitney U test for continuous variables and the chi-squared or Fisher's exact test for categorical variables, as appropriate. The association between each candidate factor and olfactory recovery was then quantified by binary logistic regression, with olfactory recovery at 12 months as the dependent variable, and expressed as odds ratios (OR) with 95% Wald confidence intervals; Firth's penalised logistic regression was used when near-separation occurred. Because the number of events and the extent of missing data varied markedly across predictors, a single model including all covariates would have been unstable. Each candidate factor was therefore entered in a separate logistic model adjusted for age, sex and smoking status, reported alongside the crude

estimates. For the GINA asthma-treatment step, smoking status was not estimable and the corresponding model was adjusted for age and sex only. Odds ratios for disease duration are expressed per year. Absolute standardised differences ≥ 0.20 were considered important when comparing patients with and without an evaluable olfactory VAS. A p-value of less than 0.05 was considered statistically significant; given the exploratory nature of the analyses, no correction for multiple testing was applied. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Study population and patient flow

Between August 2021 and December 2022, 922 patients were assessed for eligibility across the 15 participating centres and 431 were included; 39 of the patients not included had a baseline olfactory VAS $\leq 20/100$, that is, normal olfaction at enrolment. Four patients were subsequently excluded during follow-up, leaving 427 patients in the BIOPOSE cohort. A total of 311 patients were excluded from the present analysis for lack of an evaluable 12-month olfactory VAS. Thus, 116 patients had an evaluable 12-month olfactory VAS and were analysed, of whom 70 (60.3%) achieved olfactory recovery and 46 (39.7%) did not (Fig. 1). These 116 patients differed from the 311 with no available olfactory evaluation on five of thirteen baseline variables (Fig. 2), the largest difference being the GINA asthma-treatment step (0.35): among those with an available step, 22/69 (31.9%) versus 51/122 (41.8%) were at step 1, and 21/69 (30.4%) versus 27/122 (22.1%) at step 4 or 5.

Baseline characteristics

Baseline characteristics of the study population, overall and stratified by olfactory recovery status, are summarised in Table 1. Among the 116 analysed patients, the mean age was 54.0 years (SD 12.5), 55 (47.4%) were women and 12/116 (10.3%) were current smokers. Comorbid asthma was present in 84/116 (72.4%) and a history of ethmoidectomy (i.e. sinonasal surgery beyond isolated polypectomy) in 95/114 (83.3%), the remaining 19 having undergone isolated polypectomy only; the median number of prior sinonasal procedures was 1 (Q1–Q3 1–2) and the mean disease duration 20.1 years (SD 12.2). The mean baseline blood eosinophil count was 473.7 cells/ μL (SD 339.5, $n = 97$), the mean Lund-Mackay score 13.7 (SD 6.8, $n = 70$) and the mean total IgE 255.8 IU/mL (SD 392.3, $n = 63$). Dupilumab was the most frequently initiated biologic (86/116, 74.1%), followed by mepolizumab (30/116, 25.9%). A prior olfactory response to systemic corticosteroids was documented in 20/42 patients with available data (47.6%).

Table 1

Baseline characteristics of the 116 analysed patients, overall and stratified by olfactory recovery status at 12 months

Variable	Total (N = 116)	Recoverers (n = 70)	Non-recoverers (n = 46)	p (test)
Age, years – mean (SD)	54.0 (12.5)	52.8 (11.9)	56.0 (13.3)	0.17 (t-test)
Female sex – n (%)	55/116 (47.4)	30/70 (42.9)	25/46 (54.3)	0.23 (chi ²)
Disease duration, years – mean (SD)	20.1 (12.2)	18.8 (11.2)	22.1 (13.5)	0.28 (MWU)
Current smoker – n (%)	12/116 (10.3)	5/70 (7.1)	7/46 (15.2)	0.22 (Fisher)
Comorbid asthma – n (%)	84/116 (72.4)	49/70 (70.0)	35/46 (76.1)	0.47 (chi ²)
History of ethmoidectomy – n (%)	95/114 (83.3)	59/70 (84.3)	36/44 (81.8)	0.73 (chi ²)
No. of sinonasal procedures (ethmoidectomy or polypectomy) – median (Q1–Q3)	1 (1–2)	1 (1–2)	1 (1–3)	1.00 (Wilcoxon)
Lund-Mackay score – mean (SD)	13.7 (6.8)	13.2 (6.6)	14.9 (7.2)	0.27 (MWU)
Olfactory VAS at M0 – median (Q1–Q3)	100 (94.5–100), n = 104	100 (90.0–100), n = 58	100 (100–100), n = 46	–
Olfactory VAS at M12 – median (Q1–Q3)	25.0 (0.0–72.5)	9.0 (0.0–20.0)	97.5 (70.0–100)	–
Blood eosinophils M0, cells/μL – mean (SD)	473.7 (339.5)	470.6 (316.2)	477.7 (371.7)	0.82 (MWU)
Total IgE, IU/mL – mean (SD)	255.8 (392.3)	237.1 (296.0)	293.2 (543.5)	0.92 (MWU)
Prior corticosteroid olfactory response – n (%) yes	20/42 (47.6)	19/30 (63.3)	1/12 (8.3)	0.001 (chi ²)
Biologic initiated: dupilumab – n (%)	86/116 (74.1)	58/70 (82.9)	28/46 (60.9)	0.008 (chi ²)
Biologic initiated: mepolizumab – n (%)	30/116 (25.9)	12/70 (17.1)	18/46 (39.1)	–
Blood eosinophils M12, cells/μL – mean (SD)	487.6 (485.1)	558.5 (506.1)	377.4 (436.9)	0.065 (MWU)

Continuous variables are reported as mean (SD) or median (Q1–Q3), as appropriate, with n = patients with available data; categorical variables as n (%). Denominators reflect available data. IgE

immunoglobulin E, M0 baseline, M12 12 months, MWU Mann-Whitney U, SD standard deviation. Aspirin-exacerbated respiratory disease and the Nasal Polyp Score were not available in the cohort and are not reported. No p-value is given for the olfactory VAS, which defines the outcome; 12 recoverers had no baseline value.

Olfactory recovery at 12 months

At 12 months, olfactory recovery — defined a priori as an olfactory VAS $\leq 20/100$ or a reduction of ≥ 50 points from baseline — was achieved by 70 of 116 patients (60.3%; 95% CI 51.2 to 68.8, Wilson score interval); the remaining 46 (39.7%) did not recover (Fig. 3a). Fifty-four met the reduction criterion, 55 the normalisation criterion and 39 both (Fig. 3b).

Univariate analysis of factors associated with olfactory recovery

On univariate analysis (Table 1), two baseline factors were significantly associated with olfactory recovery. First, a prior olfactory response to systemic corticosteroids was strongly associated with recovery: among patients with this information available, 19/30 recoverers (63.3%) had previously reported olfactory improvement on oral corticosteroids, compared with only 1/12 non-recoverers (8.3%) ($p = 0.001$, chi-squared). Second, the biologic agent initiated differed between groups: dupilumab was initiated in 58/70 recoverers (82.9%) versus 28/46 non-recoverers (60.9%), whereas mepolizumab predominated among non-recoverers (39.1% vs 17.1%; $p = 0.008$, chi-squared).

None of the other candidate variables reached statistical significance. Current smoking was numerically less frequent among recoverers (7.1% vs 15.2%; $p = 0.22$, Fisher's exact), and neither sex (42.9% vs 54.3% women; $p = 0.23$) nor comorbid asthma (70.0% vs 76.1%; $p = 0.47$) showed any association. A history of ethmoidectomy was similarly frequent in both groups (84.3% vs 81.8%; $p = 0.73$), as was the number of prior sinonasal procedures (median 1 in both; $p = 1.00$). Age (52.8 vs 56.0 years; $p = 0.17$), disease duration (18.8 vs 22.1 years; $p = 0.28$), baseline blood eosinophil count (470.6 vs 477.7 cells/ μL ; $p = 0.82$), Lund-Mackay score (13.2 vs 14.9; $p = 0.27$), total IgE ($p = 0.92$) and GINA asthma-treatment step ($p = 0.11$) did not differ significantly between groups.

Two on-treatment (12-month) parameters were additionally examined. The blood eosinophil count at 12 months showed a non-significant trend towards higher values among recoverers (558.5 vs 377.4 cells/ μL ; $p = 0.065$, Mann-Whitney U). The biologic still ongoing at 12 months was strongly associated with recovery ($p < 0.001$, Fisher's exact): 87.1% of recoverers were still receiving dupilumab versus 54.3% of non-recoverers, and treatment had been discontinued in only 1.4% of recoverers versus 15.2% of non-recoverers.

Adjusted analysis of factors associated with olfactory recovery

Crude and adjusted odds ratios for each candidate factor are presented in Table 2 and Fig. 4. After adjustment for age, sex and smoking status, both factors identified on univariate analysis remained associated with olfactory recovery. A prior olfactory response to systemic corticosteroids was associated with a marked increase in the odds of recovery (adjusted OR 9.65, 95% CI 1.48 to 62.86; $p = 0.018$; $n = 42$), close to the crude value (OR 13.00, 95% CI 1.95 to 86.55; $p = 0.008$); both were obtained by Firth's penalised logistic regression. Initiation of dupilumab rather than mepolizumab was likewise associated with recovery, the adjusted estimate being slightly larger than the crude one (adjusted OR 3.82, 95% CI 1.55 to 9.41; $p = 0.004$ versus crude OR 3.11, 95% CI 1.32 to 7.33; $p = 0.010$).

None of the remaining candidate factors showed a detectable association with olfactory recovery, either before or after adjustment: history of ethmoidectomy (adjusted OR 1.09, 95% CI 0.38 to 3.08; $p = 0.88$), number of prior sinonasal procedures (adjusted OR 0.93 per procedure, 95% CI 0.68 to 1.27; $p = 0.64$), comorbid asthma (adjusted OR 0.57, 95% CI 0.23 to 1.45; $p = 0.24$), disease duration (adjusted OR 0.92 per year, 95% CI 0.83 to 1.03; $p = 0.14$), baseline blood eosinophil count, Lund-Mackay score, total IgE and GINA asthma-treatment step (all $p > 0.05$). Adjustment did not materially alter any of these estimates.

Table 2

Crude and adjusted odds ratios for candidate factors associated with olfactory recovery at 12 months

Variable	Comparison / unit	n	Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p
Prior corticosteroid olfactory response	yes vs no	42	13.00 (1.95–86.55)	0.008	9.65 (1.48–62.86)	0.018
Biologic initiated: dupilumab	vs mepolizumab	116	3.11 (1.32–7.33)	0.010	3.82 (1.55–9.41)	0.004
History of ethmoidectomy	yes vs no	114	1.19 (0.44–3.24)	0.73	1.09 (0.38–3.08)	0.88
Comorbid asthma	yes vs no	116	0.73 (0.31–1.71)	0.47	0.57 (0.23–1.45)	0.24
No. of sinonasal procedures	per procedure	101	0.97 (0.73–1.31)	0.86	0.93 (0.68–1.27)	0.64
Disease duration	per year	89	0.95 (0.86–1.03)	0.22	0.92 (0.83–1.03)	0.14
Blood eosinophils M0	per cell/ μ L	97	1.000 (0.999–1.001)	0.92	1.000 (0.998–1.001)	0.67
Lund-Mackay score	per point	70	0.96 (0.89–1.04)	0.35	0.96 (0.88–1.04)	0.29
Total IgE	per IU/mL	63	1.000 (0.998–1.001)	0.60	1.000 (0.998–1.001)	0.54
GINA asthma-treatment step	per step	69	1.35 (0.93–1.95)	0.11	1.37 (0.93–2.00) [†]	0.11

Each factor was entered in a separate binary logistic regression model with olfactory recovery at 12 months as the dependent variable; adjusted models included age, sex and smoking status as covariates. p values were obtained from Wald tests (type 3 analysis of effects for categorical factors) and may therefore differ slightly from the chi-squared and Mann-Whitney U tests reported in Table 1. The number of patients contributing to each model ranges from 42 to 116, so odds ratios are not directly comparable across factors. CI confidence interval, GINA Global Initiative for Asthma, IgE immunoglobulin E, M0 baseline, OR odds ratio. *Adjusted for age, sex and smoking status. [†]Adjusted for age and sex only (smoking status not estimable).

Discussion

In the BIOPOSE prospective multicentre cohort, olfactory recovery at 12 months was achieved by 60.3% of patients with severe uncontrolled CRSwNP treated with biologic therapy, a lower proportion than in

studies using a standardised olfactory test [6, 13]. Two factors were independently associated with recovery after adjustment for age, sex and smoking status: a prior olfactory response to systemic corticosteroids and initiation of dupilumab rather than mepolizumab. A higher blood eosinophil count at 12 months showed a trend in the same direction, whereas demographic, surgical and baseline inflammatory variables showed no detectable association. These findings are consistent with the emerging view that olfactory recovery under biologics is primarily driven by the reversibility of type 2 inflammation in the olfactory cleft rather than by structural disease burden.

The strongest signal in our cohort was the association between a prior olfactory response to systemic corticosteroids and subsequent recovery under biologic therapy (63.3% vs 8.3%; $p = 0.001$), which persisted after adjustment for age, sex and smoking status (adjusted OR 9.65, 95% CI 1.48 to 62.86; $p = 0.018$). This is in close agreement with Otten et al., who reported that steroid responsiveness predicts olfactory function recovery in dupilumab-treated CRSwNP [11], and extends to the biologic setting the observations of Jankowski and Bodino and of Rives et al., who found that a preoperative olfactory response to oral corticosteroids predicted postoperative olfactory recovery after sinus surgery for nasal polyposis [12, 15]. A short course of systemic corticosteroids can be viewed as an inexpensive functional test of the reversibility of olfactory-cleft inflammation: patients whose olfaction improves transiently on corticosteroids appear to retain a responsive olfactory neuroepithelium that biologic therapy can then durably restore. This supports its use as a simple prognostic marker to inform counselling and, potentially, biologic selection, although the width of the confidence interval means that the size of the effect, rather than its direction, remains uncertain.

The second independent factor was the biologic agent, dupilumab being markedly more frequent among recoverers than mepolizumab (82.9% vs 60.9%; crude OR 3.11, 95% CI 1.32 to 7.33; adjusted OR 3.82, 95% CI 1.55 to 9.41; $p = 0.004$). This is consistent with the systematic review by Barroso et al., which found the most robust and rapid smell improvement with dupilumab among the monoclonal antibodies used in CRSwNP [16], and with the primary analysis of the same BIOPOSE cohort by Mortuaire et al. [17], who reported a comparable association for the composite EUFOREA definition of excellent response at 6 months (OR 4.03, 95% CI 1.37 to 13.17). In that analysis olfaction contributed as one of five response domains, with a threshold of a 16.7/100 change in the smell VAS, and no prognostic analysis of olfactory recovery as such was performed. As both analyses draw on the same patients, the concordance is internal rather than an independent replication; the present work differs in taking olfactory recovery at 12 months as the outcome in its own right. The superior olfactory efficacy of dupilumab is biologically plausible, as blockade of the shared IL-4/IL-13 receptor targets a broader segment of the type 2 cascade than isolated anti-IL-5 blockade, with a more pronounced effect on olfactory-cleft inflammation. This interpretation must, however, be tempered by the observational, non-randomised design: the biologic was chosen by the physician, and channelling of dupilumab towards patients judged more likely to recover their sense of smell cannot be excluded — a form of confounding by indication that adjustment for age, sex and smoking status cannot remove. The strong association between the biologic still ongoing at 12 months and recovery ($p < 0.001$) is likewise best understood as partly a consequence of response.

Blood eosinophil count at 12 months was higher in recoverers, albeit without reaching significance (558.5 vs 377.4 cells/ μ L; $p = 0.065$), whereas baseline blood eosinophil counts did not differ between groups. This should be interpreted with particular caution, as the higher 12-month eosinophil count in recoverers is most likely a pharmacological consequence of dupilumab itself rather than a marker of intrinsic responsiveness. By blocking the IL-4/IL-13 receptor, dupilumab impairs eosinophil migration into tissues and is well known to induce a transient rise in circulating eosinophils [18]; because dupilumab was both more frequently initiated and continued among recoverers, the 12-month hypereosinophilia in this group is at least partly attributable to the treatment received rather than a genuine predictor of outcome. Blood eosinophils also remain an imperfect surrogate for tissue eosinophilia: Hauser et al. showed that tissue rather than blood eosinophils correlate with CRS-associated olfactory dysfunction [9], and Mori et al. identified eosinophilic inflammation among the principal risk factors for olfactory impairment in CRS [8]. These observations are compatible with the notion put forward by Cantone et al. that olfactory recovery under dupilumab is largely independent of polyp volume reduction and instead reflects resolution of type 2 mucosal inflammation [10].

Several factors classically associated with olfactory prognosis showed no detectable association with recovery in our cohort, either in crude or in adjusted analyses. Neither a history of ethmoidectomy (84.3% vs 81.8%; adjusted OR 1.09, 95% CI 0.38 to 3.08) nor the number of prior sinonasal procedures (median 1 in both groups; adjusted OR 0.93 per procedure, 95% CI 0.68 to 1.27) influenced outcome. This contrasts with the post hoc analysis of the DUPIREAL cohort by De Corso et al., in which a greater number of prior sinus surgeries was independently associated with incomplete olfactory recovery [13]; the primary analysis of that cohort, however, found no effect of prior surgery on smell improvement [19]. Our result also contrasts with the broader surgical literature in which extensive or repeated surgery is associated with poorer olfactory outcomes [20, 21]. Conversely, in the SYNAPSE sinus surgery analysis, the benefit of mepolizumab was independent of the time since the last sinus surgery [22]. The relatively low median number of previous procedures, and the limited number of patients with complete surgical data, may explain this absence of association. Age, sex, current smoking [8, 23], comorbid asthma, disease duration, Lund-Mackay score, total IgE and GINA asthma-treatment step were likewise not associated with recovery, in keeping with the modest prognostic value reported for these variables across series [17].

Taken together, these results suggest that olfactory recovery under biologic therapy is better predicted by the functional reversibility of olfactory inflammation — captured by a prior corticosteroid olfactory response — and by the choice of a broadly acting type 2 blocker, than by static structural or demographic characteristics.

This study has several limitations. Its observational, real-life design precludes causal inference and exposes the analysis to confounding by indication, particularly regarding the choice of biologic. Olfaction was assessed with a visual analogue scale rather than a standardised olfactory test; the VAS is validated in severe CRSwNP but discriminates poorly near the normosmic threshold we used [24]. Most importantly, only 116 of the 427 enrolled patients (27%) had an evaluable 12-month olfactory VAS,

raising the possibility of attrition bias: patients with an evaluable VAS were treated at a higher GINA step and may therefore not be fully representative with respect to asthma severity. Reassuringly, the difference for the prior corticosteroid olfactory response, the main candidate predictor, remained below the prespecified threshold of 0.20 (0.19). Adjustment was performed factor by factor rather than in a single fully adjusted model, because of the varying extent of missing data; residual confounding cannot be excluded. The estimate of a prior corticosteroid-related olfactory response, based on only 42 patients, remains imprecise despite penalisation; although the direction of the association appears robust, its magnitude should be interpreted with caution. In addition, certain structural abnormalities of the olfactory cleft that may contribute to persistent olfactory obstruction – particularly respiratory epithelial adenomatoid hamartomas – were not assessed in this cohort, and their systematic evaluation by imaging and endoscopy could be considered in future studies [25, 26]. Finally, prospective validation with objective olfactory testing and longer follow-up is warranted to confirm the prognostic value of a prior corticosteroid responsiveness and to clarify the comparative olfactory efficacy of the available biologics.

Conclusions

In this real-life prospective multicentre cohort, three out of five patients with severe uncontrolled CRSwNP recovered their sense of smell at 12 months under biologic therapy. Two factors were associated with recovery after adjustment: a prior olfactory response to systemic corticosteroids and initiation of dupilumab rather than mepolizumab. Neither estimate is precise enough to guide treatment on its own, but both point in the same direction – that the functional reversibility of type 2 inflammation, rather than structural disease burden, governs olfactory outcome.

A short course of systemic corticosteroids is already part of the diagnostic and therapeutic pathway of nearly every patient considered for a biologic. Recording the olfactory response to that course in the medical file costs nothing, and it may allow a more realistic discussion with the patient about the chance of regaining a sense of smell with treatments whose cost is high. Prospective validation with objective olfactory testing is now required before this simple observation can be used to guide the choice of a biologic.

Declarations

Acknowledgements

The authors thank the investigators and research staff of the 15 participating centres of the BIOPOSE cohort for patient recruitment and data collection.

Funding G. Mortuaire served as the site Principal Investigator for the BIOlogics in Severe Nasal Polyposis Survey (BIOPOSE) study, with funding provided to the institution by Sanofi and GlaxoSmithKline. The financial support was specifically allocated for the conduct of the study. The sponsors were not involved in the study design, data collection, analysis, interpretation, or the writing of the report.

Competing Interests B. Wioska and N. Ramdane declare no competing interests. The other authors report receiving personal fees as expert consultants for advisory boards from Sanofi and GlaxoSmithKline.

Ethics Approval The study conformed to the Declaration of Helsinki, the French Public Health Code and European Union Good Clinical Practice guidelines. It was approved by the French Committee for the Protection of Individuals (CPP Nord-Ouest IV; reference no. 24.00921.000280; national identifier ID-RCB 2023-A02688-37) and registered at ClinicalTrials.gov (NCT05228041).

Consent to Participate All patients provided written informed consent before enrolment.

Consent to Publish Not applicable; the manuscript contains no individually identifiable data.

Data Availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions B. Wioska: conception and design; data collection; statistical analysis; drafting of the manuscript. O. Malard: conception and design; data collection; critical revision of the manuscript. N. Ramdane: statistical analysis; critical revision of the manuscript. G. Mortuaire: design of the BIOPOSE cohort; data collection; critical revision of the manuscript. V. Favier, F. Carsuzaa, C. Daveau, E. Béquignon, C. Vandersteen, M. Fieux, J.-F. Papon, L. de Gabory, N. Saroul, B. Vérillaud, C. Rumeau, J. Michel, G. de Bonnecaze, J.-B. Lecanu and G. Lefèvre: data collection; critical revision of the manuscript. All authors read and approved the submitted version of the manuscript.

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Figures

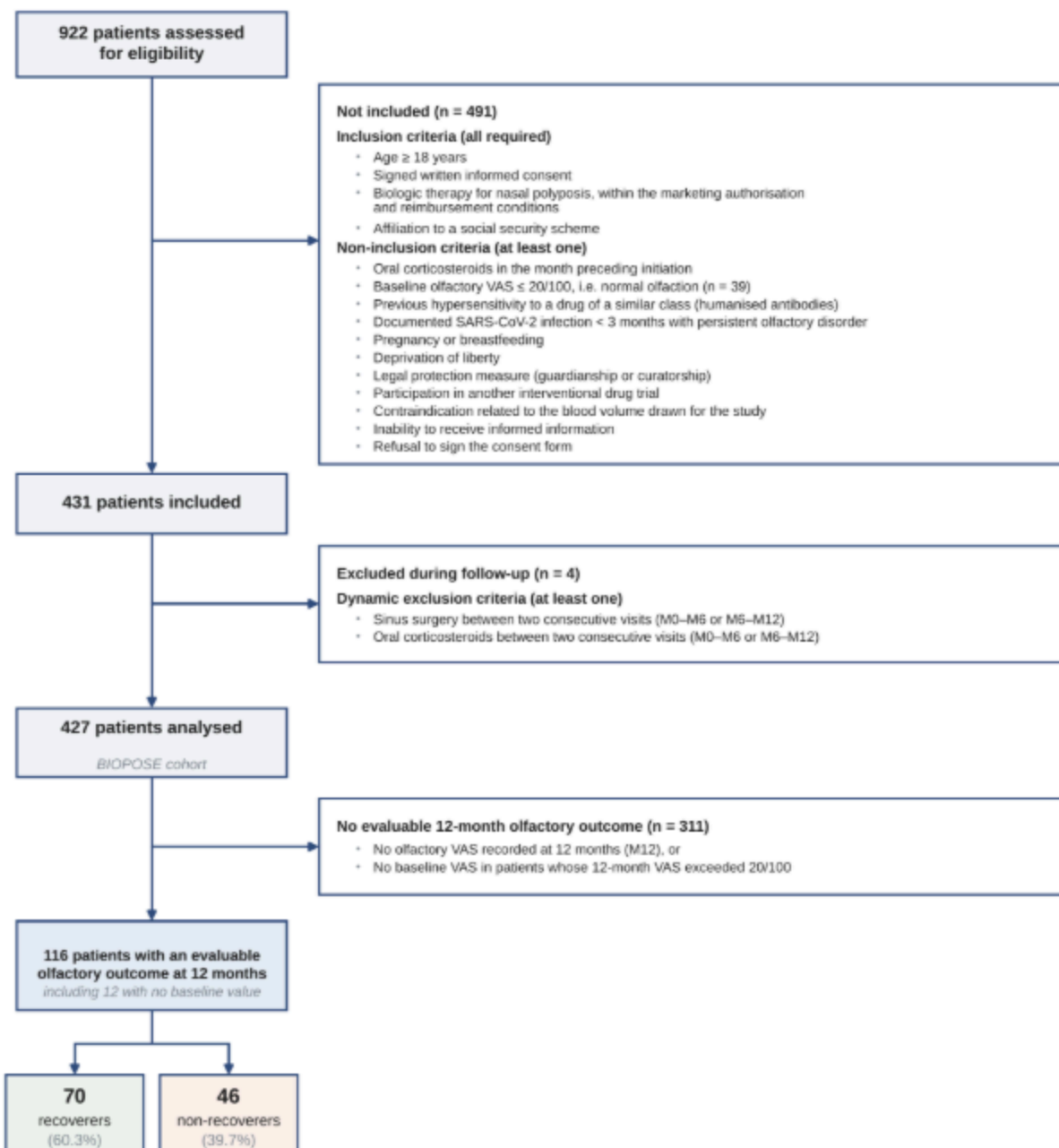


Figure 1

Study flow chart. Of 922 patients assessed for eligibility, 491 were not included – among them 39 with a baseline olfactory VAS ≤20/100, i.e. normal olfaction at enrolment – leaving 431 patients included. Four were subsequently excluded during follow-up for sinus surgery or oral corticosteroids between two consecutive visits, giving 427 patients analysed in the BIOPOSE cohort. A further 311 had no evaluable 12-month olfactory outcome, leaving 116 patients in the olfactory recovery analysis (70 recoverers, 46 non-recoverers), of whom 12 had no baseline value. VAS visual analogue scale, M0 baseline, M6 6 months, M12 12 months

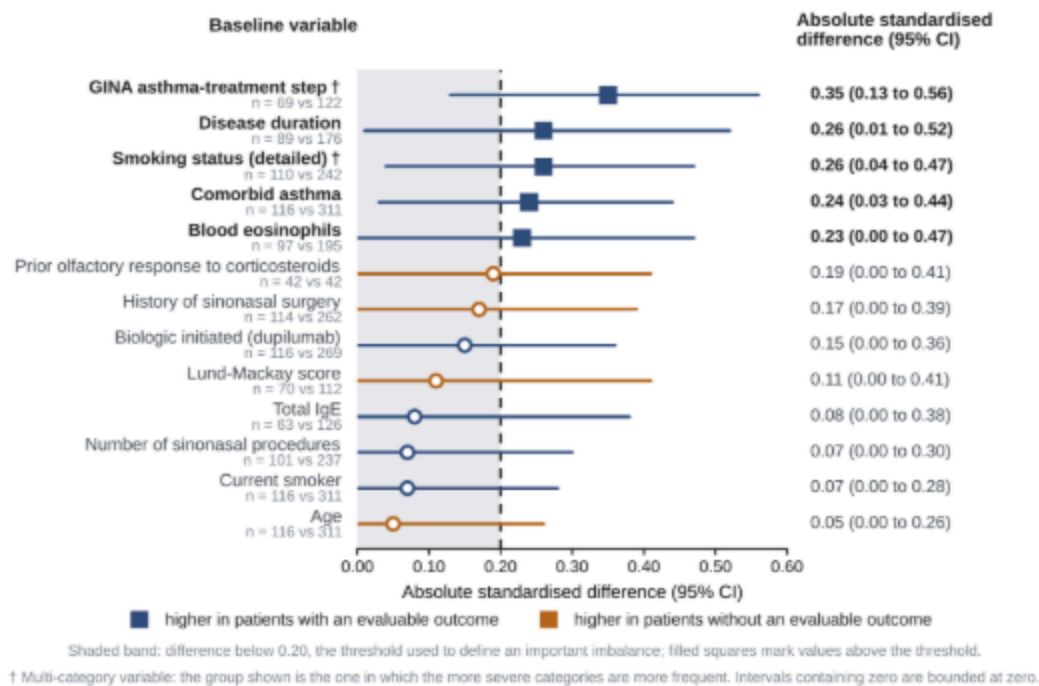


Figure 2

Absolute standardised differences between the 116 patients with an evaluable 12-month olfactory VAS and the 311 with no available olfactory evaluation. Filled squares mark differences ≥ 0.20 (outside the shaded band); the colour of the marker indicates the group in which the value was higher. The GINA step and detailed smoking status are unsigned multi-category differences, for which intervals containing zero are bounded at zero. Variables measured after baseline are not shown. Denominators differ across variables because of missing covariate data. CI confidence interval, GINA Global Initiative for Asthma, VAS visual analogue scale

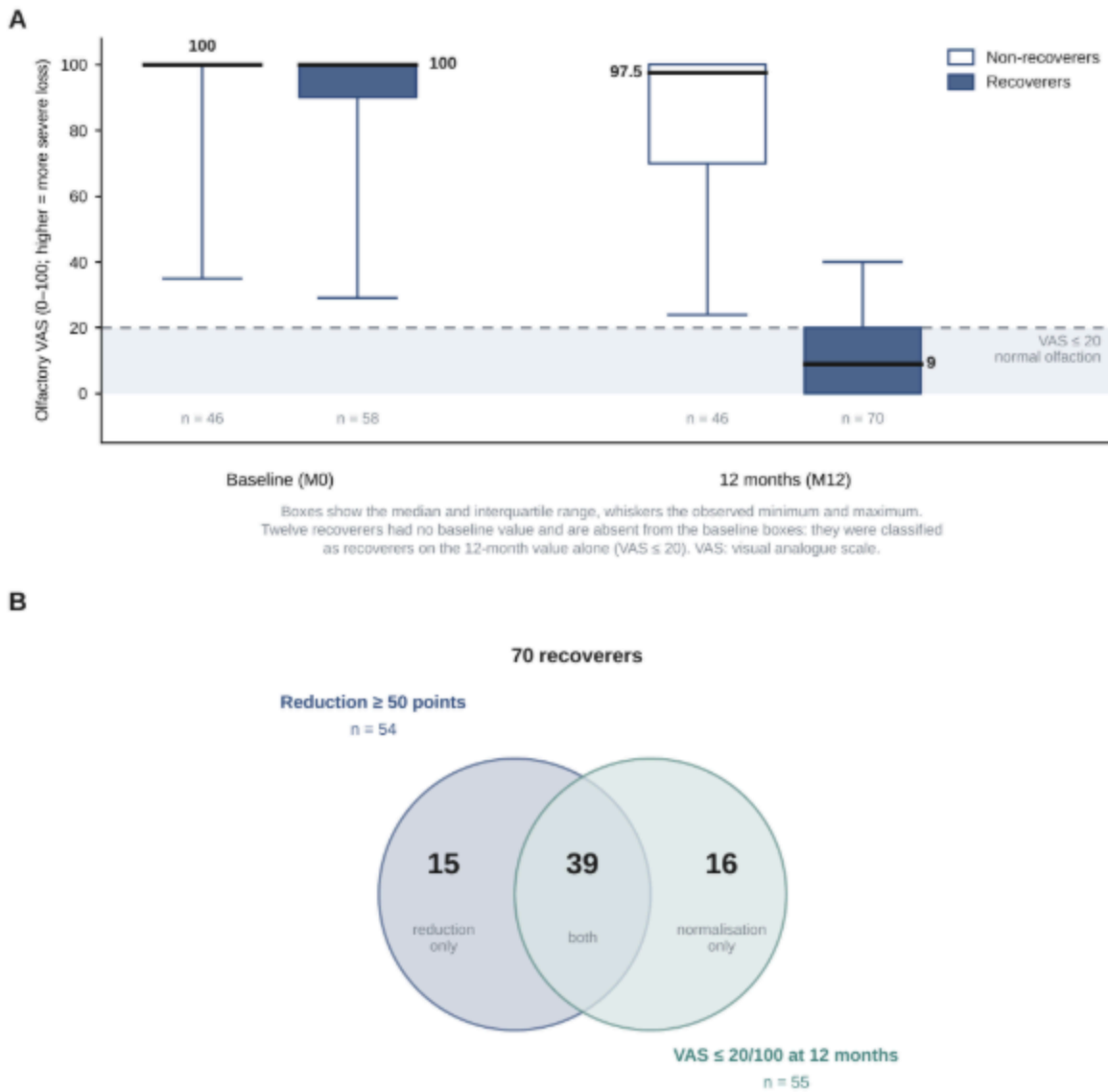


Figure 3

a Olfactory visual analogue scale at baseline and 12 months, by recovery status. Boxes show the median and interquartile range and whiskers the observed minimum and maximum; higher scores indicate greater olfactory impairment. The shaded band marks the normalisation threshold of 20/100. At baseline the interquartile range of non-recoverers is reduced to a single value of 100. Twelve recoverers had no baseline value and are absent from the baseline boxes. b Composition of the 70 recoverers according to the two branches of the composite definition. Fifty-four patients achieved a reduction of at least 50 points from baseline, 55 an olfactory VAS of 20/100 or less at 12 months, and 39 both. Twelve of the 16 patients meeting the normalisation criterion alone had no baseline value. VAS visual analogue scale, M0 baseline, M12 12 months

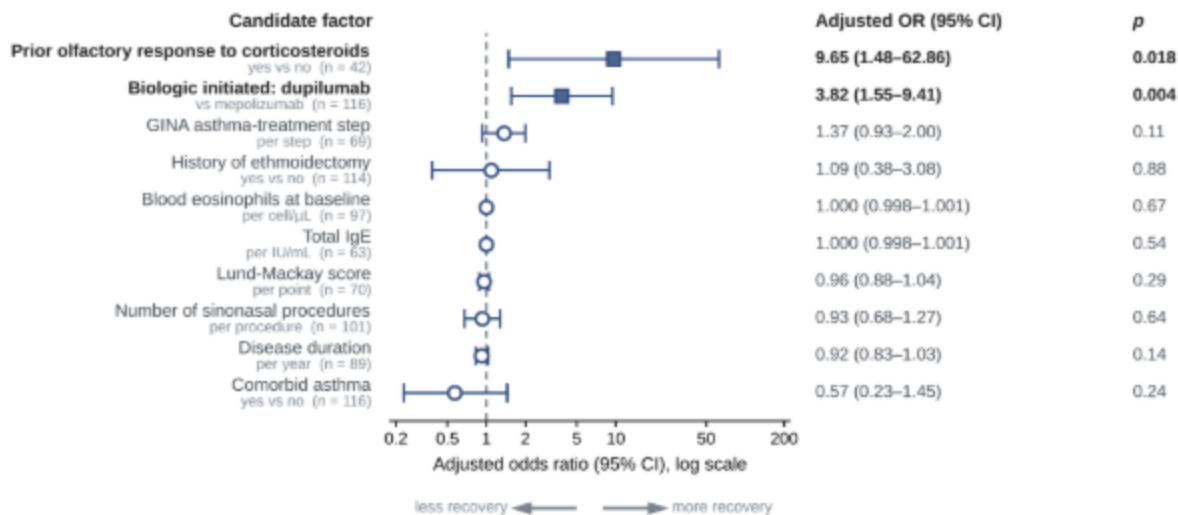


Figure 4

Adjusted odds ratios for olfactory recovery at 12 months, each factor entered in a separate model adjusted for age, sex and smoking status (GINA step: age and sex only); filled squares indicate $p < 0.05$. Odds ratios for blood eosinophils and total IgE are expressed per unit and are therefore close to 1. CI confidence interval, GINA Global Initiative for Asthma, IgE immunoglobulin E, OR odds ratio