Association between T2-related co-morbidities and effectiveness of biologics in severe asthma

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Running head: T2-related comorbidities and biologic effectiveness

Impact of research (2-3 sentences)

- Biologic treatment reduces exacerbation rate and long-term oral corticosteroid (LTOCS) daily dose and improves asthma control and lung function irrespective of the presence of T2-related comorbidities.
- However, patients with severe asthma and chronic rhinosinusitis (+/- nasal polyps) or nasal polyposis might benefit from biologic therapy to a greater extent than those without these comorbidities.
- Knowledge of the impact of T2-related comorbidities on biologic effectiveness may be useful to physicians when considering biologic therapy for patients with severe asthma.

Author contributions: All authors have made substantial contributions to acquisition or interpretation of data, have critically reviewed every draft for important intellectual content, have approved the final version to be published and agree to be accountable for all aspects of the work. Additionally, MW, GS, DL, CTD, J-M, TT, and DP contributed to the conception or design of the study. GS and DP were responsible for data analysis.

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Word count: 3410 (limit =3,500)

Abstract

Rationale

Previous studies investigating comorbidity impact on biologic effectiveness have been relatively small, of short duration, and have not compared biologic classes.

Objectives

To determine the association between T2-related comorbidities and biologic effectiveness in adults with severe asthma (SA).

Methods

This cohort study used International Severe Asthma Registry data (n=21 countries, 2017-2022) to quantify pre- to post-biologic change for four outcomes (annual asthma exacerbation rate, % predicted FEV_1 ($ppFEV_1$), asthma control, and long-term oral corticosteroid daily dose [LTOCS]) in patients with/without allergic rhinitis (AR), chronic rhinosinusitis +/- nasal polyps (CRS+/-NP), NP, or eczema/atopic dermatitis (AD).

Main results

Of 1765 patients, 1257, 421, and 87 initiated anti–IL-5/5R, anti-IgE, and anti–IL-4/13 therapies, respectively. In general, pre- to post-biologic improvements were noted in all four asthma outcomes assessed, irrespective of comorbidity status. However, patients with comorbid CRS+/-NP experienced 23% (95% CI 10-35%, p<0.001) fewer exacerbations/year and had 59% (95% CI: 26-102%, p<0.001) higher odds of better post-biologic control than those without CRS+/-NP. Similar estimates were noted for those with comorbid NP (22% less exacerbations and 56% higher odds of better post-biologic control). Patients with SA and CRS+/-NP had an additional $ppFEV_1$ improvement of 3.2% (95% CI: 1.0-5.3; p=0.004), a trend that was also noted in those with comorbid NP. The presence of AR or AD were not associated with pre- to post-biologic effect for any outcome assessed.

Conclusions

These findings highlight the importance of systematic comorbidity evaluation. The presence of CRS+/-NP or NP may be considered a predictor of biologic effectiveness in patients with severe asthma.

Keywords: allergic rhinitis; chronic rhinosinusitis; nasal polyposis

Word count: 250

Introduction

Asthma is increasingly considered as a multimorbidity syndrome rather than a discrete disease.(1, 2) This is particularly true for severe asthma (SA,), which tends to fall on the Type 2 (T2)-high side of the asthma endotype spectrum.(2, 3) T2-high asthma is associated with cytokines produced by T-helper 2 cells, with pathogenesis orchestrated by IL-4, IL-5, and IL-13 predominantly, and can be predicted from elevated fractional exhaled nitric oxide (FeNO) and sputum/blood eosinophil count.(4, 5) Most patients with SA have this type of asthma—83.8% by recent estimates.(6) Potentially T2-related comorbidities are the most common, and include allergic rhinitis (AR), chronic rhinosinusitis with or without nasal polyps (CRS+/-NP) and eczema/atopic dermatitis (AD); nearly 70% of patients with SA have at least one T2-comorbidity.(7) These comorbidities can impair quality of life, worsen asthma outcomes, and contribute to the overall socioeconomic burden of the disease, particularly in SA.(2, 4, 8) Recent data from the Finnish Nationwide Allergy Barometer Survey indicate that the annual cost of managing patients with asthma with multimorbidity was 28% higher than that for patients with asthma alone.(2)

Patients with increased T2-comorbidity burden are also more likely to experience asthma exacerbations and less likely to achieve control.(8) The scope of that impact appears to be comorbidity-dependent.(7) For example, recent data from the International Severe Asthma Registry (ISAR; using the same dataset as the present study) showed that having CRS+/-NP was associated with 29% more asthma exacerbations and a 46% greater likelihood of receiving long-term oral corticosteroid (LTOCS) compared to those without CRS +/-NP.(7) In the same study, patients with AR also experienced more frequent exacerbations than patients without.(7) This relationship between comorbidities and asthma outcomes is bi-directional: treating comorbidities is associated with improved asthma outcomes.(9–12)

Although the effectiveness of biologics in treating patients with asthma, who have a potential T2-related comorbidity, is documented,(13–17) the influence of comorbidities on biologic effectiveness is less well studied. A post-hoc analysis of the PROXIMA study showed that patients with SA and comorbid CRS with NP (CRSwNP) had a greater response to omalizumab in terms of improvement in asthma control, lung function, and annual exacerbation rate than those without CRSwNP (35.7% vs 23.0%).(18) The effectiveness of benralizumab was similarly positively associated with the presence of CRSwNP; more patients with CRSwNP compared to those without experienced a more clinically relevant improvement in asthma control (92.4% vs 79.3%), suspension of oral corticosteroid (OCS) treatment (76.6% vs 61.8%), and time free of exacerbations despite OCS discontinuation (70.2% vs 52.9%).(19) Indeed, NP is already noted by the Global Initiative for Asthma (GINA) strategy document

as a factor that may predict a positive response to anti–IL-5/5R therapy,(4) a finding supported by recent evidence.(20, 21) However, these studies included relatively small numbers of patients, assessed only one asthma comorbidity pattern, and did not compare across biologic classes (although the EVEREST study comparing omalizumab and dupilumab is currently in progress).(22)

The aim of our study was to determine the association between a range of potentially T2-related comorbidities and the effectiveness of biologics across multiple asthma domains in adult patients with SA.

Methods

Study design and data source

This was a registry-based cohort study using data from ISAR (https://isaregistries.org/), the largest adult SA registry in the world, with data from >17,000 patients from 25 countries.(23) The registry has been described elsewhere (and also in the online repository).(24) Here, we included data from 21 countries (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, South Korea, Spain, Taiwan, United Arab Emirates, United Kingdom, and United States) collected between 1 May 2017 and 24 January 2022. Study entry corresponded to date of initiation of first biologic. Asthma-related outcomes were assessed both pre- and post-biologic and a minimum of 24 weeks of follow-up (48 weeks for asthma exacerbations) was required (**Figure 1**).

Patients

All patients enrolled into ISAR and were required to have SA (defined as asthma requiring treatment at GINA 2018 Step 5 or remaining uncontrolled at GINA Step 4).(25) Those in this study were also required to have initiated a biologic on or after 1 May 2017 (date of ISAR launch). We excluded patients who were aged <18 years at biologic initiation or with missing age, had bronchial thermoplasty, had missing data for all four comorbidities considered (see details below) or had missing pre- and post-biologic paired eligible data and all four asthma outcomes considered (see details below) (**Figure 1**). Eligible patients were included irrespective of their biomarker profiles.

Comorbidity variables

We focused on four potentially T2-related physician-reported comorbidities collected by all contributing countries: AR, CRS+/-NP, nasal polyposis (NP), and atopic eczema/AD. Presence/absence of these comorbidities were assessed by physicians during routine clinical care visits (**S-Table 1**). Because data were not complete across all visits and to maximize data availability for our analysis, a history of T2-related comorbidities was assumed at study entry (biologic initiation) regardless of the visit when it was reported. However, the comorbidities were reported for the first time after study entry in <5% of the cases.

Asthma-related outcome variables

Pre- and post-biologic values were assessed for severe exacerbation rate, % predicted post-bronchodilator forced expiratory volume in one second ($ppFEV_1$), asthma control, and LTOCS daily dose (**Figure 1; S-Table 2**). A severe exacerbation was defined as an asthma-related hospital attendance/admission and/or asthma related emergency room attendance, and/or asthma worsening requiring an acute OCS course of ≥ 3 days (referred to as exacerbations from here onward). LTOCS was

defined as daily use of OCS as a background therapy for > 3 months. Asthma control was assessed using GINA 2020 criteria and categorized as well-controlled, partly controlled, or uncontrolled. If contributing countries used the Asthma Control Questionnaire or the Asthma Control Test to assess asthma control, conversions were made to fit the GINA categories (**S-Table 2**).

Pre-biologic exacerbation rates were assessed as the number of asthma exacerbation events in the 12 months preceding study entry. Post-biologic exacerbations rate computation used the number of events occurring in entire follow-up period (minimum 48 weeks required) and were annualized. For lung function, asthma control, and LTOCS daily dose, pre-biologic variables were constructed using information as close as available to date of biologic initiation. Post-biologic variables used information available as close as available to one year post-biologic initiation (minimum 24 weeks of follow-up required).

Statistics

The statistical analysis plan was pre-defined. R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct all statistical analyses.(26) For each asthma-related outcome, we quantified the difference between pre- and post-biologic values between patients with and without a comorbidity by fitting appropriate multivariable models with the post-biologic variable as the dependent variable, and comorbidity status, age, sex, plus the pre-biologic outcome variable as independent variables. Results were expressed as the average relative pre- to post-biologic differences in patients with a comorbidity compared to patients without the same comorbidity for any given pre-biologic measure (i.e., conditioning on pre-biologic measure). The impact of each of the comorbidities was assessed singly. Reference groups were patients without the single comorbidity of interest, but patients could have one or more comorbidities (e.g., the reference group for AR was patients without reported AR, although they could have CRS, NP, and/or AD).

Exacerbation rates were modelled by negative binomial regressions. Both lung function and LTOCS daily dose were modelled using multiple linear regressions. For LTOCS daily dose, the analysis was restricted to patients on LTOCS at biologic initiation, and doses were log-transformed to normalize the variables. For asthma control, we used ordinal logistic regressions. As a post-hoc analysis, whenever associations were detected, we tested the effect of adjusting for blood eosinophil count (BEC), smoking status, pre-biologic exacerbation rate, and LTOCS, and age at asthma onset. Analyses were first conducted in all patients initiating any type of anti-T2 biologic (anti-IgE, anti–IL-5/5R or anti–IL-4/13) and repeated in patients initiating anti-IgE or anti–IL-5/5R therapies separately. Separate analysis in patients initiating anti–IL-4/13 was not conducted due to low numbers in this subgroup. All statistical comparisons were two-sided.

Results

Subject disposition

As of 24 January 2022, ISAR contained data from 25 countries including 12,099 adult patients with SA (**Figure 2**). In this study, a total of 1765 patients from 21 countries were eligible for inclusion, of whom 1257 initiated anti–IL-5/5R therapy, 421 initiated anti-IgE therapy, and 87 initiated anti–IL-4/13 therapy.

Baseline characteristics

Patients were predominantly female (60.6%), aged 50 years or older (65.7%), and never or ex-smokers (97.4%), with asthma onset after 12 years of age (79.7%), and asthma phenotype characterized as eosinophilic(6) (95.8%) (**Table 1**). At biologic initiation, most patients had multiple exacerbations in the past year (41.6% with 3 or more), had reduced lung function (61.6% with $ppFEV_1$ <80%), and had uncontrolled asthma (65.4%). Almost half of the patients (48.7%) were on LTOCS, and highest median BEC, blood IgE, and FeNO concentrations were 520 cells/µL, 180 IU/mL, and 40 ppb, respectively (**Table 1**). Those who initiated anti–IL-5/5R therapy tended to have more severe disease than those in the anti-IgE therapy group, and those, who initiated anti–IL-4/13 therapy, tended to have the least severe disease. The most common potentially T2-related comorbidity was AR (60.7%), followed by CRS+/-NP (56.4%), NP (36.2%), and eczema/AD (13.9%), with 83.5% of patients having any of these comorbidities (**Table 1; S-Table 3**). Although the number of comorbidities was comparable between biologic groups, those, who initiated anti-IgE therapy, tended to have a higher prevalence of AR than their counterparts initiating an anti–IL-5/5R or anti–IL-4/13 therapy, whereas those, who initiated anti–IL-5/5R or anti–IL-4/13 therapy were more likely to have CRS+/-NP or NP (**Table 1**). Prevalence of comorbidities by country and overlap between comorbidities are available in Supplementary Materials **(S-Table 3**; **S-Figure 1**).

Patients with AR or AD were more commonly female and younger at asthma onset than patients without, whereas patients with CRS and NP were more commonly male and older at asthma onset than patients without. BEC was also higher in patients with CRS and NP than in patients without (**Table 2**).

Association between potentially T2-related comorbidities and biologic effectiveness

In general, patients showed improvement from pre- to post-biologics in exacerbation rate, lung function, asthma control and LTOCS daily dose, irrespective of comorbidity status (**Table 2**). We found evidence that patients with some comorbidities experienced additional improvement (**Figure 3 A-D**).

NP

Patients with NP experienced greater post-biologic improvements in exacerbation rate and asthma control outcomes compared to patients without NP (**Figures 3A and 3C**). Conditioning on pre-biologic values, patients with NP experienced 22% (95%CI: 7%-34%, p=0.004) fewer exacerbations/year. As a specific example, for women aged 55 years and with 3 exacerbations/year before biologics initiation, the predicted numbers of post-biologic exacerbations were 0.65 in patients with NP compared to 0.83 in patients without NP. Patients with NP also had 56% higher odds of better post-biologic asthma control (95% CI: 23%-98%, p<0.001). In terms of predicted probabilities, women with NP aged 55 years with uncontrolled asthma at biologic initiation had a 29% probability of improving to partly controlled and a 33% probability of improving to well-controlled asthma. Respective probabilities for those without NP were 27% and 24%. Adjusting for BEC attenuated the association for exacerbations (rate ratio=0.86, 95% CI: 0.72-1.02, p=0.092) and for asthma control (odds ratio=1.37, 95% CI: 1.06-1.77), p=0.015), although the trends remained. Adjusting for pre-biologic exacerbation rate, LTOCS, smoking status, or age at asthma onset did not impact the estimates (data not shown). A trend of stronger post-biologic improvement in lung function was also apparent in patients with NP compared to patients without (**Figure 3B**), which was attenuated when adjusted for BEC (+1.00 $ppFEV_1$, 95% CI: -1.3; 3.3, p=0.399). No association with NP was detected for differential post-biologic improvement in LTOCS daily dose (**Figure 3D**).

CRS+/-NP

Of 968 patients with reported CRS, 966 had information on NP, and 621 (64%) had NP reported. Irrespective of NP status, the associations between CRS and greater improvement in exacerbations and asthma control were in the same range as those observed for NP. Patients with comorbid CRS+/-NP experienced 23% (95% CI 10-35%, p<0.001) fewer exacerbations per year and had 59% (95% CI: 26-102%, p<0.001) higher odds of better post-biologic asthma control than those without CRS+/-NP. (**Figures 3A and 3C**). Adjusting for BEC had no impact on the estimate for exacerbations (rate ratio = 0.77, 95% CI: 0.65, 0.91, p=0.002), but slightly attenuated the association with better asthma control (odds ratio = 1.38, 95% CI: 1.07, 1.78, p=0.013). Adjusting for pre-biologic exacerbation rate, LTOCS, smoking status, or age at asthma onset did not impact the estimates (data not shown). When excluding patients with reported NP from the analysis, estimates remained in the same ranges: 0.81 (95% CI: 0.66, 1.00, p=0.053) for exacerbations and 1.40 (95% CI: 1.00, 1.97, p=0.051) for asthma control.

A stronger improvement in lung function was also detected in patients with CRS+/-NP compared to patients without (**Figure 3C**). Conditioning on pre-biologic ppFEV$_1$, patients with CRS+/-NP had an extra ppFEV$_1$ improvement of 3.2% (95% CI: 1.0, 5.3, p=0.004). This positive association was attenuated when adjusted for BEC (+2.1, 95%CI: -0.2, 4.3, p=0.076), but was augmented when patients with NP were excluded from the analysis (+3.7, 95%CI: 3.7, 6.5, p=0.009). Overall, the presence of CRS+/-NP was not associated with a greater post-biologic reduction in LTOCS (Difference: 0.1 [95% CI: -0.3, 0.6]).]). However, patients with CRS+/-NP who initiated anti-IgE tended to experience a smaller decrease in daily dose than patients without CRS +/-NP (**Figure 3D**). In LTOCS users and conditioning on pre-biologic dose, patients with CRS+/-NP treated with anti-IgE therapy were on average prescribed 1.3 mg/day more (95% CI: 0.1, 3.8, p=0.030) compared to patients without CRS+/-NP.

Allergic rhinitis and Eczema/atopic dermatitis

AR and AD were not associated with biologic effectiveness for any outcome assessed (**Figure 3 A-D).**

Heterogeneity between anti-IgE and anti–IL-5/5R therapy results

In general, there was no apparent differences between the estimates seen for anti-IgE and anti–IL-5/5R therapies, except for asthma control, in which the positive associations with CRS and NP seemed to be restricted to patients initiating anti–IL-5/5R therapy (p for heterogeneity = 0.08 and 0.012 for CRS+/-NP and NP, respectively).

Discussion

The effectiveness of biologics in treating SA with a T2-related comorbidity is well established.(27, 28) What is less well-known is whether the presence of a T2-related comorbidity influences the effectiveness of biologics. We investigated the association of a range of potentially T2-related comorbidities on the effectiveness of biologics (i) overall and by class, (ii) measured across four asthma outcomes, and (iii) directly compared biologic effectiveness in patients with and without a given comorbidity. We found that most patients treated with biologic therapy exhibited an improvement in each asthma-related outcome assessed, irrespective of the presence of a comorbidity (83.5% had at least one potentially T2-related comorbidity). However, additional improvements in exacerbation rate, asthma control, and lung function were noted in patients with CRS+/-NP and in those with NP compared to those without. This was likely due to the fact that these comorbidities are proxies for T2-asthma, the target of anti-T2 biologics. Assessing for the presence of potentially T2-related comorbidities is already recommended by GINA(4), is easily done during routine asthma review, and should help inform clinical decisions.

Most studies investigating the additional positive impact of potentially T2-related comorbidities on the effectiveness of biologics have focused on anti–IL-5/5R therapies and NP or CRSwNP.(19, 27, 29, 30) For example, the presence of CRSwNP increased the effectiveness of benralizumab in patients with SA, with more of these patients achieving a clinically relevant improvement in asthma control (92.4% vs 79.3%), and experiencing a significantly greater improvement in $ppFEV_1$ (23.1% vs 13.0%) than those without CRSwNP.(19) By contrast, others found that comorbid SA and CRSwNP was associated with a lower risk of exacerbating or a lower number of exacerbations in patients treated with anti–IL-5,(30, 31) or anti–IL-4/13 therapies,(21) but this additional effectiveness in those with CRSwNP was not seen for asthma control or lung function domains.(30) Improvement in lung function following omalizumab treatment has been found to be more likely in patients with asthma and CRS than in those without.(32) In our study, a greater anti–IL-5/5R therapy-associated reduction in exacerbation rates also occurred in patients with CRS+/-NP or NP. Although there was no difference in lung function improvement in patients with NP compared to patients without, additional lung function improvement was noted in patients with CRS+/-NP compared to patients without. Additionally, patients with CRS or NP had higher odds of having better controlled asthma post-anti–IL-5/5R treatment than patients without—a trend that was not observed in patients treated with anti-IgE therapy. This enhanced effect of anti–IL-5/5R in these patients is consistent with the fact that NP and CRS are both highly associated with eosinophilic inflammation of the upper airway (particularly in the US, Europe and Australia)(33, 34),

which tends to correlate with inflammation of the lower airway.(35) Indeed, the recent EPOS guidelines suggest splitting CRSsNP into eosinophilic CRS and non-eosinophilic CRS.(36)

The effectiveness of biologics in treating patients with asthma and comorbid AR or AD is well documented.(13, 37, 38). We also found that biologic treatment was associated with reduced exacerbation rate and LTOCS dose and improved lung function and asthma control in those with and without AR and AD. However, unlike CRS+/-NP and NP, neither comorbid AR nor AD were associated with improved biologic effectiveness for any asthma outcome assessed. Post-hoc analyses of the EXTRA, INNOVATE, and single-arm PROSPERO omalizumab studies also reported similar lung function improvement (albeit measured as absolute FEV_1) in omalizumab-treated patients with and without AR.(39) This may suggest a greater role of the eosinophil (with associated mucus hypersecretion and remodelling), rather than IgE in lung function impairment. The effectiveness of anti-IgE therapy in those with and without an AR or AD comorbidity is arguably a positive result in itself. Taken together, our results identify patient sub-groups that may derive greater benefit from biologic therapies.(40)

Limitations

Limitations of our study include those common to observational studies (e.g., bias, confounding, and challenges in demonstrating causality). Clinical variables were not available for all patients. Some of the missing data was due to lack of spirometry data especially during the COVID-19 pandemic. There was also potential lower power to detect differences in the anti-IgE arm due to smaller numbers of patients and less room for improvement. Those treated with anti-IgE also tended to have less severe disease, although we adjusted all estimates for baseline values. Due to insufficient numbers, we did not investigate the association of comorbidities on effectiveness of anti–IL-4/13 therapy. Results may also have been influenced by inter-country variations in comorbidity presence, how comorbidities were assessed and diagnosed, and in biologic access criteria.(41) We hypothesize that inter-country variability in comorbidity diagnosis protocols would have biased our results towards the null rather than overestimated associations. The extent to which improvement in asthma outcomes was associated with improvement in comorbidity outcomes is unknown, because improvement in comorbidities is not part of the data collected by ISAR. The presence of comorbidities was assessed using all available visits to maximise data availability, and this could have diluted our results. A small proportion (<5%) of comorbidities were found to be first reported only after biologic initiation. However, the considered comorbidities tend to be lifelong, and how they are reported by physicians varies over time and across countries. It should be noted that ‘active disease’ is different from ‘history of’, and misclassification might have further diluted our results. No statistical association was detected between AD and effectiveness of biologics.

Strengths of our study are the inclusion of a large, multi-national severe and heterogenous asthma cohort. In the context of comorbidities, the sample sizes used for our analysis were generally large and allowed the detection of the associations between the presence of comorbidities and multiple asthma-related outcomes. Rigorous statistical analyses were also employed, adjusting for pre-biologic values, as well as for age and sex. Future work to investigate the association of comorbidity on the effectiveness of other biologics (e.g. anti–IL-4/13 and anti-thymic stromal lymphopoietin therapies), the association of multimorbidity on biologic effectiveness, biomarker profiles by comorbidity status, and head-to-head comparisons between biologic classes in patients with specific comorbidity profiles are planned.

Conclusions

In conclusion, these findings suggest that patients with SA and CRS+/-NP or NP might benefit from biologic therapy to a greater extent than patients without. Our results highlight the importance of systematic evaluation for comorbidities and a multidisciplinary approach to their management in patients with severe asthma.

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682 **References**

683 1. Chanoine S, Sanchez M, Pin I, Temam S, Le Moual N, Fournier A, *et al.* Multimorbidity
684 medications and poor asthma prognosis. *Eur Respir J* 2018;51:1702114.
685 2. Jantunen J, Haahtela T, Salimäki J, Linna M, Mäkelä M, Pelkonen A, *et al.* Multimorbidity in
686 Asthma, Allergic Conditions and COPD Increase Disease Severity, Drug Use and Costs: The
687 Finnish Pharmacy Survey. *Int Arch Allergy Immunol* 2019;179:273–280.
688 3. Wang, E., Wechsler, M. E., Tran, T. N., Heaney, L. G., Jones, R. C., Menzies-Gow, A. N., *et al.*
689 Characterization of severe asthma worldwide: data from the International Severe Asthma
690 Registry (ISAR). *Chest* 2020;157:805–814.
691 4. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma Report
692 2022. 2022;at <https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-
693 FINAL-22-07-01-WMS.pdf>.[Last accessed August 2023]
694 5. Pavlidis S, Takahashi K, Ng Kee Kwong F, Xie J, Hoda U, Sun K, *et al.* "T2-high" in severe asthma
695 related to blood eosinophil, exhaled nitric oxide and serum periostin. *Eur Respir J* 2019;53.
696 6. Heaney LG, Perez de Llano L, Al-Ahmad M, Backer V, Busby J, Canonica GW, *et al.* Eosinophilic
697 and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a
698 global real-life severe asthma cohort. *Chest* 2021;160:814–830.
699 7. Scelo G. Impact of comorbidity in severe asthma patients (PRISM): prevalence of co-morbidities
700 in adult patients from the International Severe Asthma Registry. Ann Allergy Asthma Immunol
701 2023;In Press.
702 8. Price D, Menzies-Gow A, Bachert C, Canonica GW, Kocks J, Khan AH, *et al.* Association Between a
703 Type 2 Inflammatory Disease Burden Score and Outcomes Among Patients with Asthma. *J*
704 *Asthma Allergy* 2021;14:1173–1183.
705 9. De Jong H, Voorham J, Scadding G, Bachert C, Canonica GW, Smith P, *et al.* Evaluating the Real-
706 life Effect of MP-AzeFlu On Asthma Outcomes In Patients With Allergic Rhinitis and Asthma In
707 UK Primary Care. *World Allergy Organ J* 2020;13:100490.

10. Price D, Klimek L, Gálffy G, Emmeluth M, Koltun A, Kopietz F, *et al.* Allergic rhinitis and asthma symptoms in a real-life study of MP-AzeFlu to treat multimorbid allergic rhinitis and asthma. *Clin Mol Allergy* 2020;18:15.
11. Ragab S, Scadding GK, Lund VJ, Saleh H. Treatment of chronic rhinosinusitis and its effects on asthma. *Eur Respir J* 2006;28:68–74.
12. Chen F-H, Zuo K-J, Guo Y-B, Li Z-P, Xu G, Xu R, *et al.* Long-term results of endoscopic sinus surgery-oriented treatment for chronic rhinosinusitis with asthma. *Laryngoscope* 2014;124:24–28.
13. Vignola AM, Humbert M, Bousquet J, Boulet L-P, Hedgecock S, Blogg M, *et al.* Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004;59:709–717.
14. Busse WW, Maspero JF, Lu Y, Corren J, Hanania NA, Chipps BE, *et al.* Efficacy of dupilumab on clinical outcomes in patients with asthma and perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2020;125:565-576.e1.
15. Laidlaw TM, Bachert C, Amin N, Desrosiers M, Hellings PW, Mullol J, *et al.* Dupilumab improves upper and lower airway disease control in chronic rhinosinusitis with nasal polyps and asthma. *Ann Allergy Asthma Immunol* 2021;126:584-592.e1.
16. Lombardo N, Pelaia C, Ciriolo M, Della Corte M, Piazzetta G, Lobello N, *et al.* Real-life effects of benralizumab on allergic chronic rhinosinusitis and nasal polyposis associated with severe asthma. *Int J Immunopathol Pharmacol* 2020;34:2058738420950851.
17. Weinstein SF, Katial RK, Bardin P, Korn S, McDonald M, Garin M, *et al.* Effects of Reslizumab on Asthma Outcomes in a Subgroup of Eosinophilic Asthma Patients with Self-Reported Chronic Rhinosinusitis with Nasal Polyps. *J Allergy Clin Immunol Pract* 2019;7:589-596.e3.
18. Heffler E, Saccheri F, Bartezaghi M, Canonica GW. Effectiveness of omalizumab in patients with severe allergic asthma with and without chronic rhinosinusitis with nasal polyps: a PROXIMA study post hoc analysis. *Clin Transl Allergy* 2020;10:25.

19. Nolasco S, Crimi C, Pelaia C, Benfante A, Caiaffa MF, Calabrese C, *et al.* Benralizumab Effectiveness in Severe Eosinophilic Asthma with and without Chronic Rhinosinusitis with Nasal Polyps: A Real-World Multicenter Study. *J Allergy Clin Immunol Pract* 2021;doi:10.1016/j.jaip.2021.08.004.
20. Kavanagh JE, d'Ancona G, Elstad M, Green L, Fernandes M, Thomson L, *et al.* Real-World Effectiveness and the Characteristics of a "Super-Responder" to Mepolizumab in Severe Eosinophilic Asthma. *Chest* 2020;158:491–500.
21. Berger P, Menzies-Gow A, Peters AT, Kuna P, Rabe KF, Altincatal A, *et al.* Long-term efficacy of dupilumab in asthma with or without chronic rhinosinusitis and nasal polyps. *Ann Allergy Asthma Immunol* 2023;130:215–224.
22. De Prado Gomez L, Khan AH, Peters AT, Bachert C, Wagenmann M, Heffler E, *et al.* Efficacy and Safety of Dupilumab Versus Omalizumab in Chronic Rhinosinusitis With Nasal Polyps and Asthma: EVEREST Trial Design. *Am J Rhinol Allergy* 2022;19458924221112212.doi:10.1177/19458924221112211.
23. ISAR Study Group. International Severe Asthma Registry (ISAR): Mission Statement. *Chest* 2020;157:805–814.
24. FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, *et al.* International severe asthma registry (ISAR): protocol for a global registry. *BMC Med Res Methodol* 2020;20:212.
25. Global Initiative for Asthma. Global Strategy for Asthma Prevention and Treatment. 2018 update. 2018;at <https://ginasthma.org/wp-content/uploads/2019/01/2018-GINA.pdf>.
26. R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. *2021* at <https://www.R-project.org/>.
27. Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, *et al.* Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. *Allergy* 2020;75:1023–1042.

28. Bleecker ER, Wechsler ME, FitzGerald JM, Menzies-Gow A, Wu Y, Hirsch I, *et al.* Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J* 2018;52.
29. Bagnasco D, Brussino L, Bonavia M, Calzolari E, Caminati M, Caruso C, *et al.* Efficacy of Benralizumab in severe asthma in real life and focus on nasal polyposis. *Respir Med* 2020;171:106080.
30. D'Amato M, Menzella F, Altieri E, Bargagli E, Bracciale P, Brussino L, *et al.* Benralizumab in Patients With Severe Eosinophilic Asthma With and Without Chronic Rhinosinusitis With Nasal Polyps: An ANANKE Study post-hoc Analysis. *Front Allergy* 2022;3:881218.
31. Numata T, Nakayama K, Utsumi H, Kobayashi K, Yanagisawa H, Hashimoto M, *et al.* Efficacy of mepolizumab for patients with severe asthma and eosinophilic chronic rhinosinusitis. *BMC Pulm Med* 2019;19:176.
32. Clavenna MJ, Turner JH, Samuelson M, Tanner SB, Duncavage J, Chandra RK. Differential effect of omalizumab on pulmonary function in patients with allergic asthma with and without chronic rhinosinusitis. *Allergy Asthma Proc* 2016;37:23–26.
33. Gevaert P, Hellman C, Lundblad L, Lundahl J, Holtappels G, van Cauwenberge P, *et al.* Differential expression of the interleukin 5 receptor alpha isoforms in blood and tissue eosinophils of nasal polyp patients. *Allergy* 2009;64:725–732.
34. Staudacher AG, Peters AT, Kato A, Stevens WW. Use of endotypes, phenotypes, and inflammatory markers to guide treatment decisions in chronic rhinosinusitis. *Ann Allergy Asthma Immunol* 2020;124:318–325.
35. Ediger D, Sin BA, Heper A, Anadolu Y, Misirligil Z. Airway inflammation in nasal polyposis: immunopathological aspects of relation to asthma. *Clin Exp Allergy* 2005;35:319–326.
36. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, *et al.* European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* 2020;58:1–464.

37. Pose K, Laorden D, Hernández N, Villamañán E, Quirce S, Domínguez-Ortega J. Efficacy of Dupilumab for Severe Atopic Dermatitis Co-occurring With Asthma in a Real-World Setting. *J Investig Allergol Clin Immunol* 2023;33:217–219.
38. Spekhorst LS, de Graaf M, van der Rijst LP, Zuithoff NPA, Schweizer RC, Kamsteeg M, *et al.* The positive effect of dupilumab on comorbid asthma in patients with atopic dermatitis. *Clin Transl Allergy* 2023;13:e12219.
39. Chen M, Choo E, Yoo B, Raut P, Haselkorn T, Pazwash H, *et al.* No difference in omalizumab efficacy in patients with asthma by number of asthma-related and allergic comorbidities. *Ann Allergy Asthma Immunol* 2021;126:666–673.
40. Pfeffer P, Ali N, Murray R, Ulrik C, Tran, T. N., Maspero JF, *et al.* The comparative effectiveness of Anti-IL5 and Anti-IgE biologic classes in severe asthma patients eligible for both. Allergy 2023;78:1934-1948.
41. Porsbjerg CM, Menzies-Gow AN, Tran TN, Murray RB, Unni B, Audrey Ang SL, *et al.* Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma. *J Allergy Clin Immunol Pract* 2022;10:1202–16.

802 **Table 1: Patient baseline characteristics**

Characteristic	Total N=1765	Anti–IL-5/5R N=1257	Anti-IgE N=421	Anti–IL-4/13 N=87
Demographics				
Gender				
Women, n (%)	1070 (60.6)	754 (60.0)	257 (61.0)	59 (67.8)
Age at enrolment, yrs				
18-29, n (%)	119 (6.7)	61 (4.9)	47 (11.2)	11 (12.6)
30-39, n (%)	173 (9.8)	100 (8.0)	61 (14.5)	12 (13.8)
40-49, n (%)	314 (17.8)	210 (16.7)	86 (20.4)	18 (20.7)
50-59, n (%)	533 (30.2)	392 (31.2)	116 (27.6)	25 (28.7)
60-69, n (%)	430 (24.4)	344 (27.4)	73 (17.3)	13 (14.9)
70-79, n (%)	171 (9.7)	132 (10.5)	33 (7.8)	6 (6.9)
80+, n (%)	25 (1.4)	18 (1.4)	5 (1.2)	2 (2.3)
Median (Q1, Q3)	55 (45, 63)	56 (48, 64)	51 (39, 60)	51 (38, 59)
Smoking status	N=1570	N=1146	N=345	N=79
Current smoker, n (%)	41 (2.6)	23 (2.0)	18 (5.2)	0 (0.0%)
Ex-smoker, n (%)	457 (29.1)	344 (30.0)	88 (25.5)	25 (31.6)
Never smoker, n (%)	1072 (68.3)	779 (68.0)	239 (69.3)	54 (68.4)
Age at asthma onset, yrs	N=1327	N=965	N=319	N=43
<12, n (%)	270 (20.3)	168 (17.4)	89 (27.9)	13 (30.2)
≥12, n (%)	1057 (79.7)	797 (82.6)	230 (72.1)	30 (69.8)
Pre-biologic asthma-related outcomes				
LTOCS				
Yes, n (%)	860 (48.7)	687 (54.7)	149 (35.4)	24 (27.6)
Exacerbation rate	N=1651	N=1183	N=384	N=84
0, n (%)	367 (22.2)	227 (19.2)	104 (27.1)	36 (42.9)
1, n (%)	312 (18.9)	209 (17.7)	80 (20.8)	23 (27.4)
2, n (%)	286 (17.3)	194 (16.4)	79 (20.6)	13 (15.5)
3+, n (%)	686 (41.6)	553 (46.7)	121 (31.5)	12 (14.3)
$ppFEV_1$	N=1488	N=1076	N=335	N=77
<80%, n (%)	916 (61.6)	668 (62.1)	202 (60.3)	46 (59.7)
Median (Q1, Q3)	74 (59, 88)	74 (59, 89)	75 (60, 87)	74 (59, 87)
FEV_1/FVC	N=1460	N=1055	N=328	N=77
<0.70	814 (55.8)	606 (57.4)	166 (50.6)	42 (54.5)
Median (Q1, Q3)	0.68 (0.58, 0.76)	0.68 (0.57, 0.75)	0.70 (0.60, 0.79)	0.68 (0.57, 0.75)
Asthma control*	N=1338	N=980	N=298	N=60
Well controlled, n (%)	176 (13.2)	107 (10.9)	57 (19.1)	12 (20.0)
Partly controlled, n (%)	287 (21.4)	209 (21.3)	63 (21.1)	33 (55.0)
Uncontrolled, n (%)	875 (65.4)	664 (67.8)	178 (59.7)	15 (25.0)
Biomarkers				
Highest BEC, (cells/µL)	N=1455	N=1084	N=303	N=68
Median (Q1, Q3)	520 (300, 880)	600 (390, 940)	300 (200, 595)	400 (225, 600)
Highest Blood IgE, (IU/mL)	N=1306	N=926	N=323	N=57
Median (Q1, Q3)	180 (70, 465)	151 (59, 393)	283 (130, 636)	135 (41, 724)
Highest FeNO, ppb	N=1033	N=794	N=185	N=54
Median (Q1, Q3)	40 (22, 77)	45 (24, 82)	26 (14, 50)	46 (19, 80)
Potentially T2-related comorbidities				
Allergic rhinitis	N=1254254	N=826826	N=344344	N=84
Ever, n (%)	761 (6060.7)	464 (5656.2)	246 (7171.5)	51 (60.7)

Chronic rhinosinusitis (+/- NP)	N=1716	N=1220	N=410	N=86
Ever, n (%)	968 (56.4)	739 (60.6)	179 (43.7)	50 (58.1)
Nasal polyposis (NP)	N=1756	N=1251	N=419	N=86
Ever, n (%)	636 (36.2)	504 (40.3)	97 (23.2)	35 (40.7)
Eczema/atopic dermatitis	N=1753	N=1249	N=417	N=87
Ever, n (%)	243 (13.9)	144 (11.5)	71 (17.0)	28 (32.2)
Count of comorbidities	N=1208208	N=792792	N=334334	N=82
0, n (%)	199 (1616.5)	136 (1717.2)	54 (1616.2)	9 (11.0)
1, n (%)	319 (2626.4)	187 (2323.6)	109 (3232.6)	23 (28.0)
2, n (%)	338 (28.0)	224 (28.3)	90 (2626.9)	24 (29.3)
3, n (%)	294 (2424.3)	205 (2525.9)	71 (2121.3)	18 (22.0)
4, n (%)	54 (44.8)	40 (55.1)	10 (33.0)	8 (9.8)
Eosinophilic phenotype gradient(6)				
	N=1592	N=1257	N=269	N=66
Grade 0: unlikely/non-eosinophilic, n (%)	2 (0.1)	0 (0.0)	1 (0.4)	1 (1.5)
Grade 1: least likely, n (%)	24 (1.5)	0 (0.0)	19 (7.1)	5 (7.6)
Grade 2: likely, n (%)	41 (2.6)	0 (0.0)	38 (14.1)	3 (4.5)
Grade 3: most likely, n (%)	1525 (95.8)	1257 (100.0)	211 (78.4)	57 (86.4)

BEC: blood eosinophil count; IgE: immunoglobulin E; IL5/5R: interleukin 5/5 receptor; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume; FVC: forced vital capacity; LTOCS: long-term oral corticosteroid; $ppFEV_1$: percent predicted forced expiratory volume in one second (post-bronchodilator)

*GINA 2022 criteria(6)

Please see Figure 1 for assessment time points for outcome variables

Table 2: Patient characteristics and pre- to post-biologic changes by comorbidity status

Characteristics	Allergic rhinitis		Chronic rhinosinusitis		Nasal polyposis		Eczema/atopic dermatitis	
	Ever N=761	Never N=493	Ever N=968	Never N=748	Ever N=636	Never N=1120	Ever N=243	Never N=1510
Gender								
Women, n (%)	479 (62.9)	275 (55.8)	573 (59.2)	468 (62.6)	354 (55.7)	711 (63.5)	159 (65.4)	907 (60.1)
Age								
Median (Q1, Q3)	54 (44, 62)	57 (50, 66)	55 (46, 63)	54 (44, 63)	54 (46, 63)	55 (44, 64)	54 (41, 64)	55 (46, 63)
Smoking status	N=643	N=431	N=854	N=670	N=562	N=1004	N=206	N=1355
Current smoker, n (%)	18 (2.8)	13 (3.0)	18 (2.1)	22 (3.3)	10 (1.8)	31 (3.1)	6 (2.9)	35 (2.6)
Ex-smoker, n (%)	191 (29.7)	135 (31.3)	240 (28.1)	197 (29.4)	163 (29.0)	292 (29.1)	60 (29.1)	391 (28.9)
Never smoker, n (%)	434 (67.5)	283 (65.7)	596 (69.8)	451 (67.3)	389 (69.2)	681 (67.8)	140 (68.0)	929 (68.6)
Age at asthma onset, yrs	N=558	N=283	N=719	N=562	N=531	N=788	N=175	N=1146
<12, n (%)	13 (20.3)	37 (13.1)	123 (17.1)	131 (23.3)	83 (15.6)	187 (23.7)	61 (34.9)	208 (18.2)
Highest BEC (cells/µL)	N=596	N=412	N=800	N=624	N=531	N=922	N=191	N=1257
Median (Q1, Q3)	540 (300, 900)	600 (341, 915)	600 (350, 950)	449 (270, 780)	666 (400, 1000)	500 (300, 800)	500 (295, 800)	540 (300, 900)
Positive test to any allergen†	N=592	N=326	N=740	N=640	N=516	N=899	N=178	N=1234
Yes, n (%)	445 (75.2)	182 (55.8)	431 (58.2)	440 (68.7)	285 (55.2)	614 (68.3)	139 (78.1)	759 (61.5)
Exacerbation rates: mean (SD)	N=559	N=363	N=719	N=541	N=463	N=818	N=189	N=1092
Pre-biologics	2.24 (2.34)	2.16 (2.23)	2.65 (2.77)	3.37 (3.74)	2.88 (3.02)	3.05 (3.40)	1.97 (2.00)	3.15 (3.39)
Post-biologics	0.65 (1.21)	0.65 (1.04)	0.75 (1.25)	1.13 (1.62)	0.77 (1.21)	1.01 (1.55)	0.72 (1.35)	0.96 (0.46)
Change	-1.59 (2.54)	-1.51 (2.33)	-1.89 (2.74)	-2.24 (3.51)	-2.11 (2.82)	-2.04 (3.30)	-1.25 (2.30)	-2.19 (3.22)
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ppFEV$_1$: mean (SD)	N=313	N=267	N=493	N=386	N=306	N=573	N=101	N=776
Pre-biologics	76.4 (21.7)	72.2 (23.3)	75.8 (22.5)	71.0 (22.6)	76.4 (22.1)	72.2 (22.9)	73.9 (22.5)	73.6 (22.7)
Post-biologics	80.1 (22.6)	76.6 (23.2)	79.5 (23.3)	73.0 (22.1)	79.7 (23.0)	75.1 (22.8)	75.6 (21.7)	76.8 (23.1)
Change	+3.7 (17.9)	+4.4 (16.0)	+3.8 (17.1)	+2.0 (17.1)	+3.3 (17.1)	+2.9 (17.1)	+1.7 (13.7)	+3.1 (17.5)
p-value*	<0.001	<0.001	<0.001	0.023	0.001	<0.001	0.210	<0.001
Asthma control: % of uncontrolled/partly controlled/well controlled	N=430	N=237	N=570	N=450	N=414	N=629	N=118	N=923
Pre-biologics	65.6/22.6/11.9	57.8/23.2/19.0	65.8/21.2/13.0	69.6/18.9/11.6	65.2/21.3/13.5 29.5/24.9/45.7	70.3/18.6/11.1	71.2/19.5/9.3	67.8/19.7/12.5

Post-biologics p-value*	25.6/31.9/42.6 <0.001	27.0/29.1/43.9 <0.001	30.2/26.5/43.3 <0.001	42.4/25.3/32.2 <0.001	<0.001	39.6/27.2/33.2 <0.001	39.0/33.1/28.0 <0.001	35.2/25.4/39.4 <0.001
LTOCS								
Users, n (%)	283 (37.2)	202 (41.0)	445 (46.0)	383 (51.2)	312 (49.1)	543 (48.5)	243 (33.3)	772 (51.1)
LTOCS: mean daily dose in users pre-biologics (SD)	N=128	N=74	N=243	N=262	N=196	N=332	N=42	N=485
Pre-biologics	13.2 (10.9)	15.5 (15.4)	12.2 (10.0)	13.2 (10.6)	12.0 (9.3)	13.1 (10.7)	10.5 (10.1)	12.8 (10.2)
Post-biologics	11.7 (9.9)	13.9 (14.7)	10.5 (9.5)	11.0 (10.1)	9.8 (8.3)	11.4 (10.4)	8.8 (9.0)	10.9 (9.8)
Change	-1.4 (7.6)	-1.6 (11.7)	-1.7 (6.9)	-2.2 (7.6)	-2.2 (7.2)	-1.7 (7.1)	-1.7 (8.9)	-1.9 (7.0)
p-value*	0.020	0.204	<0.001	<0.001	<0.001	<0.001	0.116	<0.001

*Comparing pre- to post-biologics, using paired Wilcoxon test for exacerbations and LTOCS dose, paired t-test for $ppFEV_1$, and McNemar test (nominal symmetry test) for asthma control.

†Not available for all patients or for all allergens

BEC: blood eosinophil count; LTOCS: long term oral corticosteroid; $ppFEV_1$: percent predicted forced expiratory volume in one second; SD: standard deviation

Legend to Figures

Figure 1: Study design. LTOCS: long-term oral corticosteroid

Figure 2: Subject disposition. *Including 609 patients, who did not receive long-term OCS at biologic initiation and had no available data on any of the other three asthma-related outcomes
Abbreviations: Bx: biologic; ISAR: International Severe Asthma Registry; OCS: oral corticosteroid

Figure 3: Association between potentially T2-related comorbidity and post-biologic asthma-related outcomes, adjusted for pre-biologic status, age, and sex. The reference group is those patients without the comorbidity of interest. A: exacerbation rates; B: lung function; C: asthma control; D: long-term OCS daily dose.
Abbreviations: CI: confidence interval; $ppFEV_1$: percent predicted forced expiratory volume in one second; IgE: immunoglobulin E; IL5/5R: interleukin 5/5 receptor; OCS: oral corticosteroid.

Figure 1

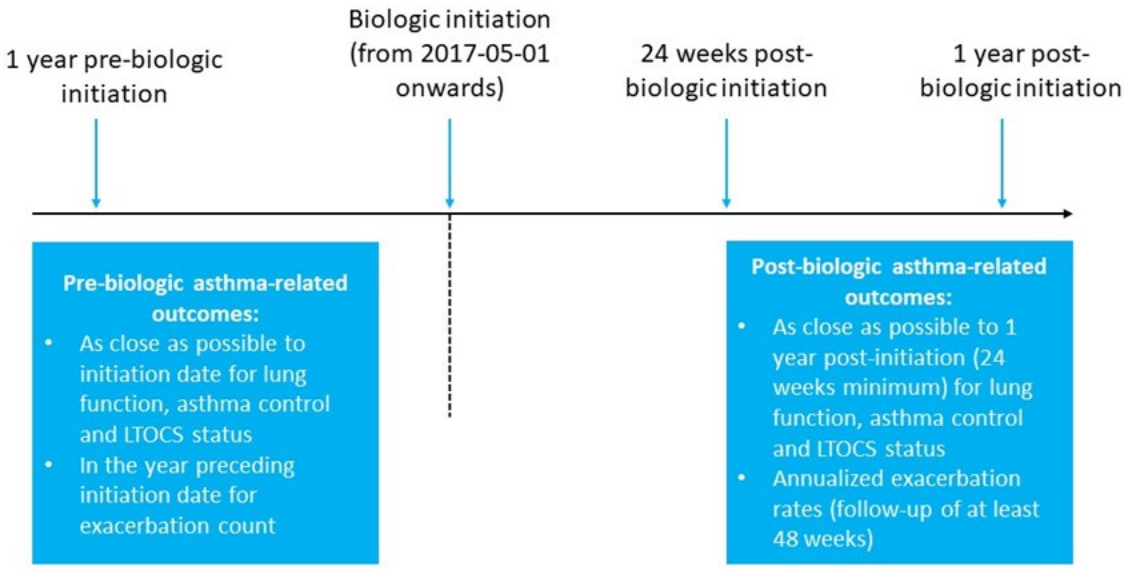

1 year pre-biologic initiation
Biologic initiation (from 2017-05-01 onwards)
24 weeks post-biologic initiation
1 year post-biologic initiation
Pre-biologic asthma-related outcomes:
As close as possible to initiation date for lung function, asthma control and LTOCS status
In the year preceding initiation date for exacerbation count
Post-biologic asthma-related outcomes:
As close as possible to 1 year post-initiation (24 weeks minimum) for lung function, asthma control and LTOCS status
Annualized exacerbation rates (follow-up of at least 48 weeks)

Figure 2

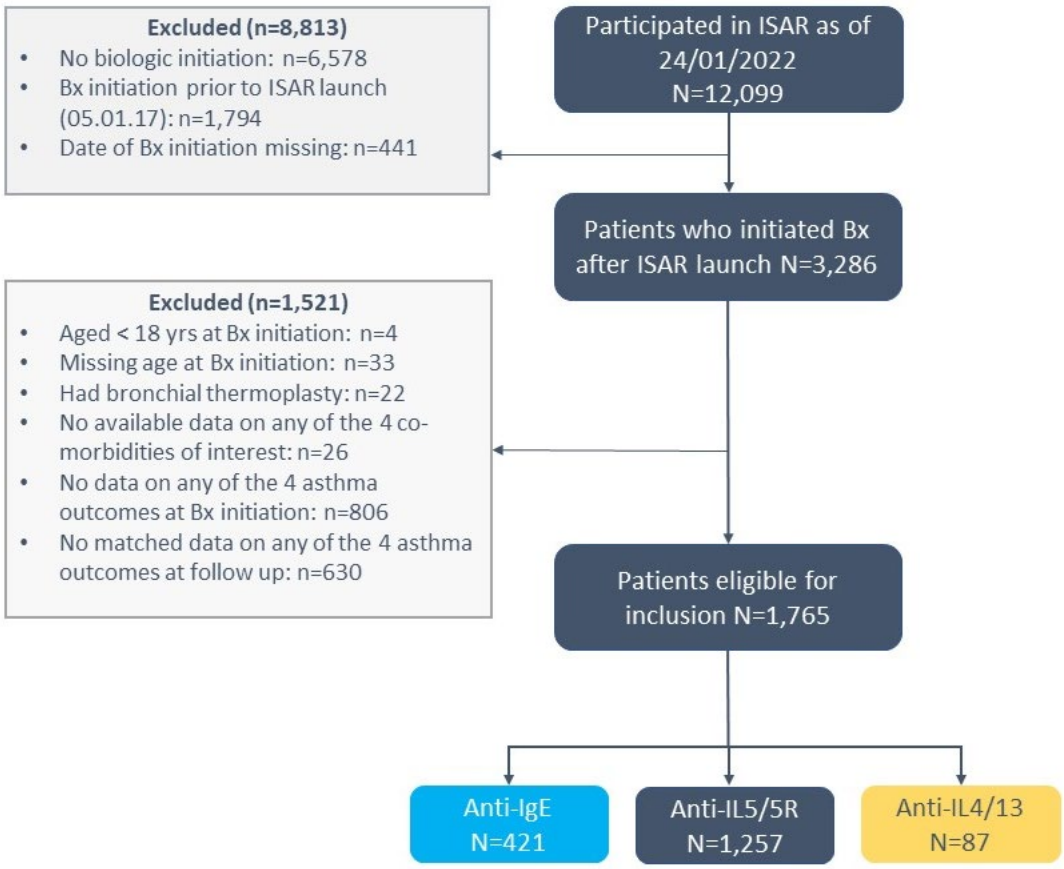
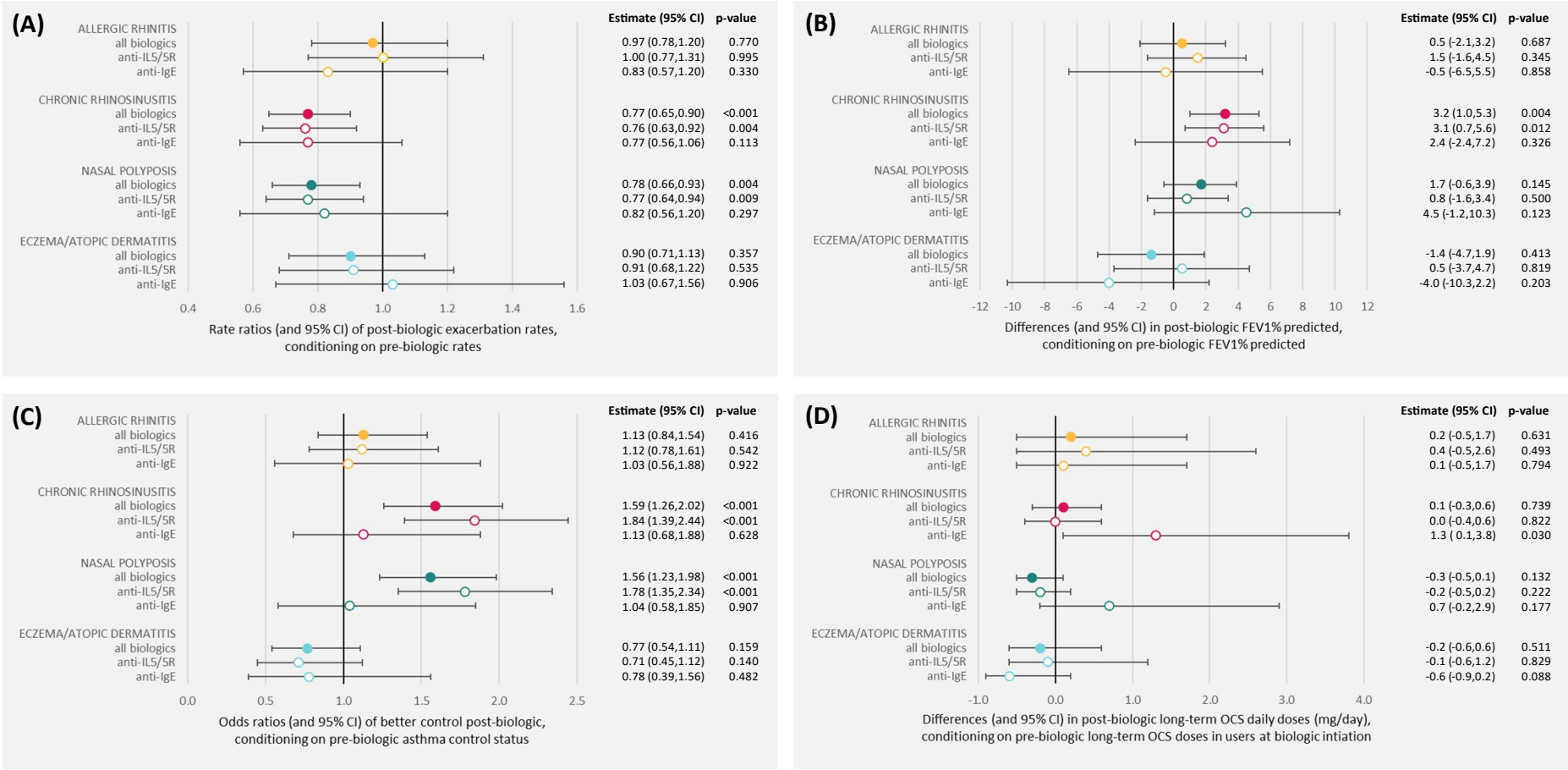

Excluded (n=8,813)
• No biologic initiation: n=6,578
• Bx initiation prior to ISAR launch (05.01.17): n=1,794
• Date of Bx initiation missing: n=441
Participated in ISAR as of 24/01/2022 N=12,099
Patients who initiated Bx after ISAR launch N=3,286
Excluded (n=1,521)
• Aged < 18 yrs at Bx initiation: n=4
• Missing age at Bx initiation: n=33
• Had bronchial thermoplasty: n=22
• No available data on any of the 4 co-morbidities of interest: n=26
• No data on any of the 4 asthma outcomes at Bx initiation: n=806
• No matched data on any of the 4 asthma outcomes at follow up: n=630
Patients eligible for inclusion N=1,765
Anti-IgE N=421
Anti-IL5/5R N=1,257
Anti-IL4/13 N=87

Figure 3


(A)
ALLERGIC RHINITIS
all biologics 0.97 (0.78,1.20) 0.770
anti-IL5/5R 1.00 (0.77,1.31) 0.995
anti-IgE 0.83 (0.57,1.20) 0.330
CHRONIC RHINOSINUSITIS
all biologics 0.77 (0.65,0.90) <0.001
anti-IL5/5R 0.76 (0.63,0.92) 0.004
anti-IgE 0.77 (0.56,1.06) 0.113
NASAL POLYPOSIS
all biologics 0.78 (0.66,0.93) 0.004
anti-IL5/5R 0.77 (0.64,0.94) 0.009
anti-IgE 0.82 (0.56,1.20) 0.297
ECZEMA/ATOPIC DERMATITIS
all biologics 0.90 (0.71,1.13) 0.357
anti-IL5/5R 0.91 (0.68,1.22) 0.535
anti-IgE 1.03 (0.67,1.56) 0.906
Estimate (95% CI) p-value
0.4 0.6 0.8 1.0 1.2 1.4 1.6
Rate ratios (and 95% CI) of post-biologic exacerbation rates, conditioning on pre-biologic rates
(B)
ALLERGIC RHINITIS
all biologics 0.5 (-2.1,3.2) 0.687
anti-IL5/5R 1.5 (-1.6,4.5) 0.345
anti-IgE -0.5 (-6.5,5.5) 0.858
CHRONIC RHINOSINUSITIS
all biologics 3.2 (1.0,5.3) 0.004
anti-IL5/5R 3.1 (0.7,5.6) 0.012
anti-IgE 2.4 (-2.4,7.2) 0.326
NASAL POLYPOSIS
all biologics 1.7 (-0.6,3.9) 0.145
anti-IL5/5R 0.8 (-1.6,3.4) 0.500
anti-IgE 4.5 (-1.2,10.3) 0.123
ECZEMA/ATOPIC DERMATITIS
all biologics -1.4 (-4.7,1.9) 0.413
anti-IL5/5R 0.5 (-3.7,4.7) 0.819
anti-IgE -4.0 (-10.3,2.2) 0.203
Estimate (95% CI) p-value
-12 -10 -8 -6 -4 -2 0 2 4 6 8 10 12
Differences (and 95% CI) in post-biologic FEV1% predicted, conditioning on pre-biologic FEV1% predicted
(C)
ALLERGIC RHINITIS
all biologics 1.13 (0.84,1.54) 0.416
anti-IL5/5R 1.12 (0.78,1.61) 0.542
anti-IgE 1.03 (0.56,1.88) 0.922
CHRONIC RHINOSINUSITIS
all biologics 1.59 (1.26,2.02) <0.001
anti-IL5/5R 1.84 (1.39,2.44) <0.001
anti-IgE 1.13 (0.68,1.88) 0.628
NASAL POLYPOSIS
all biologics 1.56 (1.23,1.98) <0.001
anti-IL5/5R 1.78 (1.35,2.34) <0.001
anti-IgE 1.04 (0.58,1.85) 0.907
ECZEMA/ATOPIC DERMATITIS
all biologics 0.77 (0.54,1.11) 0.159
anti-IL5/5R 0.71 (0.45,1.12) 0.140
anti-IgE 0.78 (0.39,1.56) 0.482
Estimate (95% CI) p-value
0.0 0.5 1.0 1.5 2.0 2.5
Odds ratios (and 95% CI) of better control post-biologic, conditioning on pre-biologic asthma control status
(D)
ALLERGIC RHINITIS
all biologics 0.2 (-0.5,1.7) 0.631
anti-IL5/5R 0.4 (-0.5,2.6) 0.493
anti-IgE 0.1 (-0.5,1.7) 0.794
CHRONIC RHINOSINUSITIS
all biologics 0.1 (-0.3,0.6) 0.739
anti-IL5/5R 0.0 (-0.4,0.6) 0.822
anti-IgE 1.3 (0.1,3.8) 0.030
NASAL POLYPOSIS
all biologics -0.3 (-0.5,0.1) 0.132
anti-IL5/5R -0.2 (-0.5,0.2) 0.222
anti-IgE 0.7 (-0.2,2.9) 0.177
ECZEMA/ATOPIC DERMATITIS
all biologics -0.2 (-0.6,0.6) 0.511
anti-IL5/5R -0.1 (-0.6,1.2) 0.829
anti-IgE -0.6 (-0.9,0.2) 0.088
Estimate (95% CI) p-value
-1.0 0.0 1.0 2.0 3.0 4.0
Differences (and 95% CI) in post-biologic long-term OCS daily doses (mg/day), conditioning on pre-biologic long-term OCS doses in users at biologic intiation

Methods

International Severe Asthma Registry

All data collection sites in ISAR have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations. The ISAR database has ethical approval from the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218) and is registered with the European Union Electronic Register of Post-Authorization studies (ENCEPP/DSPP/23720). The study was designed, implemented, and reported in compliance with the European Network Centers for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) Code of Conduct (EMA 2014; EUPAS44024) and with all applicable local and international laws and regulation, and registered with ENCEPP (https://www.encepp.eu/encepp/viewResource.htm?id=48848). Governance was provided by ADEPT (registration number: ADEPT1121).

Patients with severe asthma included in ISAR have been well characterized(1) and phenotyped.(2) T2-comorbidity information is also collected as a core variable by all contributing countries.(3) The details of this registry have been published elsewhere.(4–6)

S-Table 1. Operational definitions of potentially T2-related comorbidities.

Label	Type	Values	Data source/variable computation
Allergic rhinitis	Binary	Ever, Never, Missing	OC countries[1], Australia[2], Ireland[2], Italy[2], Portugal[2]: categorical field (Current/Past/Never) Denmark[2]: binary field (Yes/No) Spain[2]: checkbox[4] USA[3]: ICD codes plus free-text field[4] UK[2]: free-text field – data not used[5]
Chronic rhinosinusitis*	Binary	Ever, Never, Missing	OC countries[1], Ireland[2], Italy[2], Portugal[2]: categorical field (Current/Past/Never) Denmark[2]: binary field (Yes/No) Spain[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4] Australia[2]: not collected at the time of data extraction for this project.
Nasal polyposis	Binary	Ever, Never, Missing	OC countries[1], Australia[2], Ireland[2], Italy[2], Portugal[2], UK[2]: categorical field (Current/Past/Never) Denmark[2]: binary field (Yes/No) Spain[2]: checkbox[4] USA[3]: ICD codes plus free-text field[4]
Eczema/atopic dermatitis	Binary	Ever, Never, Missing	OC countries[1], Australia[2], Ireland[2], Italy[2], Portugal[2], UK[2]: categorical field (Current/Past/Never) Denmark[2]: binary field (Yes/No) Spain[2]: checkbox[4] USA[3]: ICD codes plus free-text field[4]
Any potentially T2-related comorbidity	Binary	Ever, Never, Missing	Variable computed for patients with data available for all 4 comorbid conditions.

1. Fourteen countries use the OpenClinica platform to record data in a standardized electronic case report form (eCRF): Argentina, Bulgaria, Canada, Colombia, Greece, India, Japan, Kuwait, Mexico, Poland, Saudi Arabia, South Korea, Taiwan, UAE.
2. Seven countries use their own eCRF platform: Australia, Denmark, Ireland, Italy, Portugal, Spain, UK.
3. The USA provides data extracted from the electronic medical records (EMR).
4. For comorbidities in which presence was assessed through a box field to be checked if present or through free-text field, absence of the comorbidity was assumed if the box was left unchecked or if no sign of the comorbid condition was present in the free-text field. No patients were coded with missing information.
5. Allergic rhinitis was recorded for only 3.6% of the UK patients and under-reporting of this common condition was confirmed by UK collaborators.

* Whenever nasal polyposis was reported while chronic rhinosinusitis was not reported, chronic rhinosinusitis was forced to “Ever”, except for Australia, in which chronic rhinosinusitis without nasal polyposis was not collected. Patients coded “Ever” for chronic rhinosinusitis then correspond to patients with this condition, with or without (or no information on) nasal polyposis. Patients coded “Never” for nasal polyposis and without information on chronic rhinosinusitis in general were left missing for chronic rhinosinusitis.

S-Table 2: Asthma outcomes assessed

Label	Type	Values	Data source/variable computation
Asthma-related outcomes at biologic initiation			
Exacerbation rate (count per year)	Count	0 to 24	Number of exacerbations requiring rescue steroids in the 12 months preceding biologic initiation
Lung function: post-bronchodilator forced expiratory volume in 1 second (FEV_1) percent of predicted (%)	Numerical	14 to 185%	Pre-biologic initiation closest measurement.
Lung function: ratio of post-bronchodilator FEV_1 over post-bronchodilator forced vital capacity (FVC) (FEV_1/FVC)	Numerical	0.20 to 1.00	Pre-biologic initiation closest measurement
Asthma control assessment	Ordinal	Well controlled, Partially controlled, Uncontrolled	As assessed closest to biologic initiation. Categories defined by GINA 2020(7)update. For countries providing ACQ(8) or ACT(9) instead of GINA categories, conversions were performed as follows: - ACQ: Mean ACQ ≤0.75: Well controlled 0.75 < Mean ACQ <1.5: Partly controlled Mean ACQ ≥1.5:Uncontrolled - ACT: Total ACT >19: Well controlled 15 < Total ACT ≤19: Partly controlled Total ACT ≤15: Uncontrolled
Long-term OCS use	Binary	Yes, No, Missing	-
Long-term OCS daily dose (mg/day)	Numerical	0.5 to 100	-
Asthma-related outcomes at follow-up (post-biologic initiation)			
Exacerbation rate (count per year)	Count	0 to 24	Number of exacerbations per year requiring rescue steroids after biologic initiation during the available follow-up period (min. 48 weeks)
Lung function: post-bronchodilator forced expiratory volume in 1 second (FEV_1) percent of predicted (%)	Numerical	14 to 185%	Post-biologic measurement closest to 1 year after initiation (min. 24 weeks)

Asthma control assessment	Ordinal	Well controlled, Partially controlled, Uncontrolled	As assessed closest to 1 year after biologic initiation (min. 24 weeks). Categories defined by GINA 2020(7) update. For countries providing ACQ(8) or ACT(9) instead of GINA categories, conversions were performed as follows: - ACQ: Mean ACQ ≤0.75: Well controlled 0.75 < Mean ACQ <1.5: Partly controlled Mean ACQ ≥1.5: Uncontrolled - ACT: Total ACT >19: Well controlled 15 < Total ACT ≤19: Partly controlled Total ACT ≤15: Uncontrolled
Long-term OCS daily dose (mg/day)	Numerical	0 to 100	As assessed closest to 1 year after biologic initiation (min. 24 weeks)

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; GINA: Global Initiative for Asthma; IU: international unit; OCS: oral corticosteroids.

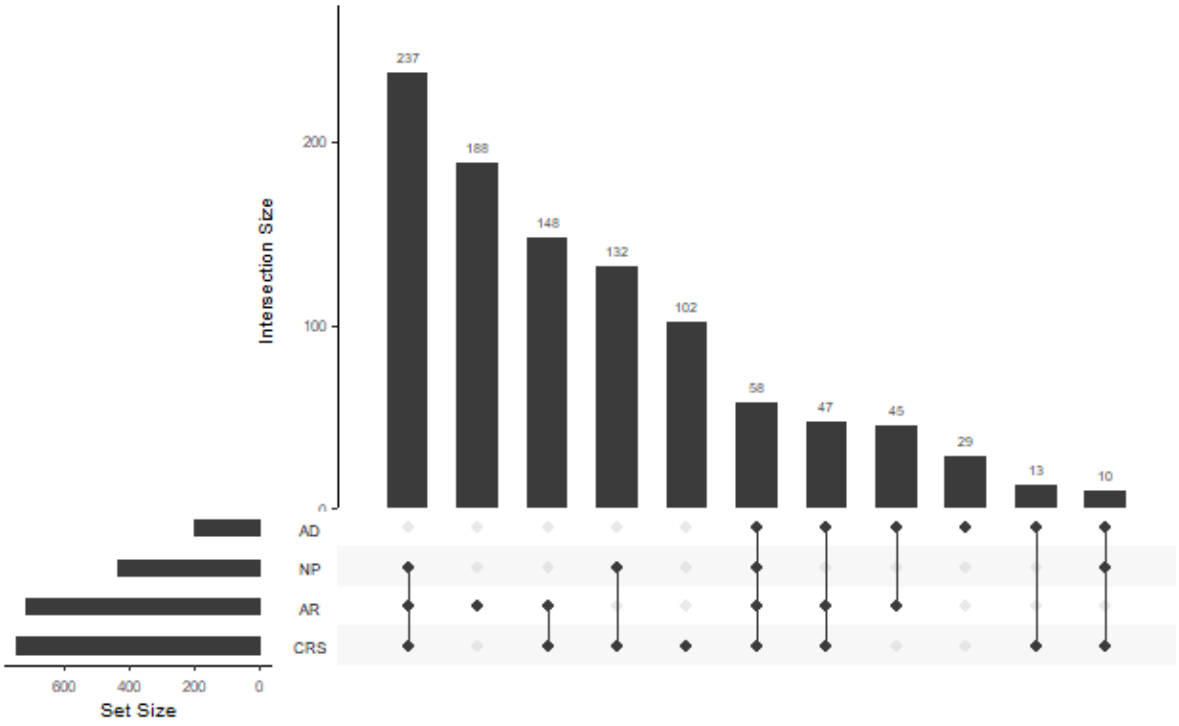
Results

S-Table 3. Prevalence of comorbidities by country.

Country	Allergic rhinitis			Chronic rhinosinutisis			Nasal polyposis			Eczema/atopic dermatitis			Any of the four*		
	Denominator	N	(%)	Denominator	N	(%)	Denominator	N	(%)	Denominator	N	(%)	Denominator	N	(%)
Italy (n=421)	305	192	(63.0)	408	269	(65.9)	418	203	(48.6)	416	21	(5.0)	301	238	(79.1)
UK (n=390)	0	-	-	390	130	(33.3)	390	116	(29.7)	390	15	(3.8)	0	-	-
USA (n=288)	288	149	(51.7)	288	192	(66.7)	288	67	(23.3)	288	54	(18.8)	288	254	(88.2)
Denmark (n=176)	176	83	(47.2)	175	106	(60.6)	176	64	(36.4)	176	31	(17.6)	175	134	(76.6)
Canada (n=108)	105	70	(66.7)	107	79	(73.8)	108	49	(45.4)	107	55	(51.4)	104	99	(95.2)
Spain (n=55)	55	26	(47.3)	55	24	(43.6)	55	19	(34.5)	55	3	(5.5)	55	41	(74.5)
Kuwait (n=53)	53	40	(75.5)	53	30	(56.6)	53	23	(43.4)	53	8	(15.1)	53	43	(81.1)
Taiwan (n=48)	48	37	(77.1)	48	16	(33.3)	48	6	(12.5)	46	9	(19.6)	46	40	(87.0)
Japan (n=37)	37	28	(75.7)	35	21	(60.0)	32	10	(31.3)	35	14	(40.0)	32	28	(87.5)
Colombia(n=33)	33	19	(57.6)	33	23	(69.7)	33	11	(33.3)	33	4	(12.1)	33	28	(84.8)
Australia (n=30)	30	23	(76.7)	0	-	-	30	15	(50.0)	29	14	(48.3)	0	-	-
Saudi Arabia (n=26)	26	21	(80.8)	26	22	(84.6)	26	21	(80.8)	26	6	(23.1)	26	24	(92.3)
Poland (n=23)	21	12	(57.1)	23	14	(60.9)	23	8	(34.8)	23	3	(13.0)	21	16	(76.2)
UAE (n=18)	18	12	(66.7)	18	11	(61.1)	18	9	(50.0)	18	0	(0.0)	18	14	(77.8)
Greece (n=16)	16	13	(81.3)	16	13	(81.3)	16	6	(37.5)	16	0	(0.0)	16	15	(93.8)
South Korea (n=13)	13	10	(76.9)	12	5	(41.7)	12	3	(25.0)	13	3	(23.1)	12	10	(83.3)
Argentina (n=9)	9	7	(77.8)	9	4	(44.4)	9	2	(22.2)	9	0	(0.0)	9	8	(88.9)
Mexico (n=9)	9	9	(100.0)	9	4	(44.4)	9	4	(44.4)	9	1	(11.1)	9	9	(100.0)
Bulgaria (n=8)	8	8	(100.0)	7	5	(71.4)	8	0	(0.0)	8	2	(25.0)	7	7	(100.0)
Portugal (n=3)	3	1	(33.3)	3	0	(0.0)	3	0	(0.0)	3	0	(0.0)	3	1	(33.3)
India (n=1)	1	1	(100.0)	1	0	(0.0)	1	0	(0.0)	0	-	-	0	-	-
Total (n=1765)	**1254**	**761**	**(60.7)**	**1716**	**968**	**(56.4)**	**1756**	**636**	**(36.2)**	**1753**	**243**	**(13.9)**	**1208**	**1009**	**(83.5)**

*In patients with available data for the 4 comorbid conditions of interest.

S-Figure 1: Overlap between comorbidities



Left-side bars represent the numbers of patients with reported AR, CRS, NP, or AR. Top bars represent the numbers of patients with reported unique (non-overlapping) combinations of 1, 2, 3, or 4 comorbidities, as illustrated on the axis. Sample size was the total number of patients with data available on all comorbidities and at least one reported comorbidity (n=10091009). AD: eczema/atopic dermatitis; AR: allergic rhinitis; CRS: chronic rhinosinusitis; NP: nasal polyposis.
Figure created with Rpackage UpsetR.

References

1. Wang, E., Wechsler, M. E., Tran, T. N., Heaney, L. G., Jones, R. C., Menzies-Gow, A. N., *et al.* Characterization of severe asthma worldwide: data from the International Severe Asthma Registry (ISAR). *Chest* 2020;157:805–814.
2. Heaney LG, Perez de Llano L, Al-Ahmad M, Backer V, Busby J, Canonica GW, *et al.* Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. *Chest* 2021;160:814–830.
3. FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, *et al.* International severe asthma registry (ISAR): protocol for a global registry. *BMC Med Res Methodol* 2020;20:212.
4. ISAR Study Group. International Severe Asthma Registry (ISAR): Mission Statement. *Chest* 2020;157:805–814.
5. FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, *et al.* International Severe Asthma Registry (ISAR): protocol for a global registry. *BMC Medical Research Methodology* 2019;Submitted:
6. Bulathsinhala L, Eleangovan N, Heaney LG, Menzies-Gow A, Gibson PG, Peters M, *et al.* Development of the International Severe Asthma Registry (ISAR): A Modified Delphi Study. *J Allergy Clin Immunol Pract* 2019;7:578-588.e2.
7. Global Initiative for Asthma. Global Strategy for Asthma Managment and Prevention. Updated 2020. at <https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf>.
8. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–907.
9. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, *et al.* Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59–65.