Study Report

ImPact of comoRbidity In Severe asthMa patients (PRISM)

Prevalence of comorbidities in adult patients with severe asthma and association with response to biologics

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Countries of study	Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, South Korea, Spain, Taiwan, United Arab Emirates, United Kingdom, United States of America
Data source	ISAR database - Comorbidity variables: data on file as of 24/01/2022 - All other variables: data on file as of 10/03/2022
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Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Explanation
ABPA	Allergic bronchopulmonary aspergillosis
ACA	Asthma Control Assessment
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADEPT	The Anonymous Data Ethics Protocols and Transparency committee
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
EGPA	Eosinophilic granulomatosis with polyangiitis
ENCePP	European Network Centres for Pharmacoepidemiology and Pharmacovigilance
FVC	Force vital capacity
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
GERD	Gastro-oesophageal reflux disease
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL-4, -5, -13	Interleukin-4, -5, -13
IL-4R, -5R	Interleukin-4 receptor, -5 receptor
ISAR	International Severe Asthma Registry
LABA	Long-acting beta-agonists
LAMA	Long-acting muscarinic antagonists
NERD	Nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease
NSAID	Nonsteroidal anti-inflammatory drug
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
REG	Respiratory Effectiveness Group
T2	Type 2 inflammation
VCD	Vocal cord dysfunction

1.0 Executive Summary

Comorbidities in severe asthma patients are conditions or diseases that coexist with asthma and may have causal connection with asthma (1,2). The associated economic burden is substantial, with overall comorbidity-attributable healthcare costs five times higher than costs attributable to asthma alone, increased risk of work disability, and significant productivity losses (3–5). In addition, patients with comorbidities are at an increased risk of poor asthma-related outcomes (6,7).

Using data from the International Severe Asthma Registry (ISAR), we investigated the real-world prevalence and patterns of comorbidities. A total of 30 individual comorbidities were studied in a sample size varying from 6,149 to 11,613 patients from 22 different countries contributing to the registry. Overall, the prevalence of having at least one comorbidity was 92%. The estimates for having at least one potentially T2-related comorbidity, at least one potentially OCS-related comorbidity, and at least one comorbidity mimicking/exacerbating asthma were 69%, 67%, and 55%, respectively. The most frequent comorbidities were allergic rhinitis (49%), gastro-esophageal reflux disease (44%), obesity (42%), chronic rhinosinusitis (with or without nasal polyposis) (38%), hypertension (23%), sleep apnea (22%), and nasal polyposis (21%). Comorbidities co-occurred across categories, with 33% of patients having at least one comorbidity from each category.

In general, the prevalence of comorbidities was higher in women than in men, except for nasal polyposis and sleep apnea that were more frequent in men. Adjusting for age, sex, and country, we found that an older age of asthma onset was associated with increased odds of chronic rhinosinusitis and nasal polyposis, and decreased odds of allergic rhinitis and eczema/atopic dermatitis. No significant associations were found between age of asthma onset and non T2-related comorbidities. Higher blood eosinophil counts, higher IgE levels, and higher FeNO test results being associated with increased odds of potentially T2-related comorbidity. On the contrary, lower biomarker measures were associated with increased odds of several non-T2-related comorbidities.

Asthma-related outcomes at registry enrolment were also associated with comorbidities. Notably, several comorbidities were associated with higher odds of receiving long-term OCS and higher exacerbation rates. Osteoporosis had the strongest association with receiving long-term OCS, and gastro-esophageal reflux disease and osteoporosis had the strongest associations with exacerbation rates. Patients with potentially T2-related comorbidities tended to have better lung function, whereas several non T2-related comorbidities were associated with poorer lung function. Some such non T2-related comorbidities included

hypertension, osteoporosis, diabetes, chronic obstructive pulmonary disease, bronchiectasis, and vocal cord dysfunction/laryngeal spasms. Finally, patients with chronic rhinosinusitis, obesity, hypertension, sleep apnea, anxiety/depression, osteoporosis, diabetes, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, and vocal cord dysfunction/laryngeal spasms had higher odds of having uncontrolled asthma at enrolment, whereas no comorbidity was significantly associated with better asthma control.

We further assessed the association between potentially T2-related comorbidities and response to biologics. Allergic rhinitis, chronic rhinosinusitis, and nasal polyposis were all associated with a greater reduction in exacerbation rates, and higher odds of improvement in asthma control. Allergic rhinitis and chronic rhinosinusitis were associated with larger improvement in lung function, as measured through FEV1 percent predicted. No studied comorbidity had a significant association with the degree of daily long-term OCS daily dose reduction. Finally, the presence of eczema or atopic dermatitis did not seem to have an association with response to biologics for the four asthma-related outcomes under investigation.

In conclusion, comorbidities are frequent in adults with severe asthma and multi-comorbidity is common. The presence of comorbidity is generally associated with poorer asthma-related outcomes. However, patients with allergic rhinitis, chronic rhinosinusitis and nasal polyposis tend to experience an enhanced response to biologics in terms of exacerbation rates and asthma control (all three comorbidities), as well as lung function (allergic rhinitis and chronic rhinosinusitis). Overall, the PRISM study highlights the importance of systematic evaluation for comorbidities and a multidisciplinary approach to their management in patients with severe asthma.

2.0 Background

Comorbid conditions – such as allergic rhinitis, gastro-oesophageal reflux disease (GERD), and obesity – are common in asthma (8). They are conditions or diseases that coexist with asthma and may have causal connection with asthma (1,2). The associated economic burden is substantial, with overall comorbidity-attributable healthcare costs five times higher than costs attributable to asthma alone, increased risk of work disability, and significant productivity losses (3–5). In addition, patients with comorbidities are at an increased risk of poor asthma-related outcomes (6,7).

Comorbidities can complicate asthma management in multiple ways: (i) they may share the same pathophysiological process as asthma (eg, rhinitis); (ii) they may mimic and/or exacerbate asthma symptoms (eg, GERD); (iii) treatment for comorbid conditions may affect asthma (eg, β-blockers for the management of cardiovascular disease, ocular hypertension or anxiety); and (iv) comorbidities may be the result of side effects of asthma-related treatment (eg, oral corticosteroids [OCS]) (1,9,10). The list of asthma comorbidities is extensive and heterogeneous. The following categories have been described:

- **Type 2 inflammatory (T2) comorbidities –** They share the same immunopathologic hallmarks with type 2 asthma, ie the production of key cytokines including interleukins (IL)-4, -5 and -13 by T-helper 2 cells and type 2 innate lymphoid cells (11). The most common of these being allergic rhinitis, eczema/atopic dermatitis, and nasal polyposis. Other potentially T2 comorbidities include allergic conjunctivitis, eosinophilic oesophagitis, food allergy, eosinophilic chronic rhinosinusitis, allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD), and urticaria.

- **Comorbidities potentially related to OCS exposure –** While not necessarily caused by OCS exposure in asthma patients, a dose-response relationship between OCS exposure and the following conditions has been documented (12–14): obstructive sleep apnoea syndrome, obesity, diabetes and insulin resistance, dyslipidemia, hypertension, cardio-/cerebrovascular disease, osteoporosis and osteopenia, peptic ulcers, cataract, glaucoma, anxiety, depression, chronic kidney disease, thromboembolism, adrenal insufficiency, skin atrophy, pneumonia and other serious infections.

- **Comorbidities that mimic or exacerbate asthma symptoms –** These can complicate the diagnosis and management of patients with asthma and lead to under- or overtreatment (1). They include ABPA and EGPA (both potentially T2-related), bronchiectasis, dysfunctional breathing, GERD, chronic obstructive pulmonary disease

(COPD), vocal cord dysfunction/laryngeal obstruction, anxiety and depression (both potentially OCS-related), as well as rare conditions such as sub glottis stenosis.

In two nationally representative samples of the United States and the United Kingdom, the proportion of asthma patients reporting having at least one comorbid condition was 54% and 63%, respectively (15,16). The prevalence of individual comorbidities may vary with age, sex, and asthma phenotype (1).

Severe asthma is defined by the European Respiratory Society and American Thoracic Society's 2014 guidelines as asthma that requires high-dose inhaled corticosteroid (ICS) treatment plus a second controller and/or OCS to prevent it from becoming uncontrolled or that remains uncontrolled despite therapy (17). Patients with severe asthma account for 3–10% of the total population of asthma patients and contribute disproportionately to asthma morbidity, mortality, and costs (18). The treatment regimen typically includes high-dose of inhaled corticosteroids combined with a long-acting β2-agonist, a leukotriene modifier or theophylline, long-acting muscarinic antagonists, and/or long-term OCS use (18). Severe asthma patients can also be eligible for biologic add-on therapies, most of which target type 2 inflammation (18). Biologics approved for severe asthma include anti-IgE therapy (omalizumab), anti-IL5/5R therapy (mepolizumab, benralizumab and reslizumab) and anti-IL4/13 therapy (dupilumab) (19).

Comorbidities in severe asthma are more common than in mild-to-moderate asthma, and multiple comorbidities may affect the same patient (10). Some comorbidities may be more common in specific phenotypes of severe asthma, although the evidence in this area is still limited, making the assessment and management of this patient group challenging (9). Moreover, severe asthma patients with serious or multiple comorbid conditions are generally excluded from clinical trials, leading to a lack of evidence to guide asthma treatment in these individuals (1). Interestingly, the presence of T2-related comorbidities could predict a better response to biologics (20). Understanding the pattern of comorbidities by severe asthma phenotypes/endotypes and assessing their impact on response to asthma treatment is important to improve the assessment of comorbidities and asthma management.

The large, multi-country cohort of severe asthma adult patients included in the International Severe Asthma Registry (ISAR) constitutes a unique resource to investigate the impact of comorbidity in severe asthma. In this study, we investigated the real-world prevalence and patterns or comorbidities in patients enrolled in ISAR and assessed the association between T2 comorbidities and response to biologics.

3.0 Study Aims and Objectives

3.1 Study Aims

To understand the pattern of comorbidities in adults with severe asthma and investigate their association with asthma-related outcomes.

3.2 Study Objectives

Objective 1: To assess the prevalence of individual comorbidities and predefined comorbidity categories in severe asthma patients and explore comorbidity co-occurrence

Comorbidity categories include: T2; mimicking/exacerbating asthma; potentially OCS-related.

Objective 2: To compare the comorbidity prevalence by demographic and clinical characteristics of severe asthma patients

The comparisons will focus on most common (≥10% prevalence overall) individual comorbidities.

Objective 3: To determine the association between T2 comorbidities/comorbidity category and response to biologics

Response to biologics measured through post-biologic status (in the period 24 weeks to approximately 1 year following biologic initiation) of four asthma-related outcomes: exacerbation rate; asthma control; lung function; and long-term OCS daily dose.

4.0 Materials and Methods

4.1 Overall Study Design

Objective 1: cross-sectional design over the timeframe of the patient visits. Data collected on comorbidities at any time during the patient visits was used to compute ever/never variables (Figure 1).

Objective 2: cross-sectional design. For time-varying demographic and clinical characteristics, values at enrolment in the registry were mainly used (Figure 2). More details are available in Section 5.

Objective 3: longitudinal cohort design. Study entry corresponded to date of initiation of first biologics. A history of T2-related comorbidities was assumed at study entry regardless of the timing (visit) when it was reported. Asthma-related outcomes have been assessed as close as possible to one year of follow-up (details available in Section 5) (Figure 3).

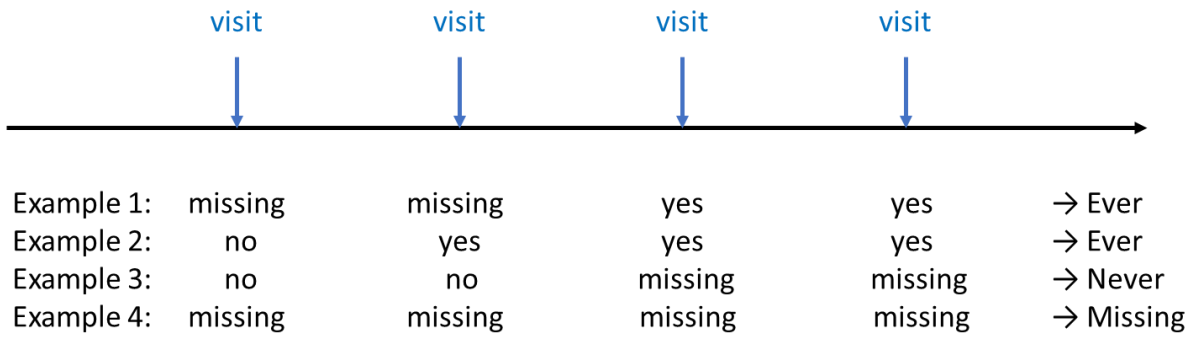

Figure 1. Study design for objective 1. All available visits were used. This figure is using the example where four visits were available.

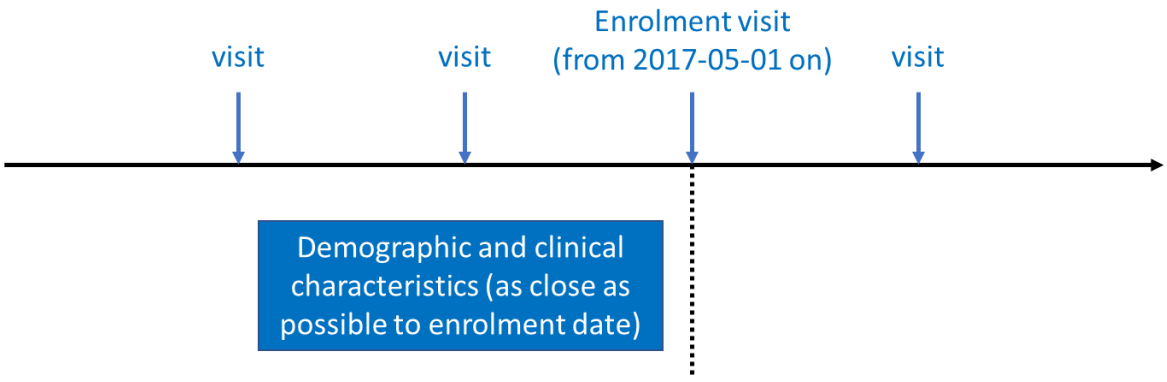

Figure 2. Study design for objective 2. Prospectively enrolled patients only.

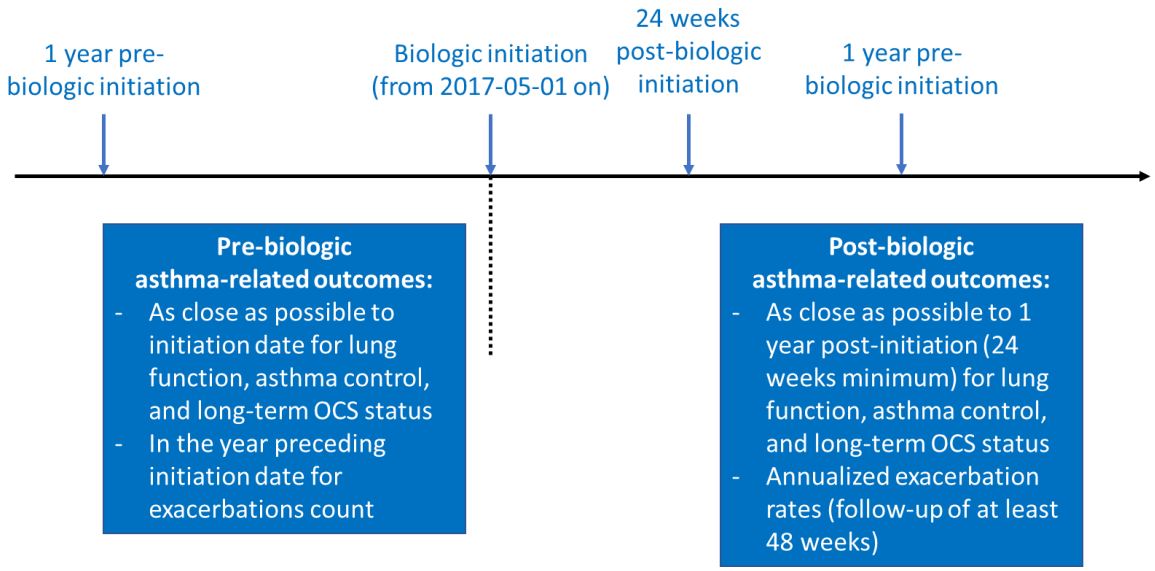

Figure 3. Study design for objective 3. Prospectively enrolled patients only.

4.2 Study Population and Data Source

ISAR is an international collaborative initiative to gather pseudonymous (de-identified), longitudinal, observational data for patients with severe asthma. Eligible participants are patients aged 18 years or more who visit a participating centre, have a diagnosis of severe asthma, and are willing to contribute with their data. In ISAR, severe asthma is defined as asthma requiring treatment with GINA 2018 Treatment Step 4 (medium- or high-dose ICS-LABA therapy) but that remains uncontrolled, OR asthma requiring treatment with GINA 2018 Step 5 (with or without add-on LAMA or biologic therapy) (21). Willingness to participate is assessed through signing a written informed consent.

As of 24 January 2021, ISAR held standardized patient-level data for 12,099 patients from 186 clinical sites in 22 countries, including over 8,500 patients enrolled prospectively since 1 May 2017 (date of ISAR launch). Data relevant to severe asthma research were collected at each visit or extracted from medical records. This includes details on asthma phenotype and endotype, asthma-related outcomes, treatment regimens, and data on comorbidities.

4.3 Inclusion and Exclusion Criteria

ISAR common inclusion criteria

- Age ≥ 18 years old
- Patient with severe asthma, as defined by asthma requiring treatment with GINA 2018 (21) recommended medications:
    - GINA Treatment Step 4 (medium- or high-dose ICS-LABA therapy) and uncontrolled asthma OR
    - GINA Treatment Step 5 (with or without add-on LAMA or biologic therapy).

PRISM-specific inclusion criteria

- All objectives: non missing data for at least one comorbidity across all visits
- Objective 3: patients who have initiated biologics
- Objective 3: data available on at least one asthma related outcome in the window 24 weeks to 1-year post-biologic initiation, and corresponding data at biologic initiation
- Objective 3: non missing data for at least one potentially T2-related comorbidity

PRISM-specific exclusion criteria

- All objectives: missing age and/or date at enrolment in ISAR
- Objectives 2 and 3: retrospectively enrolled patients (ie, before 1 May 2017)
- Objectives 2 and 3: missing gender data
- Objective 3: patient had bronchial thermoplasty

5.0 Study Variables

5.1 Objective 1

5.1.1 Demographic Variables

Country is the only demographic variable considered for objective 1. Patients were enrolled from 22 countries: Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, South Korea, Spain, Taiwan, the United Arab Emirates (UAE), the United Kingdom (UK), the United States of America (USA).

5.1.2 Comorbidity Variables

We assessed presence/absence of 30 comorbid conditions, categorized as potentially T2-related comorbidities, potentially OCS-related comorbidities, or comorbidities mimicking/exacerbating asthma. Table 1 provides details on the operational definitions of the comorbidity variables. Three categories of ISAR variables are shown: core ISAR data, bolt-on ISAR data and extra ISAR data. Core ISAR data are variables that were identified using an ISAR-led Delphi study (22). All countries participating in ISAR collect core ISAR variables. ‘Effectiveness’ bolt-on variables were OCS-related comorbidities. ‘Safety’ bolt-on variables assessed the safety of biologics: serious infection, anaphylaxis, and cancer. Not all countries in ISAR collect the bolt-on variables. Extra ISAR data are variables that do not fall within core or bolt-on ISAR variables, but that countries may collect as per their research interests (these data are typically extracted from free text).

Table 1. Operational definitions of comorbidity variables.

Label	Type	Values	Data source/variable computation
Potentially T2-related comorbidities			
Allergic rhinitis	Binary	Ever, Never, Missing	**Core ISAR data** 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] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Chronic rhinosinusitis	Binary	Ever, Never, Missing	**Core ISAR data** OC countries[1], Ireland[2], Italy[2], Portugal[2]: categorical field (Current/Past/Never) Denmark[2]: binary field (Yes/No) Australia[2], Spain[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Nasal polyposis	Binary	Ever, Never, Missing	**Core ISAR data** 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	**Core ISAR data** 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]
Urticaria	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Australia[2], Spain[2], UK[2]: free-text field[4] USA[2]: ICD codes plus free-text field[4]
Food allergy	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Australia[2], Portugal[2], Spain[2], UK[2]: free-text field[4] USA[2]: ICD codes plus free-text field[4]
Aspirin sensitivity	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Canada[1]: categorical field (Current/Past/Never) Australia[2], Spain[2]: checkbox[4] Denmark[2], Portugal[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[2]: ICD codes plus free-text field[4]
Eosinophilic esophagitis	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Australia[2], UK[2]: free-text field[4] USA[2]: ICD codes plus free-text field[4]
Any potentially T2-related comorbidity	Binary	Ever, Never, Missing	The 8 variables defined above for individual comorbid conditions. Ever was defined by any comorbidity coded Ever. Missing was assigned to patients with all 8 comorbid conditions missing. The rest was coded Never.
Number of reported potentially T2-related comorbidities	Count	0 to 8	Each of the 8 comorbid conditions listed above counts for 1 if coded Ever. Missing was assigned to patients with all 8 comorbid conditions missing. The rest was coded Never.

Label	Type	Values	Data source/variable computation
Potentially OCS-related comorbidities			
Obesity	Binary	Ever, Never, Missing	**Core ISAR data** Defined as body mass index (BMI) ≥ 30kg.m^{-2}, calculated from patient's reported height and weight
Hypertension	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** OC countries[1]: free-text field[4] ("other cardiovascular disease") Australia[2], Italy[2], Portugal[2], UK[2]: free-text field[4] Spain[2]: checkbox[4] USA[3]: ICD codes plus free-text field[4]
Sleep apnea	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Denmark[2], Ireland[2], Portugal[2]: binary field (Yes/No) Australia[2], Spain[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Dyslipidemia	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Australia[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Anxiety/depression	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Denmark[2], Ireland[2], Italy[2], Portugal[2]: binary fields (Yes/No) Australia[2], Spain[2]: checkboxes[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4] *Note: in countries with binary fields or checkboxes, anxiety and depression data were collected separately and pooled to create a single variable.*
Osteoporosis	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Ireland[2], Italy[2], Portugal[2]: binary field (Yes/No) Australia[2], Spain[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Diabetes	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Denmark[2], Ireland[2], Italy[2], Portugal[2]: binary field (Yes/No) Australia[2]: checkbox[4] Spain[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Coronary heart disease	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Ireland[2], Italy[2], Portugal[2]: two binary fields (Yes/No) for "heart failure" and "myocardial infarction", plus free-text field ("other cardiovascular disease") Australia[2]: checkbox[4] for "myocardial infarction" plus free-text field[4] Denmark[2]: checkbox[4] for "non-specified cardiovascular disease" Spain[2]: checkbox[4] for "ischemic heart disease" UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]

Label	Type	Values	Data source/variable computation
Pneumonia	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Ireland[2], Italy[2], Portugal[2]: binary field (Yes/No) Australia[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Other significant infections	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Denmark[2], Ireland[2], Italy[2], Spain[2]: binary field (Yes/No) Australia[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Peptic ulcer	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Ireland[2], Italy[2], Portugal[2]: binary field (Yes/No) Australia[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Pulmonary embolism/venous thromboembolism	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Ireland[2], Italy[2], Portugal[2]: binary field (Yes/No) Australia[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Cataract	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Ireland[2], Italy[2], Portugal[2]: binary field (Yes/No) Australia[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Chronic kidney disease	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Ireland[2], Italy[2], Portugal[2]: binary field (Yes/No) for “renal failure” Australia[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Adrenal insufficiency	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Australia[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Glaucoma	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Ireland[2], Italy[2], Portugal[2]: binary field (Yes/No) Australia[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Cerebrovascular accident	Binary	Ever, Never, Missing	**Bolt-on ISAR data[6]** OC countries[1], Ireland[2], Italy[2], Portugal[2]: binary field (Yes/No) for “stroke” Australia[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Any potentially OCS-related comorbidity	Binary	Ever, Never, Missing	The 17 variables defined above for individual comorbid conditions. Ever was defined by any comorbidity coded Ever. Missing was assigned to patients with all 17 comorbid conditions missing. The rest was coded Never.
Number of reported potentially OCS-related comorbidities	Count	0 to 17	Each of the 17 comorbid conditions listed above counts for 1 if coded Ever. Missing was assigned to patients with all 17 comorbid conditions missing. The rest was coded Never.

Label	Type	Values	Data source/variable computation
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease (GERD)	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Canada[1]: categorical field (Current/Past/Never) Australia[2], Spain[2]: checkbox[4] Denmark[2], Portugal[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Chronic obstructive pulmonary disease (COPD)	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Canada[1]: categorical field (Current/Past/Never) Australia[2], Spain[2]: checkbox[4] Denmark[2], Portugal[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Bronchiectasis	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Canada[1]: categorical field (Current/Past/Never) Australia[2], Spain[2]: checkbox[4] Denmark[2], Portugal[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Vocal cord dysfunction/laryngeal spasms	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Australia[2], Spain[2]: checkbox[4] Denmark[2], Portugal[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Dysfunctional breathing	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** Canada[1]: categorical field (Current/Past/Never) Australia[2], Spain[2]: checkbox[4] Denmark[2], Portugal[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Any comorbidity mimicking/ exacerbating asthma	Binary	Ever, Never, Missing	The 5 variables defined above for individual comorbid conditions. Ever was defined by any comorbidity coded Ever. Missing was assigned to patients with all 5 comorbid conditions missing. The rest was coded Never.
Number of comorbidities mimicking/ exacerbating asthma	Count	0 to 5	Each of the 5 comorbid conditions listed above counts for 1 if coded Ever. Missing was assigned to patients with all 5 comorbid conditions missing. The rest was coded Never.
All comorbidities			
Any comorbidity	Binary	Ever, Never, Missing	The 30 variables defined above for individual comorbid conditions. Ever was defined by any comorbidity coded Ever. Missing was assigned to patients with all 30 comorbid conditions missing. The rest was coded Never.
Number of reported comorbidities of any type	Count	0 to 30	Each of the 30 comorbid conditions listed above counts for 1 if coded Ever. Missing was assigned to patients with all 30 comorbid conditions missing. The rest was coded Never.

Label	Type	Values	Data source/variable computation

1. 14 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. 7 countries use 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 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. Additional data provided by some participating countries, outside of the ISAR framework.
6. Data for most potentially OCS-related comorbidities were collected through the ISAR effectiveness/comorbidity bolt-on fields. Data for "other significant infections" was collected through the ISAR safety bolt-on fields.

Data reported by some countries was discarded and all patients set to missing in the following situations:

- Chronic rhinosinusitis: in Australia, a checkbox field was added in the course of the data collection. Only one patient was recorded with chronic rhinosinusitis and it was not possible to define the denominator, ie it was not possible to separate the other patients between those for whom presence of chronic rhinosinusitis was not assessed and those who did not have chronic rhinosinusitis.
- Aspirin sensitivity: one patient in Argentina and one patient in Japan were recorded with aspirin sensitivity. Aspirin sensitivity was not planned to be collected in these two countries. Therefore, it was not possible to assume that the other patients with no record of aspirin sensitivity truly did not have that comorbidity.
- Hypertension: some of the OC countries recorded hypertension in the "other cardiovascular disease" field. Recorded data was not used in countries were the distribution of patients with recorded hypertension was unevenly distributed across sites as this considered as a sign that this condition was not systematically collected: Argentina, Bulgaria, Canada, Colombia, Greece, Saudi Arabia. In India and Kuwait, no patient was recorded with hypertension, and these two countries were also excluded from the analysis of hypertension.
- Dyslipidemia: two OC countries (Canada and Taiwan) recorded dyslipidemia in the field "other cardiovascular disease" for some patients. However, this condition did not seem to be systematically recorded across sites. Similarly, this condition seemed to be unevenly collected across sites in Italy and Spain. None of these four countries were included in the analysis of dyslipidemia.
- Cataract, glaucoma, and chronic kidney disease: in Spain, the data was retrieved from free-text fields for 3, 4, and 1 patient(s), respectively. As the data did not seem to be collected in all sites, Spain was excluded from the analysis of these conditions.

5.1.3 Meta-variables

The data source varied by countries and specific comorbidities. There were five categories:

- eCRF, categorical field (including binary field); or
- eCRF, checkbox; or
- eCRF, free-text field; or
- EMR, ICD-10 codes plus free-text field; or
- EMR, free-text field.

5.2 Objective 2

5.2.1 Comorbidity Variables

See Table 1. For individual comorbid conditions, the analysis was restricted to those with an overall prevalence of at least 10%.

5.2.2 Demographic Variables

Demographic variables were used to assess their association with comorbidity prevalence, as well as adjustment variables for the analysis between clinical characteristics and comorbidity prevalence. Table 2 provides details on the demographic variables selected for the study.

Table 2. Demographic variables considered for Objective 2.

Label	Type	Values	Data source/variable computation
Country	Nominal	Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Portugal, Saudi Arabia, South Korea, Spain, Taiwan, UAE, UK, USA	-
Age at enrolment	Numerical	≥18 years old	Completed years of age at the time of enrolment in the registry. The date of enrolment was defined as follows: - For patients who initiated biologics on or after 1 May 2017: date of biologic initiation; - For patients who did not initiate biologics: first visit occurring from 1 May 2017 on.
Gender	Binary	Women, Men, Missing	As assessed by physician.
Smoking status at enrolment	Ordinal	Current smoker, Ex-smoker, Never smoker, Missing	As assessed by physician.

UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America.

5.2.3 Clinical Variables

Clinical characteristics were categorized as general characteristics, asthma biomarkers, and asthma-related outcomes. Table 3 provides details on the operational definitions of the clinical variables.

Table 3. Clinical variables considered for Objective 2.

Label	Type	Values	Data source/variable computation
General characteristics			
Age at asthma onset	Numerical	≥0, Missing	As reported by patient. 0 means that asthma started before 1 year old.
Received biologics	Binary	Yes, No	At enrolment.
Asthma biomarkers			
Blood highest eosinophil count (cells/µL)	Numerical	20 to 5,000	- In patients receiving biologics: highest count recorded prior to initiating biologics - In patients not receiving biologics: highest count ever recorded
Fractional exhaled Nitric Oxide (FeNO) test result (parts per billion [ppb])	Numerical	1 to 300	- In patients receiving biologics: highest count recorded prior to initiating biologics - In patients not receiving biologics: highest count ever recorded
Count of blood IgE (IU/mL)	Numerical	0 to 15,600	- In patients receiving biologics: highest count recorded prior to initiating biologics - In patients not receiving biologics: highest count ever recorded
Eosinophilic phenotype ISAR algorithm (23)	Ordinal	Grade 0 to 3	Grade 0: Unlikely/noneosinophilic Grade 1: Least likely Grade 2: Likely Grade 3: Most likely
Asthma-related outcomes			
Exacerbation rate at enrolment (count per year)	Count	0 to 24	Number of exacerbations requiring rescue steroids in the 12 months preceding enrolment.
Lung function: post-bronchodilator forced expiratory volume in 1 second (FEV_1) percent of predicted at enrolment (%)	Numerical	14 to 185%	Measurement closest to enrolment.
Lung function: ratio of post-bronchodilator FEV_1 over post-bronchodilator forced vital capacity (FVC) (FEV_1/FVC)	Numerical	0.20 to 1.00	Measurement closest to enrolment.
Asthma control assessment	Ordinal	Well controlled, Party controlled, Uncontrolled	As assessed closest to enrolment. Categories defined by GINA 2020 (24) update. For countries providing ACQ (25) or ACT (26) 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 at enrolment	Binary	Yes, No, Missing	-

Long-term OCS daily dose at enrolment	Numerical	0.5 to 100mg	-

ACQ: Asthma control questionnaire; ACT: Asthma control test; GINA: Global Initiative for Asthma; IU: International unit; OCS: Oral corticosteroids.

5.3 Objective 3

5.3.1 Outcome Variables

Outcome variables for objective 3 are post-biologic values for four asthma-related outcomes. Variable types, values, and computations of post-biologic asthma-related outcomes were similar as for asthma-related outcomes at biologic initiation (see Table 3):

- Exacerbation rate: number of exacerbation episodes per year. The assessment was made using the entire follow-up period. A minimum of 48 weeks between assessment and biologic initiation was required.
- Lung function: post-bronchodilator FEV_1 percent of predicted (%) as measured as close as available to one-year post-biologic initiation. A minimum of 24 weeks between assessment and biologic initiation was required.
- Asthma control assessment: well controlled/partly controlled/uncontrolled, as assessed as close as available to one-year post-biologic initiation (see details on asthma control assessment in Table 3). A minimum of 24 weeks between assessment and biologic initiation was required.
- Long-term OCS daily dose (mg): daily dose use as close as available to one-year post-biologic initiation. A minimum of 24 weeks between assessment and biologic initiation was required.

5.3.2 Explanatory Variables

Potentially T2-related comorbidities were the main explanatory variables. We evaluated five variables: presence of any potentially T2-related comorbidities, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, and eczema/atopic dermatitis (see Table 1). Individual comorbid conditions were selected on the basis of having an overall prevalence of at least 10%.

5.3.3 Adjustment Variables

We primarily adjusted the analyses for the considered asthma-related outcome value at biologic initiation, and further considered adjustment for age at biologic initiation and gender.

6.0 Statistical Analysis

6.1 Objective 1

6.1.1 Sample Size

The total sample size for objective 1 analysis was 11,821 patients. The sample size varied depending on the considered comorbidity or group of comorbidities. For each analysis, the corresponding sample size is reported in the result section.
Objective 1 included patients both retrospectively and prospectively enrolled. For retrospectively enrolled patients, the enrolment visit was set as the visit closest to the launch of ISAR (1 May 2017) for patients who did not initiated biologics, and as the biologic initiation for patients who initiated biologics.

6.1.2 Descriptive analysis

Prevalence of individual comorbidities and comorbidity categories

For each individual comorbidity, the denominator was computed as the number of patients with presence/absence information available across all visits. Prevalence estimates were calculated by dividing the number of patients with reported comorbidity by the corresponding denominator and expressed in percent.

To compute the prevalence of having any comorbidity, overall and by categories, the denominator was the number of patients with non missing data at least one comorbidity (overall and by categories). As a sensitivity analysis, we calculated the prevalence in subgroups of patients with non missing data for at least two, three, etc. up to the total number of considered comorbidities.

To investigate the influence of contributing countries to the overall prevalence estimates, we conducted meta-analyses of country-specific prevalence estimates using generalised linear mixed models, where we estimated the overall prevalence from random intercept logistic regression models (random effects model estimates). [Schwarzer et al. (2019)] The overall prevalence calculated with no consideration of countries as calculated above were equivalent to meta-analysis pooled estimates from the fixed effects models.

Comorbidity counts and co-occurrences

In patients with non missing data for at least three comorbidities, overall and by categories, we counted the number of reported comorbidities and calculated the prevalence of one, two, and three or more comorbidities (overall and by categories). As a sensitivity analysis, we repeated this analysis in subgroups of patients with non missing data for at least four, five, etc. up to the total number of considered comorbidities.

In patients with non missing data for at least one comorbidity in each category, we calculated the proportions of patients having no comorbidity, potentially T2-comorbidity only, potentially OCS comorbidity only, comorbidity mimicking/exacerbating asthma only, any combination of comorbidity in two categories, and comorbidity in all three categories.

6.2 Objective 2

6.2.1 Sample Size

The total sample size for objective 2 was 8,499 patients. All patients were prospectively enrolled, ie from 1 May 2017 on. The sample size varied depending on the considered comorbidity or group of comorbidities, and data availability of demographic and clinical characteristics. For each analysis, the corresponding sample size is reported in the result section.

6.2.2 Association analysis

The prevalence of comorbidities by demographic characteristics (age, gender, and tobacco smoking at enrolment) were compared through univariate analysis. The difference in age distributions in patients with and without comorbidities was tested with Kruskal-Wallis rank sum tests. The differences in gender and tobacco smoking status distributions were tested with Pearson's Chi-squared tests.

The associations between clinical characteristics/asthma-related outcomes and comorbidities were assessed through multivariable models, adjusting for country, age at enrolment, and gender. For the analysis of clinical characteristics, presence/absence of comorbidity was the dependent variable, and clinical characteristics and adjustment variables the explanatory variables. We used logistic regression models and results were expressed as odds ratios of having comorbidity for: a 5-year increase in age at asthma onset; a doubling in blood

eosinophil concentration; a doubling in IgE concentration; a doubling in FeNO test result. To estimate the odds ratios for a doubling in biomarkers, we fitted the model with a log2-transformation of biomarker raw values. Because IgE blood concentrations contained zero values, we used log2(IgE concentration +1).

For the analysis of asthma-related outcomes, we modelled each outcome successively with comorbidity and adjustment variables as explanatory variables. We used logistic regressions for long-term OCS use with results expressed as odds ratios of receiving long-term OCS in patients with comorbidity compared to without. We used negative binomial regressions for exacerbation rates at enrolment (number of exacerbation episodes in the year preceding enrolment) and results were expressed as the ratio of means between patients with and without comorbidity. For lung function, we used linear regressions to compare the averaged difference in FEV_1 percent predicted values between patients with and without comorbidity. Finally, for asthma control, we used logistic regressions to calculate the odds ratios of being uncontrolled at enrolment in presence of comorbidity.

6.3 Objective 3

6.3.1 Sample Size

The total sample size for objective 3 was 1,769 patients. All patients were prospectively enrolled, ie from 1 May 2017 on, and initiated biologics. The sample size varied depending on the considered comorbidity and data availability of asthma-related outcomes pre- and post-biologic initiation. For each analysis, the corresponding sample size is reported in the result section.

6.3.2 Association analysis

For exacerbation rates, we used negative binomial regressions with exacerbation rates at follow-up as the outcome variable, comorbidity as the explanatory variable, and number of exacerbations in the year preceding biologic initiation as the adjustment variable. Results were expressed as rate ratios of post-biologic exacerbation rates, comparing patients with and without comorbidity, conditioning on (adjusting for) pre-biologic exacerbation rate. Results were stratified by long-term OCS status at biologic initiation. We further explored the impact of adjusting for age at biologic initiation and gender.

For lung function, we used multiple linear regressions, with FEV_1% predicted at follow-up as the outcome variable, and comorbidity and adjustment variables as the explanatory variables. Results were expressed as differences between changes, conditioning on pre-biologic FEV_1%.

For asthma control, we used logistic regressions with being well controlled at follow-up (yes/no) as the outcome variable, and comorbidity and adjustment variables as the explanatory variables. The pre-biologic asthma control assessment used for adjustment was categorized as well controlled/partly controlled/ uncontrolled. Results were expressed as conditional (adjusted) odds ratios of being well controlled after biologic initiation comparing patients with and without comorbidity. Results were stratified by long-term OCS status at biologic initiation. As a sensitivity analysis, we repeated the analyses with the positive outcome defined as well or partly controlled at follow-up.

For long-term OCS daily dose, we restricted the analysis to patients who were using long-term OCS at biologic initiation. We used multiple linear regressions with post-biologic long-term OCS daily dose as the outcome variable, and comorbidity and adjustment variables as the explanatory variables. To normalize the pre-biologic variable, we log-transformed the raw variable. Results were expressed as differences between reduction in long-term OCS daily dose between patients with and without comorbidity, conditioning on (adjusting for) pre-biologic doses.

Analyses were first conducted in all patients initiating any type of biologics and repeated in patients initiating Anti-IgE or Anti-IL5/5R separately. Stratified analysis for patients initiating anti-IL4/13 were not conducted due to low sample size. We adopted an intention to treat approach (ie, information on potential stopping or switching biologics was not considered).

6.4 Software

R version 4.1.0 (2021-05-18).

6.5 Significance testing

Comparisons were two-sided and significance was considered at an α level of 0.05.

7.0 Results

7.1 Overall Patient Population/Study cohort

Figure 4. Flow diagram of patients inclusion by sequential objectives. depicts the flow diagram of patient inclusion sequentially by objectives.

7.2 Objective 1

7.2.1 Study Population: Demographic and Clinical Characteristics

Demographic and clinical characteristics of patients contributing to objective 1 analysis are shown in Table 4, for the total study population and for the subgroup of patients with non missing data for at least one comorbidity of all three considered categories. Seven countries out of 22 contributed to this subgroup. Compared to the total study population, the proportion of women was lower (60.8% vs. 62.2%, p=0.012), the proportion of patients with age at asthma onset below 12 years old was larger (30.3% vs. 20.7%, p<0.001), and the proportion of patients who initiated biologics at enrolment was lower (40.9% vs. 45.9%, p<0.001). The age at enrolment was similar in the subgroup population (median=56, IQR=[45; 66]) and in the total population (median=57, IQR=[45; 67]).

7.2.2 Prevalence of individual comorbidities

The overall prevalence estimates of the 30 selected comorbidities in the ISAR patient population are shown in **Error! Reference source not found.** The most frequently reported comorbidities were allergic rhinitis, gastro-esophageal reflux disease, and obesity, while the less frequent comorbidities were cerebrovascular accident and eosinophilic esophagitis.

Among 4,233 patients with reported chronic rhinosinusitis, 4,065 (96%) had available information on presence/absence of both nasal polyposis and allergic rhinitis. Presence of both nasal polyposis and allergic rhinitis was reported in 870 (21%) of these patients, while absence of both nasal polyposis and allergic rhinitis was reported in 1,227 (30%); 1,554 (38%) were reported without nasal polyposis but with allergic rhinitis, and 414 (10%) were reported with nasal polyposis but without allergic rhinitis. Consequently, the prevalence of chronic rhinosinusitis without nasal polyposis was 2,781/11,009 (25%) and the prevalence of chronic rhinosinusitis without allergic rhinitis was 1,641/11,009 (15%).

Country-specific prevalence estimates and meta-analysis random effects model pooled estimates are shown in Appendix 1: Country-specific prevalence estimates for 30 comorbid conditions and random effects model pooled estimates.. For most comorbidities, the variation by country was substantial (heterogeneity I^2 >90%). Random effects model pooled prevalence estimates were lower than the fixed effect estimates for most comorbidities (eg, obesity: 33% vs. 42%; and gastro-esophageal reflux disease: 20% vs. 44%), higher for allergic rhinitis (62% vs. 49%), and of similar range for chronic rhinosinusitis (38% vs. 35%), nasal polyposis (21% vs. 23%), and eczema/atopic dermatitis (10% vs. 10%).

7.2.3 Prevalence of comorbidity categories

Overall, the prevalence of having at least one comorbidity was 92%. The estimates for having at least one potentially T2-related comorbidity, at least one potentially OCS-related comorbidity, and at least one comorbidity mimicking/exacerbating asthma were 69%, 67%, and 55%, respectively. Country-specific prevalence estimates and meta-analysis random effects model pooled estimates are shown in Appendix 2: Country-specific prevalence estimates random effects model pooled estimates for having at least one comorbidity, overall and by categories.

As only a fraction of the patients had data available for all 30 comorbidities and the amount of missing data might influence the estimates when assessing the prevalence of having at least one comorbidity, we explored the variation in prevalence estimates by minimum number of comorbidities with collected data at the patient level, overall and by categories. Results are presented in Table 6. Prevalence estimates ranged from 90% to 94% for having at least one comorbidity of any type, from 61% to 69% for having at least one potentially T2-related comorbidity, from 67% to 78% for having at least one potentially OCS-related comorbidity, and from 55% to 58% for having at least one comorbidity mimicking/exacerbating asthma. Of note, the trends were not linear due to variations in contributing countries as the minimum number of comorbidities with collected data increased.

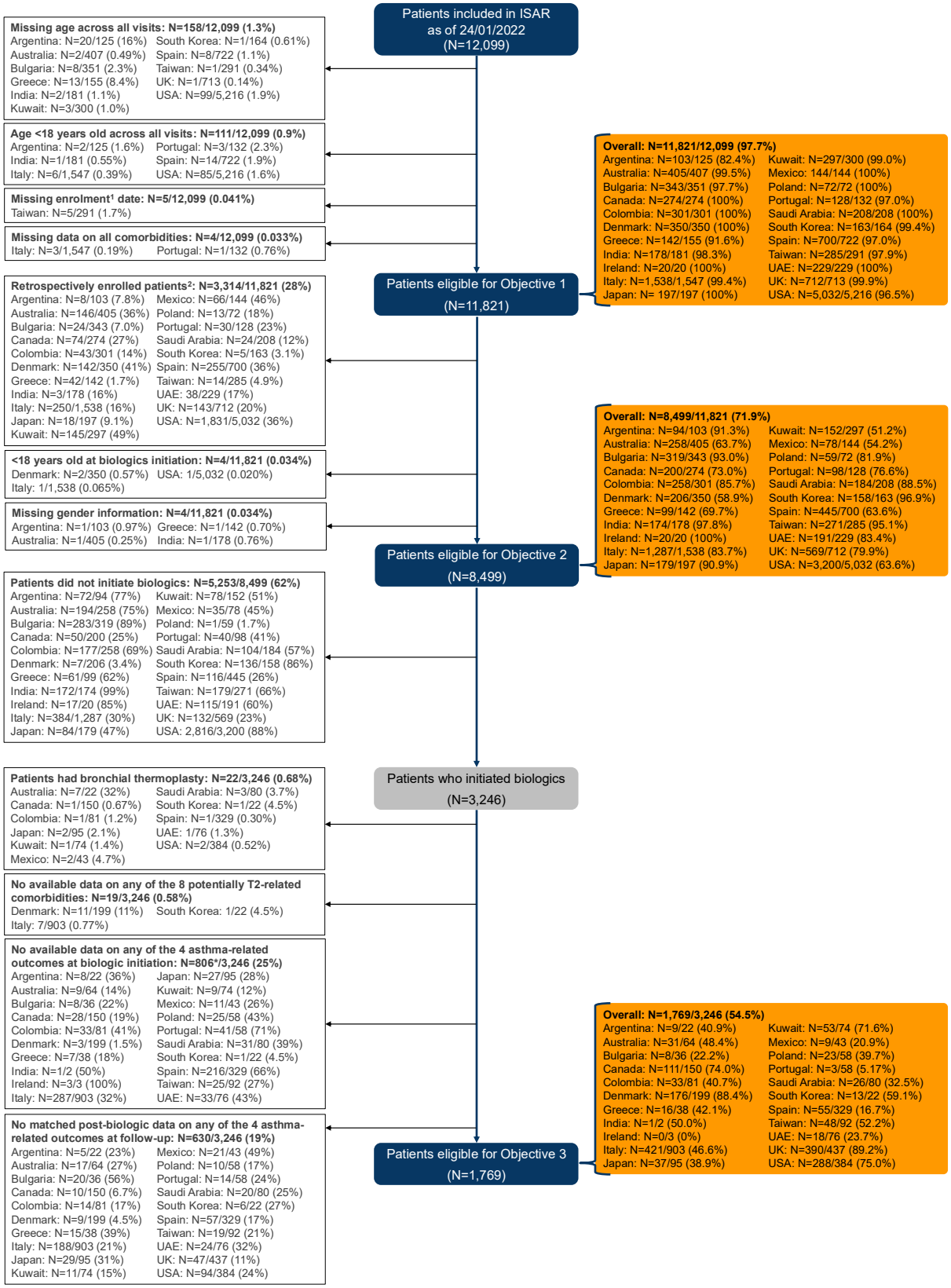

Figure 4. Flow diagram of patients inclusion by sequential objectives.

1. For prospectively enrolled patients: first visit. For retrospectively enrolled patients: most recent visit prior to 01/05/2017.
2. No visit post 01/05/2017, or biologic initiation prior to 01/05/2017.

*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. UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America.

Table 4. Description of the study populations considered for Objective 1.

Characteristics	All eligible patients (N=11,821)		Patients with non missing data for at least one comorbidity of all three categories (N=7,561)		p-values[1]
	N	(%)	N	(%)	
Gender					
Denominator	*11,811*		*7,560*		
Women	7,352	(62.2)	4,596	(60.8)	0.012[2]
Men	4,459	(37.8)	2,964	(39.2)	
Age at registry enrolment (years)					
Denominator	*11,821*		*7,561*		
18-29	942	(7.97)	622	(8.23)	
30-39	1,162	(9.83)	705	(9.32)	
40-49	1,893	(16.0)	1,141	(15.1)	
50-59	2,997	(25.4)	1,826	(24.2)	
60-69	2,867	(24.3)	1,914	(25.3)	
70-79	1,617	(13.7)	1,115	(14.7)	
80+	343	(2.90)	238	(3.15)	
Median [Q1; Q3]	56 [45; 66]		57 [45; 67]		0.111[3]
Range	18 to 95		18 to 95		
Age at asthma onset (years)					
Denominator	*5,778*		*1,889*		
<12	1,194	(20.7)	573	(30.3)	<0.001[2]
≥12	4,584	(79.3)	1,316	(69.7)	
Median [Q1; Q3]	30 [15; 45]		25 [8; 41]		
Range	1 to 84		1 to 78		
Receiving long-term OCS at enrolment					
Denominator	*11,745*		*7,552*		
Yes	2,792	(23.7)	1,877	(24.9)	0.019[2]
No	8,953	(76.2)	5,675	(75.2)	
Initiated biologics at enrolment					
Denominator	*11,821*		*7,561*		
Yes	5,428	(45.9)	3,096	(40.9)	<0.001[2]
No	6,393	(54.1)	4,465	(59.1)	
Eosinophilic gradient					
Denominator	*7,261*		*4,504*		
Grade 0: Unlikely/noneosinophilic	32	(0.441)	13	(0.289)	
Grade 1: Least likely	319	(4.39)	116	(2.56)	
Grade 2: Likely	591	(8.14)	279	(6.19)	
Grade 3: Most likely	6,319	(87.0)	4,096	(90.9)	<0.001[4]
Calendar year at enrolment					
Denominator	*11,821*		*7,561*		
2010	3	(0.0254)	3	(0.0397)	
2011	0	(0)	0	(0)	
2012	4	(0.0338)	0	(0)	
2013	5	(0.0423)	2	(0.0265)	
2014	8	(0.0677)	2	(0.0265)	
2015	523	(4.42)	515	(6.81)	
2016	615	(5.20)	608	(8.04)	
2017	4,189	(35.4)	3,862	(51.1)	
2018	2,021	(17.1)	1,410	(18.6)	
2019	1,947	(16.5)	685	(9.06)	
2020	1,602	(13.6)	333	(4.40)	
2021	892	(7.55)	140	(1.85)	
2022	12	(0.102)	1	(0.0132)	<0.001[5]
Duration of follow-up since enrolment (yrs)					
Denominator	*11,821*		*7,561*		
Median [Q1; Q3]	0.71 [0; 2.11]		1.08 [0; 3.00]		<0.001[3]
Range	0 to 4.52		0 to 4.27		
Country					
Denominator	*11,821*		*7,561*		
Argentina	103	(0.871)	0	(0)	<0.001[6]
Australia	405	(3.43)	405	(5.36)	<0.001[6]
Bulgaria	343	(2.90)	0	(0)	<0.001[6]
Canada	274	(2.32)	263	(3.48)	<0.001[6]
Colombia	301	(2.55)	0	(0)	<0.001[6]
Denmark	350	(2.96)	328	(4.34)	<0.001[6]
Greece	142	(1.20)	0	(0)	<0.001[6]
India	178	(1.51)	0	(0)	<0.001[6]
Ireland	20	(0.169)	0	(0)	<0.001[6]
Italy	1,538	(13.0)	0	(0)	<0.001[6]
Japan	197	(1.67)	0	(0)	<0.001[6]
Kuwait	297	(2.51)	0	(0)	<0.001[6]
Mexico	144	(1.22)	0	(0)	<0.001[6]
Poland	72	(0.609)	0	(0)	<0.001[6]
Portugal	128	(1.08)	121	(1.60)	<0.001[6]
Saudi Arabia	208	(1.76)	0	(0)	<0.001[6]

South Korea	163	(1.38)	0	(0)	<0.001[6]
Spain	700	(5.92)	700	(9.26)	<0.001[6]
Taiwan	285	(2.41)	0	(0)	<0.001[6]
The United Arab Emirates (UAE)	229	(1.94)	0	(0)	<0.001[6]
The United Kingdom (UK)	712	(6.02)	712	(9.42)	<0.001[6]
The United States of America (USA)	5,032	(45.6)	5,032	(66.6)	<0.001[6]

OCS: Oral corticosteroids; Q1: 1st quartile; Q3: 3rd quartile.
1. Comparisons of the subgroup to the whole study population.
2. One-sample chi-squared proportions tests with continuity correction (to compare the distributions of binary variables).
3. One-sample Wilcoxon signed-rank test with continuity correction (to compare medians).
4. One-sample chi-squared proportions tests with continuity correction comparing the proportions of patients with Grade 4.
5. One-sample chi-squared proportions tests with continuity correction comparing the proportions of patients enrolled from 2017 on.
6. One-sample chi-squared proportions tests with continuity correction comparing the proportions for each country.

Table 5. Prevalence of 30 comorbid conditions in adults with severe asthma enrolled in ISARR (24/01/2022 database; 11,821 patients from 22 countries).

Comorbidities	Number of contributing countries	Sample size*	N**	Prevalence
Potentially T2-related categories				
Allergic rhinitis	22	11,281	5,525	49%
Chronic rhinosinusitis[1]	21 (all -Australia)	11,177	4,233	38%
Nasal polyposis	22	11,613	2,413	21%
Eczema/atopic dermatitis	22	11,600	1,199	10%
Urticaria	4 (Australia, Spain, UK, USA)	6,849	243	3.5%
Food allergy	5 (Australia, Portugal, Spain, UK, USA)	6,977	230	3.3%
Aspirin sensitivity	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)	7,498	122	1.6%
Eosinophilic esophagitis	3 (Australia, UK, USA)	6,149	32	0.52%
Potentially OCS-related comorbidities				
Obesity	22	11,583	4,893	42%
Hypertension	12 (Australia, Italy, Japan, Mexico, Poland, Portugal, South Korea, Spain, Taiwan, UAE, UK, USA)	9,252	2,104	23%
Sleep apnea	21 (all -Italy)	10,094	2,256	22%
Dyslipidemia	4 (Australia, Spain, UK, USA)	6,849	1,083	16%
Anxiety/depression[2]	21 (all -Denmark)	11,019	1,565	14%
Osteoporosis	21 (all -Denmark)	10,742	1,371	13%
Diabetes	22	11,422	1,336	12%
Coronary heart disease	22	11,039	984	8.9%
Pneumonia	20 (all -Denmark, -Spain)	10,300	877	8.5%
Other significant infections	20 (all -Ireland, -Portugal)	6,918	560	8.1%
Peptic ulcer	20 (all -Denmark, -Spain)	10,323	266	2.6%
Pulmonary embolism/VTE	20 (all -Denmark, -Spain)	9,972	246	2.5%
Cataract	21 (all -Denmark)	10,923	258	2.4%
Chronic kidney disease	21 (all -Denmark)	11,032	164	1.5%
Adrenal insufficiency	3 (Australia, UK, USA)	6,149	80	1.3%
Glaucoma	21 (all -Denmark)	10,888	139	1.3%
Cerebrovascular accident	20 (all -Denmark, -Spain)	9,968	63	0.63%
Comorbidities mimicking/exacerbating asthma				
Gastro-esophageal reflux disease[3]	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)	7,400	3,243	44%
Chronic obstructive pulmonary disease	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)	7,508	1,045	14%
Bronchiectasis	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)	7,509	799	11%
VCD/laryngeal spasms	5 (Australia, Denmark, Spain, UK, USA)	7,199	758	11%
Dysfunctional breathing	6 (Australia, Canada, Denmark, Spain, UK, USA)	7,389	234	3.2%

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Variations in sample size are due to missing values for individual patients and/or at the country level. **Number of patients with comorbidity.
OCS: Oral corticosteroids; VTE: Venous thromboembolism; UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America; VCD: Vocal cord dysfunction.

Table 6. Prevalence of having at least one comorbidity, overall and by categories, by minimum number of comorbidities with available presence/absence information.

Minimum number of comorbidities with presence/absence information by categories	Number of contributing countries	Sample size	N	Prevalence of having at least one comorbidity
Comorbidities of any type				
≥1	22	11,821	10,837	92%
≥2	22	11,811	10,834	92%
≥3	22	11,794	10,826	92%
≥4	22	11,737	10,803	92%
≥5	22	11,674	10,764	92%
≥6	22	11,552	10,673	92%
≥7	22	11,468	10,596	92%
≥8	22	11,461	10,589	92%
≥9	22	11,454	10,582	92%
≥10	22	11,446	10,574	92%
≥11	22	11,438	10,566	92%
≥12	22	11,405	10,534	92%
≥13	22	11,386	10,515	92%
≥14	22	11,317	10,449	92%
≥15	22	11,119	10,265	92%
≥16	21 (all -Denmark)	10,623	9,801	92%
≥17	21 (all -Denmark)	10,510	9,701	92%
≥18	20 (all -Denmark, -Ireland)	10,173	9,399	92%
≥19	12 (Australia, Canada, Japan, Mexico, Poland, Portugal, South Korea, Spain, Taiwan, UAE, UK, USA)	8,060	7,519	93%
≥20	6 (Australia, Canada, Portugal, Spain, UK, USA)	7,096	6,649	94%
≥21	6 (Australia, Canada, Portugal, Spain, UK, USA)	7,088	6,641	94%
≥22	6 (Australia, Canada, Portugal, Spain, UK, USA)	7,035	6,588	94%
≥23	6 (Australia, Canada, Portugal, Spain, UK, USA)	6,909	6,462	94%
≥24	4 (Australia, Spain, UK, USA)	6,529	6,109	94%
≥25	3 (Australia, UK, USA)	6,122	5,723	93%
≥26	3 (Australia, UK, USA)	6,119	5,723	94%
≥27	3 (Australia, UK, USA)	6,089	5,703	94%
≥28	3 (Australia, UK, USA)	6,077	5,693	94%
≥29	3 (Australia, UK, USA)	5,987	5,614	94%
30	2 (UK, USA)	1,322	1,190	90%
Potentially T2-related categories				
≥1	22	11,743	8,120	69%
≥2	22	11,694	8,097	69%
≥3	22	11,605	8,053	69%
≥4	22	11,163	7,701	69%
≥5	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)	7,480	4,911	66%
≥6	5 (Australia, Portugal, Spain, UK, USA)	6,936	4,460	64%
≥7	4 (Australia, Spain, UK, USA)	6,805	4,353	64%
8	2 (UK, USA)	5,718	3,504	61%
Potentially OCS-related comorbidities				
≥1	22	11,809	7,936	67%
≥2	22	11,646	7,902	68%
≥3	22	11,489	7,865	68%

≥4	22	11,437	7,839	69%
≥5	22	11,427	7,834	69%
≥6	21 (all -Denmark)	11,043	7,654	69%
≥7	21 (all -Denmark)	11,034	7,647	69%
≥8	21 (all -Denmark)	11,027	7,643	69%
≥9	21 (all -Denmark)	11,015	7,634	69%
≥10	21 (all -Denmark)	10,932	7,575	69%
≥11	21 (all -Denmark)	10,823	7,491	69%
≥12	21 (all -Denmark)	10,365	7,149	69%
≥13	21 (all -Denmark)	9,892	6,876	70%
≥14	21 (all -Denmark, -Ireland)	9,660	6,744	70%
≥15	9 (Australia, Japan, Mexico, Poland, South Korea, Taiwan, UAE, UK, USA)	7,117	5,359	75%
≥16	3 (Australia, UK, USA)	6,100	4,747	78%
17	3 (Australia, UK, USA)	1,657	1,251	75%
Comorbidities mimicking/exacerbating asthma				
≥1	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)	7,583	4,193	55%
≥2	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)	7,531	4,192	56%
≥3	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)	7,496	4,181	56%
≥4	6 (Australia, Canada, Denmark, Spain, UK, USA)	7,259	4,136	57%
5	5 (Australia, Denmark, Spain, UK, USA)	7,136	4,106	58%

OCS: Oral corticosteroids; UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America.

7.2.4 Comorbidity counts and co-occurrences

The distributions of comorbidity counts within patients are shown in Table 7 for the subgroups of patients with presence/absence information on at least three comorbidities, overall and by categories. The median count of comorbidities of any type was 3 (IQR: 1; 5). More than half (54.5%) of the patients had at least 3 comorbidities of any type. By categories, the proportions of patients with at least 3 comorbidities were 12.5%, 23.2%, and 3.9% for potentially T2-related, potentially OCS-related, and mimicking/exacerbating asthma categories, respectively.

Table 7. Number of co-existing comorbidities in patients with available presence/absence information for at least three comorbidities, overall and by categories.

	Comorbidities of any type	Potentially T2-related comorbidities	Potentially OCS-related comorbidities	Comorbidities mimicking/exacerbating asthma
Sample size	11,794	11,605	11,489	7,496
Median [Q1; Q3]	3 [1; 5]	1 [0; 2]	1 [0; 2]	1 [0; 1]
Range	0 to 16	0 to 6	0 to 12	0 to 5
Categories: N (%)				
1 comorbidity	2,012 (17.1)	3,939 (33.9)	3,276 (28.5)	2,614 (34.9)
2 comorbidities	2,381 (20.2)	2,669 (23.0)	1,923 (16.7)	1,276 (17.0)
3+ comorbidities	6,433 (54.5)	1,445 (12.5)	2,666 (23.2)	291 (3.9)

OCS: Oral corticosteroids; Q1: 1st quartile; Q3: 3rd quartile.

As a sensitivity analysis, we explored the variation in these proportions when restricting to patients with increasing number of comorbidities with collected data at the patient level. Results are presented in Table 8. Prevalence estimates of having 3 or more comorbidities of any type ranged from 55% to 66%; 3 or more potentially T2-related comorbidities from 8.3% to 13%; 3 or more potentially OCS-related comorbidities from 23% to 34%; and 3 or more comorbidities mimicking/exacerbating asthma from 3.9% to 4.1%. Of note, the trends were not linear due to variations in contributing countries as the minimum number of comorbidities with collected data increased.

Table 8. Prevalence of having 1, 2, or 3+ comorbidities, overall and by categories, by minimum number of comorbidities with available presence/absence information.

Minimum number of comorbidities with presence/absence information by categories	Prevalence of having 1, 2, or 3+ comorbidities	Sample size	Number of contributing countries
Comorbidities of any type			
≥3	17%, 20%, 55%	11,794	22
≥4	17%, 20%, 55%	11,737	22
≥5	17%, 20%, 55%	11,674	22
≥6	17%, 20%, 56%	11,552	22
≥7	17%, 20%, 56%	11,468	22
≥8	17%, 20%, 56%	11,461	22
≥9	17%, 20%, 56%	11,454	22
≥10	17%, 20%, 56%	11,446	22
≥11	17%, 20%, 56%	11,438	22
≥12	17%, 20%, 56%	11,405	22
≥13	17%, 20%, 56%	11,386	22
≥14	17%, 20%, 56%	11,317	22
≥15	17%, 20%, 56%	11,119	22
≥16	17%, 20%, 56%	10,623	21 (all -Denmark)
≥17	17%, 20%, 56%	10,510	21 (all -Denmark)
≥18	16%, 19%, 57%	10,173	20 (all -Denmark, -Ireland)
≥19	15%, 17%, 62%	8,060	12 (Australia, Canada, Japan, Mexico, Poland, Portugal, South Korea, Spain, Taiwan, UAE, UK, USA)
≥20	14%, 16%, 64%	7,096	6 (Australia, Canada, Portugal, Spain, UK, USA)
≥21	14%, 16%, 64%	7,088	6 (Australia, Canada, Portugal, Spain, UK, USA)

≥22	14%, 16%, 64%	7,035	6 (Australia, Canada, Portugal, Spain, UK, USA)
≥23	14%, 16%, 64%	6,909	6 (Australia, Canada, Portugal, Spain, UK, USA)
≥24	14%, 16%, 64%	6,529	4 (Australia, Spain, UK, USA)
≥25	13%, 15%, 65%	6,122	3 (Australia, UK, USA)
≥26	13%, 15%, 65%	6,119	3 (Australia, UK, USA)
≥27	13%, 15%, 65%	6,089	3 (Australia, UK, USA)
≥28	13%, 15%, 65%	6,077	3 (Australia, UK, USA)
≥29	13%, 15%, 66%	5,987	3 (Australia, UK, USA)
30	17%, 14%, 59%	1,322	2 (UK, USA)
Potentially T2-related categories			
≥3	34%, 23%, 12%	11,605	22
≥4	33%, 23%, 13%	11,163	22
≥5	34%, 21%, 11%	7,480	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)
≥6	35%, 20%, 9.3%	6,936	5 (Australia, Portugal, Spain, UK, USA)
≥7	35%, 20%, 8.9%	6,805	4 (Australia, Spain, UK, USA)
8	34%, 18%, 8.3%	5,718	2 (UK, USA)
Potentially OCS-related comorbidities			
≥3	29%, 17%, 23%	11,489	22
≥4	28%, 17%, 23%	11,437	22
≥5	28%, 17%, 23%	11,427	22
≥6	28%, 17%, 24%	11,043	21 (all -Denmark)
≥7	28%, 17%, 24%	11,034	21 (all -Denmark)
≥8	28%, 17%, 24%	11,027	21 (all -Denmark)
≥9	28%, 17%, 24%	11,015	21 (all -Denmark)
≥10	28%, 17%, 24%	10,932	21 (all -Denmark)
≥11	28%, 17%, 24%	10,823	21 (all -Denmark)
≥12	28%, 17%, 24%	10,365	21 (all -Denmark)
≥13	28%, 17%, 25%	9,892	21 (all -Denmark)
≥14	28%, 17%, 26%	9,660	21 (all -Denmark, -Ireland)
≥15	26%, 18%, 31%	7,117	9 (Australia, Japan, Mexico, Poland, South Korea, Taiwan, UAE, UK, USA)
≥16	26%, 18%, 34%	6,100	3 (Australia, UK, USA)
17	28%, 15%, 32%	1,657	3 (Australia, UK, USA)
Comorbidities mimicking/exacerbating asthma			
≥3	35%, 17%, 3.9%	7,496	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)
≥4	36%, 17%, 4.0%	7,259	6 (Australia, Canada, Denmark, Spain, UK, USA)
5	36%, 18%, 4.1%	7,136	5 (Australia, Denmark, Spain, UK, USA)

UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America; OCS: Oral corticosteroids.

For each category of comorbidity counts (1, 2, and 3 or more), the most frequently reported individual, or combinations of, comorbidities are shown in Table 9. In the categories of 3 or more comorbidities, the most frequent combinations of individual comorbidities were allergic rhinitis + chronic rhinosinusitis + nasal polyposis overall (4.0%). The most frequent combinations by categories were allergic rhinitis + chronic rhinosinusitis + nasal polyposis (46.5%) for potentially T2-related comorbidities, obesity + sleep apnea + hypertension (3.9%) for potentially OCS-related comorbidities, and gastro-esophageal reflux disease + chronic obstructive pulmonary disease + bronchiectasis (34.7%) for comorbidities mimicking/exacerbating asthma.

Table 9. Most frequent comorbidities and combinations of comorbidities by number of reported comorbidities in patients with available presence/absence information for at least three comorbidities, overall and by categories.

Number of reported comorbidities	Sample size	Most frequent (combinations of) comorbidities		
		Types	N	(%)
Comorbidities of any type				
1	2,012	Allergic rhinitis	672	(33.4)
		Obesity	511	(25.4)
		Nasal polyposis	212	(10.5)
2	2,381	Allergic rhinitis + chronic rhinosinusitis	336	(14.1)
		Allergic rhinitis + obesity	287	(12.1)
		Allergic rhinitis + nasal polyposis	160	(6.7)
3+	6,433	Allergic rhinitis + chronic rhinosinusitis + nasal polyposis	259	(4.0)
		Allergic rhinitis + chronic rhinosinusitis + obesity	126	(2.0)
		Allergic rhinitis + chronic rhinosinusitis + nasal polyposis + obesity	101	(1.6)
Potentially T2-related comorbidities				
1	3,939	Allergic rhinitis	2,091	(53.1)
		Chronic rhinosinusitis	1,115	(28.3)
		Nasal polyposis	488	(12.4)
2	2,669	Allergic rhinitis + chronic rhinosinusitis	1,248	(46.8)
		Chronic rhinosinusitis + nasal polyposis	429	(16.1)
		Allergic rhinitis + nasal polyposis	382	(14.3)
		Allergic rhinitis + eczema/atopic dermatitis	333	(12.5)
3+	1,445	Allergic rhinitis + chronic rhinosinusitis + nasal polyposis	672	(46.5)
		Allergic rhinitis + chronic rhinosinusitis + eczema/atopic dermatitis	193	(13.4)
		Allergic rhinitis + chronic rhinosinusitis + nasal polyposis + eczema/atopic dermatitis	146	(10.1)
Potentially OCS-related comorbidities				
1	3,276	Obesity	1,709	(52.2)
		Anxiety/depression	282	(8.6)
		Osteoporosis	249	(7.6)
2	1,923	Obesity + sleep apnea	417	(21.7)
		Obesity + hypertension	156	(8.1)
		Obesity + anxiety/depression	155	(8.1)
3+	2,666	Obesity + sleep apnea + hypertension	104	(3.9)
		Obesity + sleep apnea + diabetes	84	(3.2)
		Obesity + sleep apnea + hypertension + dyslipidaemia	52	(2.0)
Comorbidities mimicking/exacerbating asthma				
1	2,614	GERD	1,778	(68.0)
		COPD	327	(12.5)
		Bronchiectasis	248	(9.5)
2	1,276	GERD + COPD	416	(32.6)
		GERD + vocal cord dysfunction/laryngeal spasms	388	(30.4)
		GERD + bronchiectasis	312	(24.5)
3+	291	GERD + COPD + bronchiectasis	101	(34.7)
		GERD + COPD + vocal cord dysfunction/laryngeal spasms	70	(24.1)
		GERD + bronchiectasis + vocal cord dysfunction/laryngeal spasms	37	(12.7)

COPD: Chronic obstructive pulmonary disease; GERD: Gastro-esophageal reflux disease; OCS: Oral corticosteroids.

A total of 7,561 patients, from seven countries (Australia, Canada, Denmark, Portugal, Spain, UK, USA), had information available on presence/absence for at least one comorbidity in each category. In this subgroup, the proportions of patients with at least one potentially T2-related comorbidity, at least one potentially OCS-related comorbidity, and/or at least one comorbidity mimicking/exacerbating asthma were 65.5%, 74.3%, and 55.5%, respectively. Co-occurrence of comorbidities across categories was analysed in this subgroup of patients. Results are shown in Figure 5. The most common combination (33%) was having at least one comorbidity of each category.

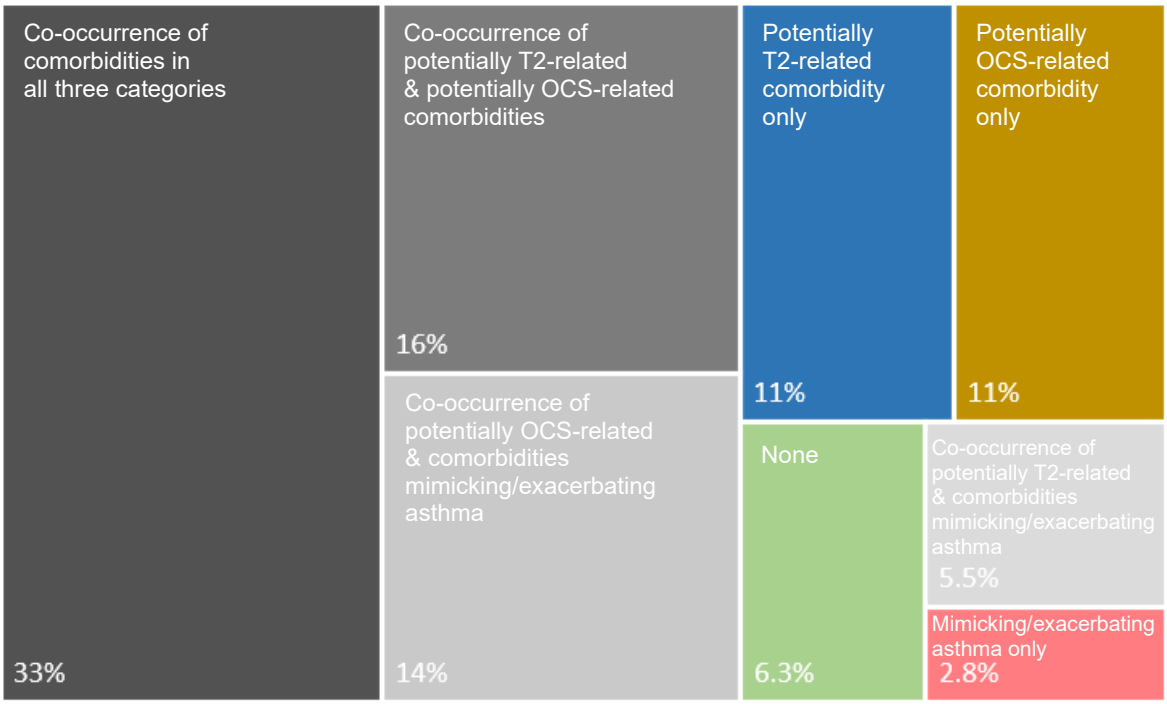

Figure 5. Co-occurrence of comorbidities across categories: proportions of patients falling in the eight possible combinations in a subgroup of patients with information available on presence/absence of at least one comorbidity in each category (N=7,561; 7 countries).

OCS: Oral corticosteroids.

7.3 Objective 2

7.3.1 Study Population: Demographic and Clinical Characteristics

Demographic and clinical characteristics of patients contributing to objective 2 are shown in Table 10.

Table 10. Demographic and clinical characteristics of patients contributing to objective 2 analysis.

Characteristics	N	(%)
Total	8,499	
Gender		
Denominator	*8,499*	
Women	5,306	(62.4)
Men	3,193	(37.6)
Age at registry enrolment (years)		
Denominator	*8,499*	
18-29	632	(7.44)
30-39	827	(9.73)
40-49	1,325	(15.6)
50-59	2,138	(25.2)
60-69	2,076	(24.4)
70-79	1,234	(14.5)
80+	267	(3.14)
Median [Q1; Q3]	56 [45; 66]	
Range	18 to 95	
Calendar year at enrolment		
Denominator	*8,499*	
2017	3,196	(37.6)
2018	1,803	(21.2)
2019	1,533	(18.0)
2020	1,290	(15.2)
2021	669	(7.87)
2022	8	(0.0941)
Duration of follow-up since enrolment (years)		
Denominator	*8,499*	
Median [Q1; Q3]	1.00 [0; 2.46]	
Range	0 to 4.64	
Country		
Denominator	*8,499*	
Argentina	94	(1.11)
Australia	258	(3.04)
Bulgaria	319	(3.75)
Canada	200	(2.35)
Colombia	258	(3.04)
Denmark	206	(2.42)
Greece	99	(1.16)
India	174	(2.05)
Ireland	20	(0.235)
Italy	1,287	(15.1)
Japan	179	(2.11)
Kuwait	152	(1.79)
Mexico	78	(0.918)
Poland	59	(0.694)
Portugal	98	(1.15)
Saudi Arabia	184	(2.16)
South Korea	158	(1.86)
Spain	445	(5.24)
Taiwan	271	(3.19)
The United Arab Emirates (UAE)	191	(2.25)
The United Kingdom (UK)	569	(6.69)
The United States of America (USA)	3,200	(37.7)

Smoking status at enrolment		
Denominator	*6,859*	
Current smoker	386	(5.63)
Ex-smoker	2,067	(30.1)
Never smoker	4,406	(64.2)
Age at asthma onset (years)		
Denominator	*4,574*	
<12	874	(19.1)
≥12	3,700	(80.9)
Median [Q1; Q3]	32 [17; 46]	
Range	1 to 84	
Receiving long-term OCS at enrolment		
Denominator	*8,423*	
Yes	1,932	(22.9)
No	6,491	(77.1)
Initiated biologics at enrolment		
Denominator	*8,499*	
Yes	3,246	(38.2)
No	5,253	(61.8)
Exacerbation rate at enrolment (number of episodes in the year preceding enrolment)		
Denominator	*7,422*	
0	3,751	(50.6)
1	1,553	(20.9)
2	826	(11.1)
3-6	1,003	(13.5)
7-12	250	(3.37)
13-24	34	(0.458)
Median [Q1; Q3]	0 [0; 2]	
Range	0 to 24	
FEV_1 percent of predicted at enrolment		
Denominator	*6,292*	
<80%	3,751	(59.6)
≥80%	2,541	(40.4)
Median [Q1; Q3]	75.2% [60.5%; 88.9%]	
Range	14% to 185%	
Ratio of FEV_1/FVC at enrolment		
Denominator	*6,199*	
<0.70	3,014	(48.6)
≥0.70	3,185	(51.4)
Median [Q1; Q3]	0.70 [0.61; 0.78]	
Range	0.20 to 1.00	
Asthma control assessment at enrolment (GINA 2020)		
Denominator	*5,031*	
Uncontrolled	2,752	(54.7)
Partly controlled	1,294	(25.7)
Well controlled	985	(19.6)
Highest blood eosinophil count (cells/µL)		
Denominator	*5,819*	
Median [Q1; Q3]	400 [200; 650]	
Range	20 to 5000	
Highest blood IgE count (IU/mL)		
Denominator	*4,896*	
Median [Q1; Q3]	136 [42.4; 392]	
Range	0 to 12,200	
Highest FeNO test result (ppb)		
Denominator	*3,581*	
Median [Q1; Q3]	30 [16; 59]	
Range	1 to 300	
Eosinophilic gradient		
Denominator	*5,751*	
Grade 0: Unlikely/noneosinophilic	28	(0.487)
Grade 1: Least likely	286	(4.97)
Grade 2: Likely	466	(8.10)
Grade 3: Most likely	4,971	(86.4)

FeNo: FeV_1: post-bronchodilatator forced expiratory volume in 1 second, percent of predicted; FVC: Forced vital capacity; GINA: Global Initiative for Asthma; IU: International unit; ppb: parts per billion; Q3: 1st quartile; Q3: 3rd quartile.

7.3.2 Prevalence of comorbidity by demographic characteristics

Prevalence estimates of comorbidities by gender are shown in Table 11. The prevalence of allergic rhinitis, chronic rhinosinusitis, eczema/atopic dermatitis, obesity, anxiety/depression, osteoporosis, diabetes, gastro-esophageal reflux disease, bronchiectasis, and vocal cord dysfunction/laryngeal spasms were higher in women than in men. On the contrary, the prevalence of nasal polyposis and sleep apnea was higher in men than in women.

The prevalence estimates of comorbidities by age groups at enrolment are shown in Table 12. We compared age distributions between patients with and without comorbidity using Kruskal-Wallis tests. Patients with allergic rhinitis, nasal polyposis, and eczema/atopic dermatitis were younger than patients without these comorbidities. On the contrary, patients with chronic rhinosinusitis, obesity, hypertension, sleep apnea, dyslipidemia, anxiety/depression, osteoporosis, diabetes, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, and bronchiectasis were older than patients without these comorbidities.

The prevalence estimates of comorbidities by tobacco smoking status at enrolment are shown in Table 13. The prevalence estimates were significantly different for allergic rhinitis, nasal polyposis, eczema/atopic dermatitis, all seven potentially OCS-related comorbidities, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, and bronchiectasis. Potentially T2-related comorbidities were more prevalent in never smokers than in current/ex-smokers. Obesity, hypertension, sleep apnea, and gastro-esophageal reflux disease were more prevalent in ex-smokers than in current/never smokers. Dyslipidemia, anxiety/depression, diabetes, chronic obstructive pulmonary disease were more prevalent in current/ex-smokers than in never smokers. Osteoporosis and bronchiectasis were less prevalent in current smokers than in ex-/never smokers.

Table 11. Prevalence of most common comorbidities by gender.

Comorbidities	Women	Men	p value*
Potentially T2-related categories			
Allergic rhinitis	50%	46%	0.003
Chronic rhinosinusitis[1]	37%	35%	0.041
Nasal polyposis	19%	24%	<0.001
Eczema/atopic dermatitis	10%	8.6%	0.006
Potentially OCS-related comorbidities			
Obesity	43%	36%	<0.001
Hypertension	22%	23%	0.249
Sleep apnea	21%	24%	0.003
Dyslipidemia	16%	17%	0.156
Anxiety/depression[2]	17%	10%	<0.001
Osteoporosis	15%	6.7%	<0.001
Diabetes	12%	10%	0.007
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease[3]	45%	42%	0.035
Chronic obstructive pulmonary disease	15%	16%	0.352
Bronchiectasis	11%	9.3%	0.027
VCD/laryngeal spasms	13%	6.6%	<0.001

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.

*Pearson's Chi-squared test.
OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

Table 12. Prevalence of most common comorbidities by age at registry enrolment.

Comorbidities	<40	40-49	50-59	60-69	70+	p value*
Potentially T2-related categories						
Allergic rhinitis	56%	55%	48%	46%	40%	<0.001
Chronic rhinosinusitis[1]	32%	35%	37%	40%	34%	0.012
Nasal polyposis	20%	22%	26%	21%	15%	<0.001
Eczema/atopic dermatitis	16%	11%	7.8%	8.4%	7.6%	<0.001
Potentially OCS-related comorbidities						
Obesity	35%	41%	43%	43%	38%	0.007
Hypertension	5.0%	13%	20%	29%	40%	<0.001
Sleep apnea	11%	21%	24%	28%	27%	<0.001
Dyslipidemia	1.6%	8.0%	15%	21%	31%	<0.001
Anxiety/depression[2]	12%	11%	15%	16%	16%	<0.001
Osteoporosis	3.4%	4.5%	11%	17%	21%	<0.001
Diabetes	6.4%	7.8%	12%	14%	17%	<0.001
Comorbidities mimicking/exacerbating asthma						
Gastro-esophageal reflux disease[3]	34%	42%	42%	49%	48%	<0.001
Chronic obstructive pulmonary disease	3.0%	7.5%	17%	19%	23%	<0.001
Bronchiectasis	4.1%	6.8%	9.3%	13%	17%	<0.001
VCD/laryngeal spasms	11%	10%	11%	11%	8.7%	0.214

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.

*Kruskal-Wallis rank sum test comparing age distributions in patients with versus without comorbidity.
OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

Table 13. Prevalence of most common comorbidities by smoking status registry enrolment.

Comorbidities	Current smokers	Ex-smokers	Never smokers	p value*
Potentially T2-related categories				
Allergic rhinitis	46%	42%	49%	<0.001
Chronic rhinosinusitis[1]	34%	37%	36%	0.559
Nasal polyposis	10%	16%	21%	<0.001
Eczema/atopic dermatitis	8.0%	7.5%	9.8%	0.007
Potentially OCS-related comorbidities				
Obesity	38%	47%	40%	<0.001
Hypertension	22%	29%	22%	<0.001
Sleep apnea	21%	31%	22%	<0.001
Dyslipidemia	19%	21%	16%	<0.001
Anxiety/depression[2]	21%	18%	13%	<0.001
Osteoporosis	6.1%	14%	12%	<0.001
Diabetes	14%	14%	12%	0.036
Comorbidities mimicking/exacerbating asthma				
Gastro-esophageal reflux disease[3]	45%	51%	45%	<0.001
Chronic obstructive pulmonary disease	42%	28%	7.4%	<0.001
Bronchiectasis	4.9%	11%	11%	0.017
VCD/laryngeal spasms	10%	11%	12%	0.668

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Pearson's Chi-squared test.
OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

7.3.3 Association between comorbidities and clinical characteristics

The association between age at asthma onset and presence of comorbidities are shown in Table 14. Older age at asthma onset was associated with increased odds of chronic rhinosinusitis and nasal polyposis, and decreased odds of allergic rhinitis and eczema/atopic dermatitis. Potentially OCS-related comorbidities and comorbidities mimicking/exacerbating asthma were not significantly associated with age at asthma onset.

The association between blood eosinophil concentration and presence of comorbidities are shown in Table 15. Higher blood eosinophil concentrations were associated with increased odds of potentially T2-related comorbidities and bronchiectasis. On the contrary, higher blood eosinophil concentrations were associated with decreased odds of obesity, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, and vocal cord dysfunction/laryngeal spasms.

The association between blood IgE concentration and presence of comorbidities are shown in Table 16. Higher blood IgE concentrations were associated with increased odds of potentially T2-related comorbidities and decreased odds of obesity, sleep apnea, dyslipidemia, anxiety/depression, osteoporosis, diabetes, gastro-esophageal reflux disease, and vocal cord dysfunction/laryngeal spasms.

The association between FeNO test results and presence of comorbidities are shown in Table 17. Higher FeNO test results were associated with increased odds allergic rhinitis, chronic rhinosinusitis, nasal polyposis and decreased odds of obesity, hypertension, sleep apnea, dyslipidemia, anxiety/depression, diabetes, gastro-esophageal reflux disease, and chronic obstructive pulmonary disease.

Table 14. Odds ratios and 95% confidence intervals of having comorbidity for a 5 year-increase of age at asthma onset, adjusted for country, age at registry enrolment, and gender.

Comorbidities	Sample size	OR (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	4,179	0.93 (0.91-0.96)	<0.001
Chronic rhinosinusitis[1]	4,189	1.03 (1.01-1.06)	0.008
Nasal polyposis	4,463	1.03 (1.00-1.05)	0.031
Eczema/atopic dermatitis	4,449	0.92 (0.89-0.95)	<0.001
Potentially OCS-related comorbidities			
Obesity	4,435	0.99 (0.96-1.01)	0.233
Hypertension	2,816	1.00 (0.96-1.04)	0.865
Sleep apnea	3,342	0.99 (0.96-1.03)	0.754
Dyslipidemia	1,027	0.99 (0.86-1.13)	0.870
Anxiety/depression[2]	4,220	0.98 (0.95-1.02)	0.307
Osteoporosis	3,953	0.99 (0.96-1.03)	0.697
Diabetes	4,335	0.97 (0.94-1.00)	0.077
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease[3]	1,258	0.95 (0.91-1.00)	0.074
Chronic obstructive pulmonary disease	1,318	0.96 (0.88-1.05)	0.413
Bronchiectasis	1,323	0.96 (0.90-1.02)	0.213
VCD/laryngeal spasms	1,133	0.99 (0.89-1.10)	0.838

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Wald's test.
OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

Table 15. Odds ratios and 95% confidence intervals of having comorbidity for a doubling in blood eosinophil concentration, adjusted for country, age at registry enrolment, and gender.

Comorbidities	Sample size	OR (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	5,594	1.11 (1.06-1.16)	<0.001
Chronic rhinosinusitis[1]	5,623	1.29 (1.23-1.36)	<0.001
Nasal polyposis	5,750	1.48 (1.39-1.58)	<0.001
Eczema/atopic dermatitis	5,727	1.11 (1.02-1.19)	0.010
Potentially OCS-related comorbidities			
Obesity	5,758	0.95 (0.90-0.99)	0.028
Hypertension	4,490	0.96 (0.90-1.03)	0.257
Sleep apnea	5,046	0.95 (0.89-1.01)	0.078
Dyslipidemia	3,310	1.03 (0.95-1.12)	0.500
Anxiety/depression[2]	5,524	0.94 (0.88-1.00)	0.055
Osteoporosis	5,309	1.07 (1.00-1.15)	0.050
Diabetes	5,719	1.07 (0.99-1.14)	0.072
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease[3]	3,582	0.94 (0.86-1.00)	0.046
Chronic obstructive pulmonary disease	3,625	0.84 (0.77-0.91)	<0.001
Bronchiectasis	3,633	1.16 (1.06-1.28)	0.001
VCD/laryngeal spasms	3,492	0.85 (0.77-0.94)	0.001

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Wald's test.
OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

Table 16. Odds ratios and 95% confidence intervals of having comorbidity for a doubling in blood IgE concentration, adjusted for country, age at registry enrolment, and gender.

Comorbidities	Sample size	OR (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	4,591	1.13 (1.09-1.16)	<0.001
Chronic rhinosinusitis[1]	4,703	1.04 (1.01-1.07)	0.012
Nasal polyposis	4,849	1.05 (1.01-1.09)	0.007
Eczema/atopic dermatitis	4,837	1.20 (1.15-1.26)	<0.001
Potentially OCS-related comorbidities			
Obesity	4,845	0.97 (0.95-1.00)	0.045
Hypertension	3,723	0.98 (0.95-1.02)	0.393
Sleep apnea	4,246	0.94 (0.90-0.97)	<0.001
Dyslipidemia	2,790	0.93 (0.89-0.98)	0.003
Anxiety/depression[2]	4,611	0.93 (0.90-0.97)	<0.001
Osteoporosis	4,400	0.96 (0.92-1.00)	0.045
Diabetes	4,759	0.95 (0.92-0.99)	0.020
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease[3]	3,018	0.93 (0.90-0.97)	<0.001
Chronic obstructive pulmonary disease	3,050	0.98 (0.93-1.02)	0.297
Bronchiectasis	3,055	1.02 (0.97-1.07)	0.383
VCD/laryngeal spasms	2,928	0.93 (0.88-0.97)	0.003

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Wald's test.
OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.
Note: IgE concentration was transformed in model as log2(IgE +1).

Table 17. Odds ratios and 95% confidence intervals of having comorbidity for a doubling in FeNO test result, adjusted for country, age at registry enrolment, and gender.

Comorbidities	Sample size	OR (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	3,423	1.14 (1.08-1.21)	<0.001
Chronic rhinosinusitis[1]	3,431	1.22 (1.15-1.29)	<0.001
Nasal polyposis	3,554	1.46 (1.36-1.57)	<0.001
Eczema/atopic dermatitis	3,551	1.03 (0.94-1.13)	0.538
Potentially OCS-related comorbidities			
Obesity	3,550	0.87 (0.82-0.92)	<0.001
Hypertension	3,043	0.84 (0.78-0.91)	<0.001
Sleep apnea	3,100	0.88 (0.82-0.95)	<0.001
Dyslipidemia	2,298	0.82 (0.74-0.91)	<0.001
Anxiety/depression[2]	3,308	0.88 (0.81-0.95)	<0.001
Osteoporosis	3,115	0.95 (0.87-1.04)	0.242
Diabetes	3,472	0.86 (0.78-0.94)	<0.001
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease[3]	2,498	0.85 (0.79-0.91)	<0.001
Chronic obstructive pulmonary disease	2,530	0.73 (0.66-0.81)	<0.001
Bronchiectasis	2,535	0.91 (0.83-1.01)	0.075
VCD/laryngeal spasms	2,456	0.98 (0.89-1.07)	0.610

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Wald's test.
FeNO: Fractional exhaled nitric oxide; OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

7.3.4 Association between comorbidities and asthma-related outcomes

The association between long-term OCS use at enrolment and presence/absence of comorbidities are shown in Table 18. Patients with chronic rhinosinusitis, nasal polyposis, hypertension, sleep apnea, dyslipidemia, anxiety/depression, osteoporosis, diabetes, gastro-esophageal reflux disease, bronchiectasis, and vocal cord dysfunction/laryngeal spasms had higher odds of receiving long-term OCS. No comorbidity was associated with lower odds of receiving long-term OCS.

The association between exacerbation rates at enrolment and presence/absence of comorbidities are shown in Table 19. Patients with allergic rhinitis, chronic rhinosinusitis, nasal polyposis, hypertension, dyslipidemia, anxiety/depression, osteoporosis, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, and bronchiectasis had higher exacerbation rates than patients without these comorbidities. No comorbidity was associated with lower exacerbation rates.

The association between lung function at enrolment and presence/absence of comorbidities are shown in Table 20. Patients with allergic rhinitis, chronic rhinosinusitis, nasal polyposis, and vocal cord dysfunction/laryngeal spasms had higher FEV_1% predicted than patients without these comorbidities. On the contrary, patients with hypertension, osteoporosis, diabetes, chronic obstructive pulmonary disease, and bronchiectasis had lower FEV_1% predicted than patients without these comorbidities.

The association between asthma control at enrolment and presence/absence of comorbidities are shown in Table 21. Patients with chronic rhinosinusitis, obesity, hypertension, sleep apnea, anxiety/depression, osteoporosis, diabetes, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, and vocal cord dysfunction/laryngeal spasms had higher odds of being uncontrolled. No comorbidity was associated with lower odds of being uncontrolled.

Table 18. Association between most common comorbidities and receiving long-term OCS at registry enrolment: odds ratios and 95% confidence intervals of receiving long-term OCS associated with presence of comorbidities, adjusted for country, age at registry enrolment, and gender.

Comorbidities	Sample size	OR (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	7,976	0.97 (0.86-1.10)	0.653
Chronic rhinosinusitis[1]	7,980	1.46 (1.29-1.65)	<0.001
Nasal polyposis	8,271	1.40 (1.22-1.60)	<0.001
Eczema/atopic dermatitis	8,255	0.87 (0.71-1.06)	0.172
Potentially OCS-related comorbidities			
Obesity	8,252	1.12 (1.00-1.27)	0.057
Hypertension	6,452	1.33 (1.13-1.56)	<0.001
Sleep apnea	7,058	1.23 (1.04-1.46)	0.014
Dyslipidemia	4,465	1.48 (1.18-1.86)	<0.001
Anxiety/depression[2]	7,894	1.42 (1.21-1.66)	<0.001
Osteoporosis	7,661	2.77 (2.35-3.27)	<0.001
Diabetes	8,139	1.39 (1.17-1.66)	<0.001
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease[3]	4,831	1.51 (1.27-1.80)	<0.001
Chronic obstructive pulmonary disease	4,900	1.18 (0.95-1.48)	0.132
Bronchiectasis	4,906	1.57 (1.26-1.96)	<0.001
VCD/laryngeal spasms	4,668	1.37 (1.06-1.77)	0.016

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Wald's test.
OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

Table 19. Association between most common comorbidities and exacerbation rates at registry enrolment: ratios of means and 95% confidence intervals of number of exacerbations in the year preceding enrolment associated with presence of comorbidities, adjusted for country, age at registry enrolment, and gender.

Comorbidities	Sample size	Ratio of means (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	7,060	1.12 (1.04-1.21)	0.003
Chronic rhinosinusitis[1]	7,001	1.30 (1.20-1.39)	<0.001
Nasal polyposis	7,283	1.16 (1.07-1.25)	<0.001
Eczema/atopic dermatitis	7,265	1.11 (0.99-1.23)	0.072
Potentially OCS-related comorbidities			
Obesity	7,278	1.04 (0.97-1.11)	0.254
Hypertension	5,699	1.15 (1.03-1.28)	0.015
Sleep apnea	6,390	1.09 (0.99-1.20)	0.072
Dyslipidemia	4,233	1.21 (1.04-1.40)	0.013
Anxiety/depression[2]	6,971	1.40 (1.28-1.54)	<0.001
Osteoporosis	6,734	1.61 (1.45-1.79)	<0.001
Diabetes	7,181	1.07 (0.96-1.19)	0.233
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease[3]	4,519	1.68 (1.50-1.87)	<0.001
Chronic obstructive pulmonary disease	4,573	1.38 (1.21-1.58)	<0.001
Bronchiectasis	4,578	1.36 (1.17-1.57)	<0.001
VCD/laryngeal spasms	4,427	1.24 (1.06-1.45)	0.008

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Wald's test.
OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

Table 20. Association between most common comorbidities and lung function at registry enrolment: averaged differences and 95% confidence intervals of FEV_1 percent predicted at enrolment associated with presence of comorbidities, adjusted for country, age at registry enrolment, and gender.

Comorbidities	Sample size	Average difference (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	6,061	3.16 (2.02;4.30)	<0.001
Chronic rhinosinusitis[1]	6,109	1.64 (0.50;2.77)	0.005
Nasal polyposis	6,230	1.86 (0.45;3.27)	0.010
Eczema/atopic dermatitis	6,206	1.80 (-0.09;3.68)	0.062
Potentially OCS-related comorbidities			
Obesity	6,288	-0.52 (-1.61;0.57)	0.347
Hypertension	5,000	-2.64 (-4.08;-1.20)	<0.001
Sleep apnea	5,561	0.82 (-0.54;2.19)	0.235
Dyslipidemia	3,768	-0.43 (-2.23;1.38)	0.643
Anxiety/depression[2]	5,974	-0.74 (-2.21;0.73)	0.326
Osteoporosis	5,747	-3.42 (-5.06;-1.77)	<0.001
Diabetes	6,167	-3.54 (-5.13;-1.96)	<0.001
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease[3]	4,036	0.10 (-1.31;1.50)	0.892
Chronic obstructive pulmonary disease	4,076	-15.9 (-17.6;-14.2)	<0.001
Bronchiectasis	4,081	-5.24 (-7.32;-3.16)	<0.001
VCD/laryngeal spasms	3,955	4.82 (2.78;6.85)	<0.001

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Wald's test.
FEV_1: post-bronchodilatator forced expiratory volume in 1 second, percent of predicted; OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

Table 21. Association between most common comorbidities and asthma control at registry enrolment: odds ratio and 95% confidence intervals of being uncontrolled at enrolment associated with presence of comorbidities, adjusted for country, age at registry enrolment, and gender.

Comorbidities	Sample size	Odds ratio (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	4,722	0.95 (0.83-1.09)	0.436
Chronic rhinosinusitis[1]	4,669	1.17 (1.02-1.35)	0.025
Nasal polyposis	4,930	0.91 (0.78-1.06)	0.222
Eczema/atopic dermatitis	4,917	1.22 (0.99-1.51)	0.063
Potentially OCS-related comorbidities			
Obesity	4,945	1.47 (1.29-1.69)	<0.001
Hypertension	3,646	1.38 (1.15-1.65)	<0.001
Sleep apnea	4,088	1.59 (1.32-1.92)	<0.001
Dyslipidemia	2,333	0.93 (0.72-1.20)	0.575
Anxiety/depression[2]	4,697	1.68 (1.40-2.02)	<0.001
Osteoporosis	4,454	1.29 (1.05-1.57)	0.015
Diabetes	4,862	1.31 (1.06-1.60)	0.011
Comorbidities mimicking/exacerbating asthma			
Gastro-esophageal reflux disease[3]	2,530	1.81 (1.48-2.23)	<0.001
Chronic obstructive pulmonary disease	2,578	1.57 (1.22-2.03)	<0.001
Bronchiectasis	2,585	1.08 (0.80-1.46)	0.613
VCD/laryngeal spasms	2,494	1.81 (1.38-2.37)	<0.001

1. With or without nasal polyposis; with or without allergic rhinitis.
2. Can also mimic/exacerbate asthma.
3. Can also be OCS-related.
*Wald's test.
OCS: Oral corticosteroids; VCD: Vocal cord dysfunction.

7.4 Objective 3

7.4.1 Study Population: Demographic and Clinical Characteristics

Demographic and clinical characteristics of patients contributing to objective 3 are shown in Table 22.

Table 22. Demographic and clinical characteristics of patients contributing to Objective 3 analysis.

Characteristics	N	(%)
Total	1,769	
Gender		
Denominator	*1,769*	
Women	1,074	(60.7)
Men	695	(39.3)
Age at registry enrolment (years)		
Denominator	*1,769*	
18-29	119	(6.73)
30-39	174	(9.84)
40-49	314	(17.7)
50-59	534	(30.2)
60-69	431	(24.4)
70-79	172	(9.72)
80+	25	(1.41)
Median [Q1; Q3]	55 [45; 63]	
Range	18 to 92	
Calendar year at enrolment		
Denominator	*1,769*	
2017	484	(27.4)
2018	633	(35.8)
2019	416	(23.5)
2020	202	(11.4)
2021	34	(1.92)
Country		
Denominator	*1,769*	
Argentina	9	(0.509)
Australia	31	(1.75)
Bulgaria	8	(0.452)
Canada	111	(6.27)
Colombia	33	(1.86)
Denmark	176	(9.95)
Greece	16	(0.904)
India	1	(0.0565)
Ireland	0	(0)
Italy	421	(23.8)
Japan	37	(2.09)
Kuwait	53	(3.00)
Mexico	9	(0.509)
Poland	23	(1.30)
Portugal	3	(0.170)
Saudi Arabia	26	(1.47)
South Korea	13	(0.735)
Spain	55	(3.11)
Taiwan	48	(2.71)
The United Arab Emirates (UAE)	18	(1.02)
The United Kingdom (UK)	390	(22.0)
The United States of America (USA)	288	(16.3)
Smoking status at biologic initiation		
Denominator	*1,572*	
Current smoker	41	(2.61)
Ex-smoker	457	(29.1)
Never smoker	1,074	(68.3)

Age at asthma onset (years)		
Denominator	*1,330*	
<12	271	(20.4)
≥12	1,059	(79.6)
Median [Q1; Q3]	30 [16; 45]	
Range	1 to 77	
Receiving long-term OCS at biologic initiation		
Denominator	*1,769*	
Yes	861	(48.7)
No	908	(51.3)
Class of initiated biologics		
Denominator	*1,825*	
Anti-IgE	421	(23.8)
Anti-IL5/5R	1,261	(71.3)
Anti-IL4	87	(4.92)
Exacerbation rate at biologic initiation (number of episodes in the year preceding initiation)		
Denominator	*1,653*	
0	367	(22.2)
1	312	(18.9)
2	287	(17.4)
3-6	508	(30.7)
7-12	158	(9.56)
13-24	21	(1.27)
Median [Q1; Q3]	2 [1; 4]	
Range	0 to 24	
FEV_1 percent of predicted at biologic initiation		
Denominator	*1,489*	
<80%	916	(61.5)
≥80%	573	(38.5)
Median [Q1; Q3]	74.1% [59.1%; 88.4%]	
Range	14.0% to 166%	
Ratio of FEV_1/FVC at biologic initiation		
Denominator	*1,461*	
<0.70	814	(55.7)
≥0.70	647	(44.3)
Median [Q1; Q3]	0.68 [0.58; 0.76]	
Range	0.20 to 1.00	
Asthma control assessment at biologic initiation (GINA 2020)		
Denominator	*1,339*	
Uncontrolled	875	(65.3)
Partly controlled	287	(21.4)
Well controlled	177	(13.2)
Highest blood eosinophil count (cells/µL)		
Denominator	*1,457*	
Median [Q1; Q3]	520 [300; 880]	
Range	20 to 4,720	
Highest blood IgE count (IU/mL)		
Denominator	*1,306*	
Median [Q1; Q3]	180 [70.0; 465]	
Range	0 to 9,173	
Highest FeNO test resut (ppb)		
Denominator	*1,034*	
Median [Q1; Q3]	40 [21; 77]	
Range	1 to 300	
Potentially T2-related comorbidities		
Any		
Denominator	*1,769*	
Ever	1,290	(72.9)
Allergic rhinitis		
Denominator	*1,644*	
Ever	775	(47.1)
Chronic rhinosinusitis		
Denominator	*1,704*	
Ever	677	(39.7)

Nasal polyposis		
Denominator	*1,756*	
Ever	636	(36.2)
Eczema/atopic dermatitis		
Denominator	*1,753*	
Ever	243	(13.9)
Eosinophilic gradient		
Denominator	*1,596*	
Grade 0: Unlikely/noneosinophilic	2	(0.125)
Grade 1: Least likely	24	(1.50)
Grade 2: Likely	41	(2.57)
Grade 3: Most likely	1,529	(95.8)

FEV_1: post-bronchodilatator forced expiratory volume in 1 second, percent of predicted; FVC: Forced vital capacity; GINA: Global Initiative for Asthma.

7.4.2 Association between potentially T2-related comorbidities and post-biologic asthma-related outcomes

Exacerbation rates

These analyses were restricted to patients with at least 48 weeks of follow-up after biologic initiation. Post-biologic exacerbation rates were assessed at a median follow-up time of 107 weeks (IQR: 72-149 weeks). Rate ratios shown in **Error! Reference source not found.** correspond to the rates in patients with comorbidity divided by the rates in patients without comorbidity. Crude rate ratios are mostly to be ignored as given the imbalance at biologic initiation between studied groups (patients with or without comorbidity), it is necessary to condition on pre-biologic value for meaningful comparisons. Both patients with and without comorbidity tended to experience a reduction in exacerbation rates as shown by significant within group paired tests. The reduction tended to be larger in patients with any potentially T2-related comorbidity, allergic rhinitis, and nasal polyposis (overall and for each class of biologics), and chronic rhinosinusitis for anti-IL5/5R. Taking nasal polyposis as an example for all classes of biologics together (rate ratio = 0.77; p = 0.002): for any given pre-biologic rate, the post-biologic rates were 23% lower in patients with nasal polyposis than without. In patients with 4 exacerbations per year at biologic initiation, this translated post-biologic exacerbation rates of 0.80 and 1.04 exacerbations per year in patients with and without nasal polyposis, respectively. No association was found between eczema/atopic dermatitis and the amount of reduction in exacerbation rates. Whether the patients were using long-term OCS at biologic initiation did not substantially change the estimates for allergic rhinitis, nasal polyposis, and eczema/atopic dermatitis. For chronic rhinosinusitis, the association was more apparent in patients receiving long-term OCS.

Lung function

Post-biologics FEV_1 percent predicted values were measured at a median follow-up time of 53 weeks (IQR: 46-62 weeks). Estimates shown in **Error! Reference source not found.** correspond to differences between post-biologic FEV_1 percent predicted values in patients with comorbidity compared to patients without. Both patients with and without comorbidity tended to experience an improvement in FEV_1 percent predicted for all classes of biologics together and for anti-IL5/5R. Conditioning on pre-biologic values, the overall improvement was larger in patients with allergic rhinitis than without (+2.7 points of improvement on an absolute scale of FEV_1 percent predicted; p=0.018) and in patients with chronic rhinosinusitis compared to patients without (+3.0 points of improvement; p=0.006). Results were similar when restricting the analysis to anti-IL5/5R. No significant associations were detected for nasal polyposis or eczema/atopic dermatitis, or in patients initiating anti-IgE.

Asthma control

Post-biologics asthma control assessment was performed at a median follow-up time of 53 weeks (IQR: 48-63 weeks). Globally, asthma control significantly improved post-biologic initiation (**Error! Reference source not found.**). The odds of being well controlled post-biologic initiation were globally higher in patients with comorbidity than without (Table 25). Similarly, the odds of being well or partly controlled were globally higher in patients with comorbidity than in patients without (Table 26). The positive associations were observed for allergic rhinitis, chronic rhinosinusitis, or nasal polyposis, whereas patients with eczema/atopic dermatitis tended to have lower odds of being well or partly controlled post-biologic initiation. For allergic rhinitis, the association was significant both for anti-IgE and anti-IL5/5R, whereas for chronic rhinosinusitis and nasal polyposis, the association was significant only for anti-IL5/5R. For chronic rhinosinusitis, the association was more apparent in patients receiving long-term OCS, whereas for allergic rhinitis and nasal polyposis, the association was more apparent in patients not receiving long-term OCS.

Long-term OCS daily dose

These analyses were restricted to patients receiving long-term OCS at biologic initiation. Globally, there was a significant decrease in daily doses after biologic initiation (Table 27). Adjusting for daily dose at biologic initiation, the reduction tended to be more substantial in patients with nasal polyposis or eczema/atopic dermatitis than in patients without but the

differences were not significant. On the contrary, the reduction was larger in patients without chronic rhinosinusitis than in patients with ($p = 0.031$) and in patients without allergic rhinitis than in patients with (non-significant association).

Table 23. Association between potentially T2-related comorbidities and change in exacerbation rates pre- to post-biologics: within groups before/after paired comparisons, and across group differences.

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity and LTOCS status				Post-biologic rate ratios comparing patients with and without comorbidity**, by LTOCS status					
		Pre-biologics mean (SD)	Post-biologics mean (SD)	Change mean (SD)	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
						Rate ratio (95% CI)	p	Rate ratio (95% CI)	p	Rate ratio (95% CI)	p
Any potentially T2-related comorbidity						**All biologics**					
Overall											
Never	334	4.19 (4.20)	1.40 (1.77)	-2.79 (3.97)	<0.001	Ref.		Ref.		Ref.	
Ever	953	2.56 (2.74)	0.75 (1.26)	-1.81 (2.73)	<0.001	0.53 (0.45; 0.63)	<0.001	0.65 (0.55; 0.78)	<0.001	0.65 (0.55; 0.78)	0.251
Not receiving LTOCS											
Never	152	3.55 (3.77)	1.09 (1.42)	-2.47 (3.60)	<0.001	Ref.		Ref.		Ref.	
Ever	569	2.19 (2.32)	0.62 (1.13)	-1.57 (2.40)	<0.001	0.57 (0.44; 0.74)	<0.001	0.68 (0.53; 0.88)	0.004	0.68 (0.53; 0.88)	0.004
Receiving LTOCS											
Never	182	4.72 (4.47)	1.67 (1.98)	-3.05 (4.25)	<0.001	Ref.		Ref.		Ref.	
Ever	384	3.11 (3.19)	0.94 (1.42)	-2.17 (3.13)	<0.001	0.56 (0.45; 0.71)	<0.001	0.67 (0.53; 0.84)	<0.001	0.67 (0.53; 0.84)	<0.001
						Anti-IgE					
Overall											
Never	71	3.86 (4.46)	1.59 (2.05)	-2.26 (4.02)	<0.001	Ref.		Ref.		Ref.	
Ever	220	1.86 (2.10)	0.60 (0.86)	-1.25 (2.16)	<0.001	0.38 (0.27; 0.52)	<0.001	0.51 (0.36; 0.70)	<0.001	0.51 (0.37; 0.71)	<0.001
Not receiving LTOCS											
Never	43	2.53 (2.77)	1.18 (1.55)	-1.35 (2.44)	0.001	Ref.		Ref.		Ref.	
Ever	162	1.73 (1.95)	0.48 (0.67)	-1.25 (2.00)	<0.001	0.41 (0.27; 0.60)	<0.001	0.47 (0.32; 0.69)	<0.001	0.47 (0.32; 0.69)	<0.001
Receiving LTOCS											
Never	28	5.89 (5.70)	2.21 (2.56)	-3.68 (5.40)	0.001	Ref.		Ref.		Ref.	
Ever	58	2.22 (2.48)	0.95 (1.19)	-1.28 (2.57)	<0.001	0.43 (0.26; 0.71)	0.001	0.58 (0.34; 1.01)	0.054	0.60 (0.35; 1.03)	0.063
						Anti-IL5/5R					
Overall											
Never	257	4.34 (4.15)	1.37 (1.69)	-2.97 (3.99)	<0.001	Ref.		Ref.		Ref.	
Ever	679	2.87 (2.88)	0.82 (1.39)	-2.05 (2.90)	<0.001	0.60 (0.49; 0.74)	<0.001	0.71 (0.58; 0.86)	<0.001	0.70 (0.58; 0.86)	<0.001
Not receiving LTOCS											
Never	105	4.07 (4.06)	1.08 (1.38)	-2.99 (3.94)	<0.001	Ref.		Ref.		Ref.	
Ever	365	2.51 (2.44)	0.72 (1.31)	-1.79 (2.59)	<0.001	0.70 (0.48; 0.92)	0.015	0.78 (0.56; 1.09)	0.146	0.79 (0.57; 1.09)	0.150
Receiving LTOCS											
Never	152	4.53 (2.22)	1.57 (1.86)	-2.96 (4.04)	<0.001	Ref.		Ref.		Ref.	
Ever	314	3.29 (3.27)	0.95 (1.47)	-2.35 (3.20)	<0.001	0.60 (0.46; 0.78)	<0.001	0.68 (0.53; 0.88)	0.003	0.68 (0.53; 0.87)	0.003

*Paired Wilcoxon tests.
**Negative binomial models.

Table 23 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity and LTOCS status				Post-biologic rate ratios comparing patients with and without comorbidity**, by LTOCS status					
		Pre-biologics mean (SD)	Post-biologics mean (SD)	Change mean (SD)	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
						Rate ratio (95% CI)	p	Rate ratio (95% CI)	p	Rate ratio (95% CI)	p
Allergic rhinitis		**All biologics**									
Overall											
Never	656	3.68 (3.79)	1.17 (1.60)	-2.51 (3.55)	<0.001	Ref.		Ref.		Ref.	
Ever	570	2.26 (2.35)	0.67 (1.23)	-1.59 (2.55)	<0.001	0.57 (0.48; 0.67)	0.003	0.70 (0.59; 0.83)	<0.001	0.69 (0.58; 0.81)	<0.001
Not receiving LTOCS											
Never	311	3.14 (3.29)	0.91 (1.33)	-2.23 (3.11)	<0.001	Ref.		Ref.		Ref.	
Ever	382	1.99 (1.07)	0.59 (1.12)	-1.41 (2.29)	<0.001	0.65 (0.51; 0.82)	<0.001	0.78 (0.62; 0.98)	0.033	0.76 (0.60; 0.96)	0.022
Receiving LTOCS											
Never	345	4.17 (4.13)	1.41 (1.77)	-2.76 (3.89)	<0.001	Ref.		Ref.		Ref.	
Ever	188	2.79 (2.78)	0.82 (1.43)	-1.96 (2.97)	<0.001	0.59 (0.46; 0.75)	<0.001	0.70 (0.55; 0.90)	0.005	0.69 (0.54; 0.88)	0.003
		Anti-IgE									
Overall											
Never	115	3.17 (3.85)	1.26 (1.75)	-1.91 (3.38)	<0.001	Ref.		Ref.		Ref.	
Ever	173	1.84 (2.08)	0.58 (0.86)	-1.26 (2.24)	<0.001	0.46 (0.33; 0.63)	<0.001	0.59 (0.43; 0.81)	<0.001	0.58 (0.42; 0.80)	<0.001
Not receiving LTOCS											
Never	69	2.29 (2.58)	0.99 (1.32)	-1.30 (2.28)	<0.001	Ref.		Ref.		Ref.	
Ever	134	1.72 (1.90)	0.45 (0.65)	-1.28 (2.00)	<0.001	0.45 (0.31; 0.67)	<0.001	0.51 (0.35; 0.74)	<0.001	0.51 (0.35; 0.74)	<0.001
Receiving LTOCS											
Never	46	4.50 (4.95)	1.67 (2.19)	-2.83 (4.44)	<0.001	Ref.		Ref.		Ref.	
Ever	39	2.23 (2.61)	1.03 (1.27)	-1.20 (2.93)	0.025	0.61 (0.36; 1.04)	0.070	0.84 (0.49; 1.42)	0.512	0.77 (0.45; 1.31)	0.331
		Anti-IL5/5R									
Overall											
Never	515	3.88 (3.79)	1.19 (1.59)	-2.69 (3.60)	<0.001	Ref.		Ref.		Ref.	
Ever	363	2.56 (2.47)	0.73 (1.40)	-1.83 (2.73)	<0.001	0.61 (0.50; 0.75)	<0.001	0.73 (0.59; 0.89)	0.002	0.72 (0.59; 0.88)	0.001
Not receiving LTOCS											
Never	222	3.54 (3.47)	0.94 (1.37)	-2.59 (3.32)	<0.001	Ref.		Ref.		Ref.	
Ever	222	2.28 (2.17)	0.70 (1.35)	-1.58 (2.53)	<0.001	0.75 (0.56; 1.00)	0.049	0.89 (0.66; 1.19)	0.415	0.86 (0.64; 1.15)	0.304
Receiving LTOCS											
Never	293	4.13 (4.00)	1.37 (1.71)	-2.76 (3.81)	<0.001	Ref.		Ref.		Ref.	
Ever	141	2.99 (2.84)	0.77 (1.48)	-2.22 (3.00)	<0.001	0.56 (0.41; 0.75)	<0.001	0.64 (0.48; 0.85)	0.002	0.64 (0.48; 0.86)	0.003

*Paired Wilcoxon tests.
**Negative binomial models.

Table 23 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity and LTOCS status				Post-biologic rate ratios comparing patients with and without comorbidity**, by LTOCS status					
		Pre-biologics mean (SD)	Post-biologics mean (SD)	Change mean (SD)	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
						Rate ratio (95% CI)	p	Rate ratio (95% CI)	p	Rate ratio (95% CI)	p
Chronic rhinoisinusitis		**All biologics**									
Overall											
Never	737	3.43 (3.68)	1.11 (1.58)	-2.32 (3.43)	<0.001	Ref.		Ref.		Ref.	
Ever	519	2.28 (2.32)	0.65 (1.15)	-1.63 (2.47)	<0.001	0.59 (0.50; 0.70)	<0.001	0.72 (0.61; 0.85)	<0.001	0.73 (0.61; 0.86)	<0.001
Not receiving LTOCS											
Never	375	2.81 (3.13)	0.82 (1.24)	-1.99 (2.94)	<0.001	Ref.		Ref.		Ref.	
Ever	328	2.05 (2.13)	0.63 (1.20)	-1.42 (2.41)	<0.001	0.77 (0.61; 0.97)	0.026	0.90 (0.71; 1.13)	0.356	0.91 (0.72; 1.14)	0.407
Receiving LTOCS											
Never	362	4.07 (4.07)	1.40 (1.83)	-2.67 (3.85)	<0.001	Ref.		Ref.		Ref.	
Ever	191	2.69 (2.57)	0.69 (1.06)	-2.00 (2.54)	<0.001	0.49 (0.38; 0.63)	<0.001	0.58 (0.45; 0.75)	<0.001	0.60 (0.47; 0.77)	<0.001
		Anti-IgE									
Overall											
Never	189	2.56 (3.29)	0.94 (1.50)	-1.61 (2.98)	<0.001	Ref.		Ref.		Ref.	
Ever	100	1.98 (2.27)	0.67 (0.90)	-1.31 (2.31)	<0.001	0.71 (0.50; 1.02)	0.061	0.84 (0.60; 1.18)	0.304	0.84 (0.60; 1.18)	0.310
Not receiving LTOCS											
Never	130	1.96 (2.17)	0.65 (1.08)	-1.31 (2.04)	<0.001	Ref.		Ref.		Ref.	
Ever	73	1.81 (2.18)	0.59 (0.72)	-1.22 (2.22)	<0.001	0.90 (0.59; 1.37)	0.624	0.95 (0.64; 1.42)	0.810	0.96 (0.64; 1.43)	0.824
Receiving LTOCS											
Never	59	3.86 (4.71)	1.58 (2.03)	-2.29 (4.34)	<0.001	Ref.		Ref.		Ref.	
Ever	27	2.44 (2.47)	0.89 (1.25)	-1.56 (2.56)	0.006	0.56 (0.31; 1.03)	0.061	0.69 (0.38; 1.22)	0.202	0.69 (0.39; 1.22)	0.199
		Anti-IL5/5R									
Overall											
Never	519	3.84 (3.78)	1.19 (1.63)	-2.65 (3.59)	<0.001	Ref.		Ref.		Ref.	
Ever	389	2.43 (2.33)	0.68 (1.23)	-1.75 (2.53)	<0.001	0.57 (0.47; 0.69)	<0.001	0.69 (0.58; 0.84)	<0.001	0.70 (0.58; 0.85)	<0.001
Not receiving LTOCS											
Never	223	3.48 (3.52)	0.96 (1.34)	-2.52 (3.35)	<0.001	Ref.		Ref.		Ref.	
Ever	231	2.19 (2.10)	0.68 (1.35)	-1.51 (2.49)	<0.001	0.70 (0.53; 0.94)	0.016	0.84 (0.63; 1.12)	0.225	0.85 (0.63; 1.13)	0.260
Receiving LTOCS											
Never	296	4.11 (3.95)	1.36 (1.80)	-2.75 (3.76)	<0.001	Ref.		Ref.		Ref.	
Ever	158	2.78 (2.61)	0.68 (1.04)	-2.11 (2.56)	<0.001	0.50 (0.37; 0.66)	<0.001	0.59 (0.44; 0.78)	<0.001	0.60 (0.45; 0.79)	<0.001

*Paired Wilcoxon tests.
**Negative binomial models.

Table 23 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity and LTOCS status				Post-biologic rate ratios comparing patients with and without comorbidity**, by LTOCS status					
		Pre-biologics mean (SD)	Post-biologics mean (SD)	Change mean (SD)	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
						Rate ratio (95% CI)	p	Rate ratio (95% CI)	p	Rate ratio (95% CI)	p
Nasal polyposis		**All biologics**									
Overall											
Never	818	3.05 (3.40)	1.01 (1.55)	-2.04 (3.30)	<0.001	Ref.		Ref.		Ref.	
Ever	463	2.88 (3.02)	0.77 (1.21)	-2.11 (2.82)	<0.001	0.76 (0.64; 0.91)	0.002	0.77 (0.65; 0.91)	0.002	0.78 (0.66; 0.93)	0.004
Not receiving LTOCS											
Never	464	2.45 (2.85)	0.77 (1.30)	-1.68 (2.88)	<0.001	Ref.		Ref.		Ref.	
Ever	252	2.53 (2.56)	0.63 (1.04)	-1.90 (2.43)	<0.001	0.82 (0.64; 1.04)	0.107	0.80 (0.63; 1.01)	0.062	0.80 (0.63; 1.02)	0.071
Receiving LTOCS											
Never	354	3.83 (3.87)	1.32 (1.79)	-2.51 (3.74)	<0.001	Ref.		Ref.		Ref.	
Ever	211	3.30 (3.44)	0.93 (1.37)	-2.37 (3.21)	<0.001	0.71 (0.56; 0.90)	0.005	0.74 (0.59; 0.93)	0.011	0.75 (0.59; 0.94)	0.012
		Anti-IgE									
Overall											
Never	217	2.38 (3.20)	0.91 (1.44)	-1.47 (2.91)	<0.001	Ref.		Ref.		Ref.	
Ever	74	2.24 (2.21)	0.65 (0.91)	-1.59 (2.27)	<0.001	0.71 (0.48; 1.06)	0.091	0.78 (0.54; 1.14)	0.204	0.82 (0.56; 1.20)	0.297
Not receiving LTOCS											
Never	154	1.86 (2.29)	0.68 (1.02)	-1.17 (2.18)	<0.001	Ref.		Ref.		Ref.	
Ever	51	2.02 (1.73)	0.47 (0.76)	-1.55 (1.80)	<0.001	0.69 (0.42; 1.13)	0.140	0.70 (0.44; 1.13)	0.147	0.68 (0.42; 1.10)	0.114
Receiving LTOCS											
Never	63	3.67 (4.52)	1.48 (2.04)	-2.19 (4.13)	<0.001	Ref.		Ref.		Ref.	
Ever	23	2.74 (3.02)	1.04 (1.11)	-1.70 (3.11)	0.02	0.71 (0.38; 1.31)	0.273	0.84 (0.47; 1.52)	0.572	0.96 (0.53; 1.74)	0.882
		Anti-IL5/5R									
Overall											
Never	568	3.37 (3.46)	1.07 (1.62)	-2.30 (3.46)	<0.001	Ref.		Ref.		Ref.	
Ever	363	3.14 (3.16)	0.83 (1.29)	-2.31 (2.94)	<0.001	0.78 (0.64; 0.95)	0.012	0.78 (0.64; 0.94)	0.010	0.77 (0.64; 0.94)	0.009
Not receiving LTOCS											
Never	282	2.90 (3.12)	0.87 (1.46)	-2.03 (3.25)	<0.001	Ref.		Ref.		Ref.	
Ever	184	2.80 (2.71)	0.71 (1.13)	-2.09 (2.56)	<0.001	0.81 (0.61; 1.09)	0.169	0.79 (0.59; 1.06)	0.119	0.80 (0.60; 1.07)	0.139
Receiving LTOCS											
Never	286	3.84 (3.72)	1.27 (1.74)	-2.57 (3.65)	<0.001	Ref.		Ref.		Ref.	
Ever	179	3.49 (3.53)	0.96 (1.43)	-2.52 (3.28)	<0.001	0.75 (0.58; 0.99)	0.039	0.77 (0.59; 0.99)	0.043	0.75 (0.58; 0.98)	0.032

*Paired Wilcoxon tests.
**Negative binomial models.

Table 23 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity and LTOCS status				Post-biologic rate ratios comparing patients with and without comorbidity**, by LTOCS status					
		Pre-biologics mean (SD)	Post-biologics mean (SD)	Change mean (SD)	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
						Rate ratio (95% CI)	p	Rate ratio (95% CI)	p	Rate ratio (95% CI)	p
Eczema/atopic dermatitis		**All biologics**									
Overall											
Never	1,092	3.15 (3.39)	0.96 (0.46)	-2.19 (3.22)	<0.001	Ref.		Ref.		Ref.	
Ever	189	1.97 (2.00)	0.72 (1.35)	-1.25 (2.30)	<0.001	0.75 (0.59; 0.96)	0.021	0.92 (0.73; 1.17)	0.495	0.90 (0.71; 1.13)	0.357
Not receiving LTOCS											
Never	584	2.60 (2.88)	0.75 (1.19)	-1.85 (2.79)	<0.001	Ref.		Ref.		Ref.	
Ever	132	1.90 (1.82)	0.61 (1.33)	-1.29 (2.24)	<0.001	0.82 (0.60; 1.11)	0.205	0.94 (0.70; 1.17)	0.679	0.92 (0.68; 1.24)	0.591
Receiving LTOCS											
Never	508	3.78 (3.80)	1.20 (1.69)	-2.59 (3.61)	<0.001	Ref.		Ref.		Ref.	
Ever	57	2.12 (2.38)	0.96 (1.36)	-1.16 (2.46)	<0.001	0.80 (0.54; 1.20)	0.283	1.00 (0.69; 1.47)	0.984	0.97 (0.67; 1.42)	0.894
		Anti-IgE									
Overall											
Never	242	2.44 (3.14)	0.85 (1.37)	-1.58 (2.92)	<0.001	Ref.		Ref.		Ref.	
Ever	49	1.90 (1.95)	0.80 (1.10)	-1.10 (1.73)	<0.001	0.93 (0.60; 1.45)	0.750	1.04 (0.69; 1.59)	0.838	1.03 (0.67; 1.56)	0.906
Not receiving LTOCS											
Never	168	1.96 (2.27)	0.66 (1.03)	-1.30 (2.21)	<0.001	Ref.		Ref.		Ref.	
Ever	37	1.59 (1.59)	0.49 (0.61)	-1.11 (1.45)	<0.001	0.74 (0.42; 1.28)	0.279	0.80 (0.47; 1.38)	0.429	0.81 (0.47; 1.40)	0.448
Receiving LTOCS											
Never	74	3.51 (4.38)	1.30 (1.87)	-2.22 (4.04)	<0.001	Ref.		Ref.		Ref.	
Ever	12	2.83 (2.66)	1.75 (1.66)	-1.08 (2.50)	0.165	1.35 (0.65; 2.79)	0.419	1.53 (0.78; 3.00)	0.211	0.53 (0.79; 2.96)	0.204
		Anti-IL5/5R									
Overall											
Never	814	3.42 (3.46)	1.01 (1.50)	-2.42 (3.32)	<0.001	Ref.		Ref.		Ref.	
Ever	116	2.12 (1.86)	0.76 (1.53)	-1.36 (2.52)	<0.001	0.75 (0.55; 1.02)	0.069	0.94 (0.70; 1.27)	0.701	0.91 (0.68; 1.22)	0.535
Not receiving LTOCS											
Never	389	2.93 (3.09)	0.81 (1.27)	-2.12 (3.01)	<0.001	Ref.		Ref.		Ref.	
Ever	76	2.37 (1.92)	0.78 (1.67)	-1.59 (2.69)	<0.001	0.96 (0.65; 1.42)	0.832	1.09 (0.75; 1.59)	0.653	1.04 (0.71; 1.52)	0.837
Receiving LTOCS											
Never	425	3.87 (3.72)	1.19 (1.66)	-2.68 (3.56)	<0.001	Ref.		Ref.		Ref.	
Ever	40	1.65 (1.64)	0.72 (1.24)	-0.92 (2.14)	0.011	0.61 (0.37; 1.01)	0.055	0.83 (0.51; 1.35)	0.449	0.82 (0.50; 1.33)	0.419

*Paired Wilcoxon tests.
**Negative binomial models.

Table 24. Association between potentially T2-related comorbidities and change in FEV_1 percent predicted pre- to post-biologics: within groups before/after paired comparisons, and across group differences.

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity status				Post-biologic differences between patients with and without comorbidity**					
		Pre-biologics	Post-biologics	Change	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
		mean (SD)	mean (SD)	mean (SD)		Difference (95% CI)	p	Difference (95% CI)	p	Difference (95% CI)	p
All biologics											
Any T2-related comorbidity											
Never	255	70.0 (23.3)	72.4 (22.5)	2.4 (17.5)	0.028	Ref.		Ref.		Ref.	
Ever	625	75.2 (22.3)	78.4 (23.0)	3.3 (17.0)	<0.001	6.0 (2.6; 9.3)	<0.001	2.3 (-0.1; 4.6)	0.057	2.3 (0.00; 4.7)	0.050
Allergic rhinitis											
Never	507	71.6 (23.1)	73.8 (22.9)	2.2 (16.4)	0.002	Ref.		Ref.		Ref.	
Ever	323	76.4 (21.8)	80.0 (22.6)	3.6 (18.0)	<0.001	6.2 (3.0; 9.4)	<0.001	2.7 (0.5; 4.9)	0.018	2.7 (0.5; 4.9)	0.017
Chronic rhinosinusitis											
Never	537	72.3 (22.9)	74.4 (22.8)	2.1 (17.1)	0.004	Ref.		Ref.		Ref.	
Ever	337	75.7 (22.1)	79.9 (22.7)	4.2 (17.1)	<0.001	5.5 (2.4; 8.6)	0.001	3.0 (0.8; 5.2)	0.006	3.1 (0.9; 5.2)	0.006
Nasal polyposis											
Never	573	72.2 (22.9)	75.1 (22.8)	2.9 (17.1)	<0.001	Ref.		Ref.		Ref.	
Ever	306	76.4 (22.1)	79.7 (23.0)	3.3 (17.1)	0.001	4.6 (1.4; 7.8)	0.005	1.6 (-0.7; 3.8)	0.169	1.7 (-0.6; 3.9)	0.145
Eczema/atopic dermatitis											
Never	776	73.6 (22.7)	76.8 (23.1)	3.1 (17.5)	<0.001	Ref.		Ref.		Ref.	
Ever	101	73.9 (22.5)	75.6 (21.7)	1.7 (13.7)	0.210	-1.2 (-6.0; 3.6)	0.620	-1.4 (-4.7; 2.0)	0.423	-1.4 (-4.7; 1.9)	0.413

*Paired t-tests.
**ANCOVA models.

Table 24 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity status				Post-biologic differences between patients with and without comorbidity**					
		Pre-biologics mean (SD)	Post-biologics mean (SD)	Change mean (SD)	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
						Difference (95% CI)	p	Difference (95% CI)	p	Difference (95% CI)	p
Anti-IgE											
Any T2-related comorbidity											
Never	46	70.2 (21.8)	71.0 (21.7)	0.8 (21.4)	0.799	Ref.		Ref.		Ref.	
Ever	140	76.2 (22.5)	77.3 (23.2)	1.2 (16.5)	0.408	6.3 (-1.3; 14.0)	0.103	2.1 (-3.5; 7.7)	0.458	2.8 (-2.8; 8.4)	0.326
Allergic rhinitis											
Never	82	71.9 (24.1)	72.5 (24.3)	0.6 (18.3)	0.752	Ref.		Ref.		Ref.	
Ever	102	77.4 (20.7)	78.3 (21.9)	1.0 (17.4)	0.573	5.8 (-0.9; 12.5)	0.088	1.9 (-3.0; 6.8)	0.443	2.4 (-2.5; 7.3)	0.330
Chronic rhinosinusitis											
Never	122	74.3 (21.0)	75.6 (21.7)	1.3 (19.8)	0.485	Ref.		Ref.		Ref.	
Ever	62	75.7 (25.1)	76.0 (25.8)	0.3 (13.2)	0.880	0.4 (-6.7; 7.4)	0.920	-0.6 (-5.7; 4.5)	0.814	-0.2 (-5.3; 4.9)	0.942
Nasal polyposis											
Never	143	73.0 (21.9)	73.8 (22.2)	0.7 (18.4)	0.637	Ref.		Ref.		Ref.	
Ever	42	80.4 (23.6)	82.3 (24.6)	2.0 (16.1)	0.414	8.6 (0.7; 16.4)	0.032	3.4 (-2.3; 9.2)	0.244	4.5 (-1.2; 10.3)	0.123
Eczema/atopic dermatitis											
Never	151	75.2 (22.7)	76.8 (23.4)	1.6 (19.0)	0.301	Ref.		Ref.		Ref.	
Ever	33	73.5 (20.7)	71.4 (21.0)	2.0 (11.0)	0.298	-5.4 (-14.0; 3.3)	0.225	-4.1 (-10.4; 2.2)	0.198	-4.0 (-10.3; 2.2)	0.203

*Paired t-tests.
**ANCOVA models.

Table 24 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity status				Post-biologic differences between patients with and without comorbidity**					
		Pre-biologics mean (SD)	Post-biologics mean (SD)	Change mean (SD)	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
						Difference (95% CI)	p	Difference (95% CI)	p	Difference (95% CI)	p
Anti-IL5/5R											
Any T2-related comorbidity											
Never	205	70.1 (23.4)	72.8 (22.5)	2.7 (16.6)	0.019	Ref.		Ref.		Ref.	
Ever	463	74.9 (22.3)	78.7 (23.1)	3.7 (17.1)	<0.001	5.9 (2.1; 9.6)	0.002	2.3 (-0.3; 4.9)	0.083	2.4 (-0.2; 5.0)	0.073
Allergic rhinitis											
Never	412	71.7 (22.7)	74.2 (22.6)	2.5 (16.1)	0.002	Ref.		Ref.		Ref.	
Ever	208	75.8 (22.7)	80.5 (23.4)	4.7 (18.2)	<0.001	6.3 (2.5; 10.1)	0.001	3.3 (0.7: 5.9)	0.014	3.3 (0.6; 5.9)	0.015
Chronic rhinosinusitis											
Never	402	71.8 (23.5)	74.2 (23.1)	2.4 (16.5)	0.004	Ref.		Ref.		Ref.	
Ever	262	75.8 (21.5)	80.6 (22.1)	4.8 (17.6)	<0.001	6.5 (2.9; 10.0)	<0.001	3.6 (1.1; 6.0)	0.004	3.5 (1.1; 6.0)	0.005
Nasal polyposis											
Never	415	72.0 (23.2)	75.5 (23.0)	3.6 (16.7)	<0.001	Ref.		Ref.		Ref.	
Ever	253	75.8 (21.9)	79.1 (23.0)	3.2 (17.3)	0.003	3.5 (-0.1; 7.1)	0.055	0.7 (-1.8; 3.2)	0.581	0.8 (-1.6; 3.4)	0.500
Eczema/atopic dermatitis											
Never	606	73.3 (22.6)	76.7 (23.1)	3.4 (17.2)	<0.001	Ref.		Ref.		Ref.	
Ever	61	74.0 (24.1)	77.7 (22.3)	3.7 (14.1)	0.047	1.0 (-5.1; 7.0)	0.758	0.4 (-3.7; 4.6)	0.835	0.5 (-3.7; 4.7)	0.819

*Paired t-tests.
**ANCOVA models.

Table 25. Association between potentially T2-related comorbidities and pre- to post-biologic improvement in asthma control: within groups before/after paired comparisons, and odds ratios and 95% confidence intervals of being well controlled post-biologic initiation comparing patients with and without comorbidity.

Patient characteristics	Comparison of pre- and post-biologic status by comorbidity and LTOCS status				Comparison of odds of being well controlled between patients with and without comorbidity**, by LTOCS status					
					Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
	N	Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Any T2-related comorbidity	**All biologics**									
Overall										
Never	308	73.1; 16.9; 10.1	47.4; 21.8; 30.8	<0.001	Ref.		Ref.		Ref.	
Ever	740	65.8; 21.1; 13.1	30.8; 28.0; 41.2	<0.001	1.57 (1.18; 2.09)	0.002	1.49 (1.11; 2.00)	0.008	1.49 (1.11; 2.00)	0.008
Not receiving LTOCS										
Never	139	60.4; 24.5; 15.1	37.4; 25.2; 37.4	<0.001	Ref.		Ref.		Ref.	
Ever	407	61.4; 23.3; 15.2	23.8; 31.2; 45.0	<0.001	1.37 (0.92; 2.03)	0.121	1.41 (0.93; 2.12)	0.103	1.40 (0.92; 2.11)	0.111
Receiving LTOCS										
Never	169	83.4; 10.7; 5.9	55.6; 18.9; 25.4	<0.001	Ref.		Ref.		Ref.	
Ever	333	71.2; 18.3; 10.5	39.3; 24.0; 36.6	<0.001	1.69 (1.12; 2.56)	0.012	1.49 (0.97; 2.28)	0.067	1.49 (0.97; 2.28)	0.067
	Anti-IgE									
Overall										
Never	72	65.3; 15.3; 19.4	48.6; 20.8; 30.6	0.020	Ref.		Ref.		Ref.	
Ever	170	60.6; 21.8; 17.6	26.5; 34.1; 39.4	<0.001	1.48 (0.82; 2.66)	0.193	1.56 (0.82; 2.94)	0.173	1.47 (0.77; 2.81)	0.237
Not receiving LTOCS										
Never	44	50.0; 22.7; 27.3	34.1; 27.3; 38.6	0.187	Ref.		Ref.		Ref.	
Ever	117	58.1; 23.9; 17.9	23.9; 36.8; 39.3	<0.001	1.03 (0.50, 2.10)	0.937	1.23 (0.57; 2.66)	0.589	1.18 (0.55; 2.56)	0.666
Receiving LTOCS										
Never	28	89.3; 3.6; 7.1	71.4; 10.7; 17.9	0.112	Ref.		Ref.		Ref.	
Ever	53	66.0; 17.0; 17.0	32.1; 28.3; 39.6	0.001	3.02 (0.99; 9.18)	0.052	2.10 (0.62; 7.07)	0.231	2.42 (0.68; 8.65)	0.174
	Anti-IL5/5R									
Overall										
Never	234	76.1; 17.1; 6.8	47.4; 22.2; 30.3	<0.001	Ref.		Ref.		Ref.	
Ever	539	68.3; 21.0; 10.8	32.7; 26.7; 40.6	<0.001	1.57 (1.13; 2.18)	0.007	1.46 (1.05; 2.05)	0.026	1.47 (1.05; 2.06)	0.026
Not receiving LTOCS										
Never	93	66.7; 24.7; 8.6	39.8; 24.7; 35.5	<0.001	Ref.		Ref.		Ref.	
Ever	265	64.5; 23.4; 12.1	24.9; 29.8; 45.3	<0.001	1.50 (0.92; 2.45)	0.101	1.47 (0.89; 2.44)	0.132	1.45 (0.87; 2.41)	0.154
Receiving LTOCS										
Never	141	82.3; 12.1; 5.7	52.5; 20.6; 27.0	<0.001	Ref.		Ref.		Ref.	
Ever	274	71.9; 18.6; 9.5	40.1; 23.7; 36.1	<0.001	1.53 (0.98; 2.40)	0.060	1.39 (0.88; 2.20)	0.156	1.41 (0.89; 2.23)	0.146

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 25 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic status by comorbidity and LTOCS status: Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Comparison of odds of being well controlled between patients with and without comorbidity**, by LTOCS status: Crude Odds ratio (95% CI)	p	Adjusting for baseline value Odds ratio (95% CI)	p	Adjusting for baseline value, age, and gender Odds ratio (95% CI)	p
Allergic rhinitis					**All biologics**					
Overall										
Never	524	72.7; 15.3; 12.0	45.8; 21.9; 32.3	<0.001	Ref.		Ref.		Ref.	
Ever	441	65.8; 22.2; 12.0	27.2; 31.1; 41.7	<0.001	1.50 (1.16; 1.96)	0.002	1.47 (1.12; 1.94)	0.006	1.49 (1.13; 1.97)	0.004
Not receiving LTOCS										
Never	231	62.3; 21.2; 16.5	35.1; 27.3; 37.7	<0.001	Ref.		Ref.		Ref.	
Ever	275	62.9; 23.3; 13.8	23.3; 33.1; 43.6	<0.001	1.28 (0.90; 1.83)	0.174	1.35 (0.93; 1.96)	0.113	1.38 (0.95; 2.00)	0.094
Receiving LTOCS										
Never	293	80.9; 10.6; 8.5	54.3; 17.7; 28.0	<0.001	Ref.		Ref.		Ref.	
Ever	166	70.5; 20.5; 9.0	33.7; 27.7; 38.6	<0.001	1.61 (1.08; 2.42)	0.020	1.49 (0.97; 2.27)	0.065	1.50 (0.98; 2.29)	0.061
					Anti-IgE					
Overall										
Never	101	63.4; 16.8; 19.8	44.6; 25.7; 29.7	0.004	Ref.		Ref.		Ref.	
Ever	137	61.3; 22.6; 16.1	25.5; 32.1; 42.3	<0.001	1.74 (1.01; 3.00)	0.047	1.98 (1.09; 3.60)	0.024	2.00 (1.09; 3.64)	0.024
Not receiving LTOCS										
Never	59	49.2; 25.4; 25.4	28.6; 35.6; 35.6	0.073	Ref.		Ref.		Ref.	
Ever	99	59.6; 23.2; 17.2	26.3; 32.3; 41.4	<0.001	1.28 (0.66; 2.49)	0.469	1.56 (0.76; 3.19)	0.226	1.54 (0.75; 3.19)	0.241
Receiving LTOCS										
Never	42	83.3; 4.8; 11.9	66.7; 11.9; 21.4	0.029	Ref.		Ref.		Ref.	
Ever	38	65.8; 21.1; 13.2	23.7; 31.6; 44.7	0.003	2.97 (1.12; 7.87)	0.029	2.79 (0.90; 8.66)	0.076	2.95 (0.91; 9.52)	0.071
					Anti-IL5/5R					
Overall										
Never	417	75.5; 14.9; 9.6	46.3; 21.1; 32.6	<0.001	Ref.		Ref.		Ref.	
Ever	277	69.3; 22.0; 8.7	28.9; 32.1; 39.0	<0.001	1.32 (0.96; 1.81)	0.085	1.29 (0.93; 1.79)	0.128	1.30 (0.93; 1.81)	0.118
Not receiving LTOCS										
Never	168	68.5; 19.6; 11.9	38.1; 24.4; 37.5	<0.001	Ref.		Ref.		Ref.	
Ever	153	67.3; 23.5; 9.2	22.9; 35.9; 41.2	<0.001	1.17 (0.74; 1.83)	0.501	1.21 (0.76; 1.92)	0.428	1.23 (0.77; 1.96)	0.392
Receiving LTOCS										
Never	249	80.3; 11.6; 8.0	51.8; 18.9; 29.3	<0.001	Ref.		Ref.		Ref.	
Ever	124	71.8; 20.2; 8.1	36.3; 27.4; 36.3	<0.001	1.37 (0.87; 2.17)	0.173	1.29 (0.80; 2.07)	0.291	1.28 (0.80; 2.06)	0.305

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 25 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic status by comorbidity and LTOCS status: Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Comparison of odds of being well controlled between patients with and without comorbidity**, by LTOCS status: Crude Odds ratio (95% CI)	p	Adjusting for baseline value Odds ratio (95% CI)	p	Adjusting for baseline value, age, and gender Odds ratio (95% CI)	p
Chronic rhinosinusitis					**All biologics**					
Overall										
Never	666	68.3; 18.5; 13.2	39.5; 23.7; 36.8	<0.001	Ref.		Ref.		Ref.	
Ever	349	66.2; 23.2; 10.6	28.4; 30.1; 41.5	<0.001	1.22 (0.94; 1.59)	0.139	1.25 (0.95; 1.64)	0.115	1.24 (0.94; 1.63)	0.130
Not receiving LTOCS										
Never	329	59.0; 24.0; 17.0	28.9; 27.1; 44.1	<0.001	Ref.		Ref.		Ref.	
Ever	198	63.1; 24.7; 12.1	24.2; 33.3; 42.4	<0.001	0.93 (0.65; 1.33)	0.712	1.00 (0.69; 1.45)	0.992	0.98 (0.68; 1.42)	0.920
Receiving LTOCS										
Never	337	77.4; 13.1; 9.5	49.9; 20.5; 29.7	<0.001	Ref.		Ref.		Ref.	
Ever	151	70.2; 21.2; 8.6	33.8; 25.8; 40.4	<0.001	1.61 (1.08; 2.40)	0.020	1.55 (1.02; 2.35)	0.041	1.55 (1.02; 2.35)	0.041
					Anti-IgE					
Overall										
Never	170	58.8; 18.8; 22.4	33.5; 27.6; 38.8	<0.001	Ref.		Ref.		Ref.	
Ever	67	68.7; 23.9; 7.5	31.3; 34.3; 34.3	<0.001	0.82 (0.46; 1.49)	0.520	1.08 (0.57; 2.04)	0.807	1.04 (0.54; 2.00)	0.898
Not receiving LTOCS										
Never	111	49.5; 25.2; 25.2	25.2; 32.4; 42.3	<0.001	Ref.		Ref.		Ref.	
Ever	45	68.9; 22.2; 8.9	28.9; 35.6; 35.6	0.001	0.75 (0.37; 1.54)	0.434	1.01 (0.47; 2.17)	0.979	0.94 (0.43; 2.04)	0.867
Receiving LTOCS										
Never	59	76.3; 6.8; 16.9	49.2; 18.6; 32.2	0.001	Ref.		Ref.		Ref.	
Ever	22	68.2; 27.3; 4.5	36.4; 31.8; 31.8	0.098	0.98 (0.34; 2.81)	0.974	0.88 (0.25; 3.04)	0.838	1.05 (0.29; 3.75)	0.944
					Anti-IL5/5R					
Overall										
Never	478	72.0; 18.6; 9.4	42.1; 22.8; 35.1	<0.001	Ref.		Ref.		Ref.	
Ever	268	67.5; 22.4; 10.1	28.4; 29.5; 42.2	<0.001	1.34 (0.99; 1.83)	0.058	1.31 (0.96; 1.80)	0.091	1.31 (0.96; 1.80)	0.093
Not receiving LTOCS										
Never	202	64.4; 24.3; 11.4	31.7; 25.2; 43.1	<0.001	Ref.		Ref.		Ref.	
Ever	142	64.8; 24.6; 10.6	24.6; 33.1; 42.3	<0.001	0.97 (0.63; 1.49)	0.880	0.97 (0.62; 1.53)	0.912	0.97 (0.62; 1.52)	0.885
Receiving LTOCS										
Never	276	77.5; 14.5; 8.0	49.6; 21.0; 29.3	<0.001	Ref.		Ref.		Ref.	
Ever	126	70.6; 19.8; 9.5	32.5; 25.4; 42.1	<0.001	1.75 (1.13; 2.71)	0.013	1.68 (1.07; 2.63)	0.025	1.71 (1.09; 2.68)	0.021

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 25 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic status by comorbidity and LTOCS status: Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Comparison of odds of being well controlled between patients with and without comorbidity**, by LTOCS status: Crude Odds ratio (95% CI)	p	Adjusting for baseline value Odds ratio (95% CI)	p	Adjusting for baseline value, age, and gender Odds ratio (95% CI)	p
Nasal polyposis	**All biologics**									
Overall										
Never	629	70.3; 18.6; 11.1	39.6; 27.2; 33.2	<0.001	Ref.		Ref.		Ref.	
Ever	414	65.2; 21.3; 13.5	29.5; 24.9; 45.7	<0.001	1.69 (1.31; 2.18)	<0.001	1.65 (1.27; 2.15)	<0.001	1.64 (1.26; 2.14)	<0.001
Not receiving LTOCS										
Never	318	61.9, 24.5, 13.5	31.4, 31.8, 36.8	<0.001	Ref.		Ref.		Ref.	
Ever	225	60.9, 22.2, 16.9	21.3, 27.1, 51.6	<0.001	1.83 (1.26; 2.57)	0.001	1.84 (1.28; 2.64)	0.001	1.80 (1.26; 2.59)	0.001
Receiving LTOCS										
Never	311	78.8, 12.5, 8.7	47.9, 22.5, 29.6	<0.001	Ref.		Ref.		Ref.	
Ever	189	70.4, 20.1, 9.5	39.2, 22.2, 38.6	<0.001	1.50 (1.02; 2.19)	0.038	1.40 (0.94; 2.08)	0.099	1.40 (0.94; 2.08)	0.098
	Anti-IgE									
Overall										
Never	174	64.9; 17.8; 17.2	32.8; 33.9; 33.3	<0.001	Ref.		Ref.		Ref.	
Ever	67	55.2; 23.9; 20.9	32.8; 20.9; 46.3	0.005	1.72 (0.97; 3.06)	0.064	1.64 (0.89; 3.03)	0.116	1.45 (0.77; 2.74)	0.246
Not receiving LTOCS										
Never	116	56.9, 23.3, 19.8	25.9, 38.8, 35.3	<0.001	Ref.		Ref.		Ref.	
Ever	44	54.5, 22.7, 22.7	27.3, 22.7, 50.0	0.026	1.83 (0.91; 3.69)	0.092	1.86 (0.89; 3.92)	0.100	1.73 (0.80; 3.78)	0.165
Receiving LTOCS										
Never	58	81.0, 6.9, 12.1	46.6, 24.1, 29.3	<0.001	Ref.		Ref.		Ref.	
Ever	23	56.5, 26.1, 17.4	43.5, 17.4, 39.1	0.158	1.55 (0.56; 4.26)	0.395	0.96 (0.29; 3.17)	0.947	0.87 (0.25; 3.08)	0.832
	Anti-IL5/5R									
Overall										
Never	438	72.8; 18.7; 8.4	42.9; 25.3; 31.7	<0.001	Ref.		Ref.		Ref.	
Ever	331	68.6; 20.8; 10.6	29.3; 25.7; 45.0	<0.001	1.76 (1.31; 2.37)	<0.001	1.73 (1.28; 2.35)	<0.001	1.74 (1.28; 2.37)	<0.001
Not receiving LTOCS										
Never	188	66.0, 25.0, 9.0	36.7, 29.3, 34.0	<0.001	Ref.		Ref.		Ref.	
Ever	168	64.9, 22.6, 12.5	20.2, 28.0, 51.8	<0.001	2.08 (1.36; 3.19)	0.001	2.11 (1.35; 3.28)	0.001	2.09 (1.34; 3.26)	0.001
Receiving LTOCS										
Never	250	78.0, 14.0, 8.0	47.6, 22.4, 30.0	<0.001	Ref.		Ref.		Ref.	
Ever	163	72.4, 19.0, 8.6	38.7, 23.3, 38.0	<0.001	1.43 (0.94; 2.17)	0.091	1.38 (0.90; 2.11)	0.142	1.40 (0.91; 2.16)	0.125

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 25 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic status by comorbidity and LTOCS status: Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Comparison of odds of being well controlled between patients with and without comorbidity**, by LTOCS status: Crude Odds ratio (95% CI)	p	Adjusting for baseline value Odds ratio (95% CI)	p	Adjusting for baseline value, age, and gender Odds ratio (95% CI)	p
Eczema/atopic dermatitis					**All biologics**					
Overall										
Never	923	67.8; 19.7; 12.5	35.2; 25.4; 39.4	<0.001	Ref.		Ref.		Ref.	
Ever	118	71.2; 19.5; 9.3	39.0; 33.1; 28.0	<0.001	0.60 (0.39; 0.91)	0.017	0.61 (0.39; 0.94)	0.026	0.61 (0.40; 0.95)	0.029
Not receiving LTOCS										
Never	459	59.5; 24.4; 16.1	26.4; 28.1; 45.5	<0.001	Ref.		Ref.		Ref.	
Ever	82	73.2; 18.3; 8.5	32.9; 39.0; 28.0	<0.001	0.47 (0.28; 0.78)	0.004	0.52 (0.31; 0.88)	0.016	0.53 (0.31; 0.90)	0.019
Receiving LTOCS										
Never	464	76.1; 15.1; 8.8	44.0; 22.6; 33.4	<0.001	Ref.		Ref.		Ref.	
Ever	36	66.7; 22.2; 11.1	52.8; 19.4; 27.8	0.261	0.77 (0.36; 1.63)	0.767	0.66 (0.30; 1.45)	0.304	0.66 (0.30; 1.45)	0.303
					Anti-IgE					
Overall										
Never	206	60.2; 19.9; 19.9	31.6; 29.1; 39.3	<0.001	Ref.		Ref.		Ref.	
Ever	35	74.3; 17.1; 8.6	40.0; 37.1; 22.9	0.032	0.46 (0.20; 1.06)	0.067	0.55 (0.23; 1.33)	0.185	0.58 (0.24; 1.42)	0.235
Not receiving LTOCS										
Never	133	52.6; 24.1; 23.3	24.8; 32.3; 42.9	<0.001	Ref.		Ref.		Ref.	
Ever	27	74.1; 18.5; 7.4	33.3; 44.4; 22.2	0.040	0.38 (0.14; 1.00)	0.051	0.49 (0.18; 1.33)	0.159	0.51 (0.18; 1.42)	0.196
Receiving LTOCS										
Never	73	74.0; 12.3; 13.7	43.8; 23.3; 32.9	<0.001	Ref.		Ref.		Ref.	
Ever	8	75.0; 12.5; 12.5	62.5; 12.5; 25.0	NA	0.68 (0.13; 3.63)	0.652	0.64 (0.10; 4.13)	0.640	0.77 (0.11; 5.51)	0.798
					Anti-IL5/5R					
Overall										
Never	693	70.9; 1938; 9.4	36.7; 24.8; 38.5	<0.001	Ref.		Ref.		Ref.	
Ever	74	71.6; 18.9; 9.5	41.9; 31.1; 27.0	0.002	0.59 (0.35; 1.01)	0.054	0.57 (0.33; 1.00)	0.050	0.57 (0.33; 1.00)	0.049
Not receiving LTOCS										
Never	306	63.7; 25.2; 11.1	27.8; 27.5; 44.8	<0.001	Ref.		Ref.		Ref.	
Ever	48	77.1; 14.6; 8.3	37.5; 35.4; 27.1	0.001	0.46 (0.23; 0.90)	0.023	0.49 (0.25; 0.99)	0.046	0.49 (0.25; 0.99)	0.047
Receiving LTOCS										
Never	387	76.5; 15.5; 8.0	43.7; 22.7; 33.6	<0.001	Ref.		Ref.		Ref.	
Ever	26	61.5; 26.9; 11.5	50.0; 23.1; 26.9	0.550	0.73 (0.30; 1.78)	0.486	0.60 (0.24; 1.52)	0.284	0.61 (0.24; 1.54)	0.298

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 26. Association between potentially T2-related comorbidities and pre- to post-biologic improvement in asthma control: within groups before/after paired comparisons, and odds ratios and 95% confidence intervals of being well or partly controlled post-biologic initiation comparing patients with and without comorbidity.

Patient characteristics		Comparison of pre- and post-biologic status by comorbidity and LTOCS status			Comparison of odds of being well or partly controlled between patients with and without comorbidity**, by LTOCS status					
					Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
	N	Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Any T2-related comorbidity					**All biologics**					
Overall										
Never	308	73.1; 16.9; 10.1	47.4; 21.8; 30.8	<0.001	Ref.		Ref.		Ref.	
Ever	740	65.8; 21.1; 13.1	30.8; 28.0; 41.2	<0.001	2.02 (1.54; 2.66)	<0.001	1.96 (1.47; 2.61)	<0.001	1.96 (1.47; 2.62)	<0.001
Not receiving LTOCS										
Never	139	60.4; 24.5; 15.1	37.4; 25.2; 37.4	<0.001	Ref.		Ref.		Ref.	
Ever	407	61.4; 23.3; 15.2	23.8; 31.2; 45.0	<0.001	1.91 (1.26; 2.88)	0.002	2.08 (1.34; 3.23)	0.001	2.10 (1.35; 3.28)	0.001
Receiving LTOCS										
Never	169	83.4; 10.7; 5.9	55.6; 18.9; 25.4	<0.001	Ref.		Ref.		Ref.	
Ever	333	71.2; 18.3; 10.5	39.3; 24.0; 36.6	<0.001	1.93 (1.33; 2.81)	0.001	1.71 (1.16; 2.54)	0.007	1.73 (1.17; 2.58)	0.006
					Anti-IgE					
Overall										
Never	72	65.3; 15.3; 19.4	48.6; 20.8; 30.6	0.020	Ref.		Ref.		Ref.	
Ever	170	60.6; 21.8; 17.6	26.5; 34.1; 39.4	<0.001	2.63 (1.48; 4.67)	0.001	2.96 (1.58; 5.54)	0.001	2.81 (1.49; 5.30)	0.001
Not receiving LTOCS										
Never	44	50.0; 22.7; 27.3	34.1; 27.3; 38.6	0.187	Ref.		Ref.		Ref.	
Ever	117	58.1; 23.9; 17.9	23.9; 36.8; 39.3	<0.001	1.64 (0.77; 3.49)	0.196	2.02 (0.90; 4.50)	0.087	2.12 (0.93; 4.81)	0.073
Receiving LTOCS										
Never	28	89.3; 3.6; 7.1	71.4; 10.7; 17.9	0.112	Ref.		Ref.		Ref.	
Ever	53	66.0; 17.0; 17.0	32.1; 28.3; 39.6	0.001	5.29 (1.94; 14.4)	0.001	4.49 (1.47; 13.8)	0.008	5.91 (1.59; 21.97)	0.008
					Anti-IL5/5R					
Overall										
Never	234	76.1; 17.1; 6.8	47.4; 22.2; 30.3	<0.001	Ref.		Ref.		Ref.	
Ever	539	68.3; 21.0; 10.8	32.7; 26.7; 40.6	<0.001	1.86 (1.36; 2.55)	<0.001	1.75 (1.26; 2.43)	0.001	1.78 (1.28; 2.48)	0.001
Not receiving LTOCS										
Never	93	66.7; 24.7; 8.6	39.8; 24.7; 35.5	<0.001	Ref.		Ref.		Ref.	
Ever	265	64.5; 23.4; 12.1	24.9; 29.8; 45.3	<0.001	1.99 (1.21; 3.28)	0.007	2.08 (1.22; 3.56)	0.007	2.06 (1.20; 3.54)	0.009
Receiving LTOCS										
Never	141	82.3; 12.1; 5.7	52.5; 20.6; 27.0	<0.001	Ref.		Ref.		Ref.	
Ever	274	71.9; 18.6; 9.5	40.1; 23.7; 36.1	<0.001	1.65 (1.09; 2.48)	0.017	1.49 (0.97; 2.28)	0.066	1.55 (1.01; 2.38)	0.046

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 26 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic status by comorbidity and LTOCS status: Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Comparison of odds of being well controlled between patients with and without comorbidity**, by LTOCS status: Crude Odds ratio (95% CI)	p	Adjusting for baseline value Odds ratio (95% CI)	p	Adjusting for baseline value, age, and gender Odds ratio (95% CI)	p
Allergic rhinitis					**All biologics**					
Overall										
Never	524	72.7; 15.3; 12.0	45.8; 21.9; 32.3	<0.001	Ref.		Ref.		Ref.	
Ever	441	65.8; 22.2; 12.0	27.2; 31.1; 41.7	<0.001	2.26 (1.72; 2.96)	<0.001	2.26 (1.70; 3.01)	<0.001	2.31 (1.74; 3.09)	<0.001
Not receiving LTOCS										
Never	231	62.3; 21.2; 16.5	35.1; 27.3; 37.7	<0.001	Ref.		Ref.		Ref.	
Ever	275	62.9; 23.3; 13.8	23.3; 33.1; 43.6	<0.001	1.78 (1.21; 2.63)	0.004	1.93 (1.28; 2.91)	0.002	1.97 (1.30; 2.98)	0.001
Receiving LTOCS										
Never	293	80.9; 10.6; 8.5	54.3; 17.7; 28.0	<0.001	Ref.		Ref.		Ref.	
Ever	166	70.5; 20.5; 9.0	33.7; 27.7; 38.6	<0.001	2.33 (1.57; 3.46)	<0.001	2.24 (1.48; 3.39)	<0.001	2.33 (1.53; 3.54)	<0.001
					Anti-IgE					
Overall										
Never	101	63.4; 16.8; 19.8	44.6; 25.7; 29.7	0.004	Ref.		Ref.		Ref.	
Ever	137	61.3; 22.6; 16.1	25.5; 32.1; 42.3	<0.001	2.34 (1.35; 4.05)	0.002	2.68 (1.48; 4.84)	0.001	2.65 (1.46; 4.80)	0.001
Not receiving LTOCS										
Never	59	49.2; 25.4; 25.4	28.6; 35.6; 35.6	0.073	Ref.		Ref.		Ref.	
Ever	99	59.6; 23.2; 17.2	26.3; 32.3; 41.4	<0.001	1.14 (0.55; 2.33)	0.728	1.34 (0.63; 2.86)	0.445	1.37 (0.64; 2.95)	0.415
Receiving LTOCS										
Never	42	83.3; 4.8; 11.9	66.7; 11.9; 21.4	0.029	Ref.		Ref.		Ref.	
Ever	38	65.8; 21.1; 13.2	23.7; 31.6; 44.7	0.003	6.44 (2.41; 17.3)	<0.001	7.16 (2.40; 21.4)	<0.001	8.13 (2.41; 27.4)	0.001
					Anti-IL5/5R					
Overall										
Never	417	75.5; 14.9; 9.6	46.3; 21.1; 32.6	<0.001	Ref.		Ref.		Ref.	
Ever	277	69.3; 22.0; 8.7	28.9; 32.1; 39.0	<0.001	2.12 (1.53; 2.93)	<0.001	2.11 (1.51; 2.97)	<0.001	2.16 (1.53; 3.04)	<0.001
Not receiving LTOCS										
Never	168	68.5; 19.6; 11.9	38.1; 24.4; 37.5	<0.001	Ref.		Ref.		Ref.	
Ever	153	67.3; 23.5; 9.2	22.9; 35.9; 41.2	<0.001	2.07 (1.27; 3.38)	0.003	2.24 (1.33; 3.76)	0.002	2.29 (1.35; 3.86)	0.002
Receiving LTOCS										
Never	249	80.3; 11.6; 8.0	51.8; 18.9; 29.3	<0.001	Ref.		Ref.		Ref.	
Ever	124	71.8; 20.2; 8.1	36.3; 27.4; 36.3	<0.001	1.89 (1.21; 2.94)	0.005	1.82 (1.15; 2.88)	0.010	1.85 (1.16; 2.95)	0.009

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 26 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic status by comorbidity and LTOCS status: Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Comparison of odds of being well controlled between patients with and without comorbidity**, by LTOCS status: Crude Odds ratio (95% CI)	p	Adjusting for baseline value Odds ratio (95% CI)	p	Adjusting for baseline value, age, and gender Odds ratio (95% CI)	p
Chronic rhinosinusitis					**All biologics**					
Overall										
Never	666	68.3; 18.5; 13.2	39.5; 23.7; 36.8	<0.001	Ref.		Ref.		Ref.	
Ever	349	66.2; 23.2; 10.6	28.4; 30.1; 41.5	<0.001	1.65 (1.25; 2.18)	<0.001	1.72 (1.28; 2.31)	<0.001	1.69 (1.26; 2.28)	<0.001
Not receiving LTOCS										
Never	329	59.0; 24.0; 17.0	28.9; 27.1; 44.1	<0.001	Ref.		Ref.		Ref.	
Ever	198	63.1; 24.7; 12.1	24.2; 33.3; 42.4	<0.001	1.27 (0.85; 1.90)	0.247	1.41 (0.92; 2.15)	0.113	1.36 (0.88; 2.08)	0.162
Receiving LTOCS										
Never	337	77.4; 13.1; 9.5	49.9; 20.5; 29.7	<0.001	Ref.		Ref.		Ref.	
Ever	151	70.2; 21.2; 8.6	33.8; 25.8; 40.4	<0.001	1.95 (1.31; 2.90)	0.001	1.93 (1.27; 2.93)	0.002	1.91 (1.25; 2.90)	0.003
					Anti-IgE					
Overall										
Never	170	58.8; 18.8; 22.4	33.5; 27.6; 38.8	<0.001	Ref.		Ref.		Ref.	
Ever	67	68.7; 23.9; 7.5	31.3; 34.3; 34.3	<0.001	1.10 (0.60; 2.03)	0.747	1.45 (0.77; 2.75)	0.254	1.42 (0.74; 2.73)	0.286
Not receiving LTOCS										
Never	111	49.5; 25.2; 25.2	25.2; 32.4; 42.3	<0.001	Ref.		Ref.		Ref.	
Ever	45	68.9; 22.2; 8.9	28.9; 35.6; 35.6	0.001	0.83 (0.38; 1.80)	0.638	1.12 (0.50; 2.50)	0.785	1.01 (0.44; 2.31)	0.976
Receiving LTOCS										
Never	59	76.3; 6.8; 16.9	49.2; 18.6; 32.2	0.001	Ref.		Ref.		Ref.	
Ever	22	68.2; 27.3; 4.5	36.4; 31.8; 31.8	0.098	1.69 (0.62; 0.63)	0.306	1.85 (0.61; 5.59)	0.273	2.08 (0.63; 6.87)	0.230
					Anti-IL5/5R					
Overall										
Never	478	72.0; 18.6; 9.4	42.1; 22.8; 35.1	<0.001	Ref.		Ref.		Ref.	
Ever	268	67.5; 22.4; 10.1	28.4; 29.5; 42.2	<0.001	1.83 (1.33; 2.53)	<0.001	1.83 (1.31; 2.57)	<0.001	1.82 (1.30; 2.56)	0.001
Not receiving LTOCS										
Never	202	64.4; 24.3; 11.4	31.7; 25.2; 43.1	<0.001	Ref.		Ref.		Ref.	
Ever	142	64.8; 24.6; 10.6	24.6; 33.1; 42.3	<0.001	1.42 (0.87; 2.30)	0.157	1.49 (0.89; 2.48)	0.125	1.46 (0.88; 2.44)	0.146
Receiving LTOCS										
Never	276	77.5; 14.5; 8.0	49.6; 21.0; 29.3	<0.001	Ref.		Ref.		Ref.	
Ever	126	70.6; 19.8; 9.5	32.5; 25.4; 42.1	<0.001	2.04 (1.31; 3.18)	0.001	1.99 (1.26; 3.14)	0.003	2.00 (1.26; 3.17)	0.003

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 26 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic status by comorbidity and LTOCS status: Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Comparison of odds of being well controlled between patients with and without comorbidity**, by LTOCS status: Crude Odds ratio (95% CI)	p	Adjusting for baseline value Odds ratio (95% CI)	p	Adjusting for baseline value, age, and gender Odds ratio (95% CI)	p
Nasal polyposis					**All biologics**					
Overall										
Never	629	70.3; 18.6; 11.1	39.6; 27.2; 33.2	<0.001	Ref.		Ref.		Ref.	
Ever	414	65.2; 21.3; 13.5	29.5; 24.9; 45.7	<0.001	1.57 (1.20; 2.04)	0.001	1.52 (1.15; 2.01)	0.003	1.51 (1.14; 2.00)	0.004
Not receiving LTOCS										
Never	318	61.9, 24.5, 13.5	31.4, 31.8, 36.8	<0.001	Ref.		Ref.		Ref.	
Ever	225	60.9, 22.2, 16.9	21.3, 27.1, 51.6	<0.001	1.69 (1.14; 2.52)	0.009	1.73 (1.14; 2.63)	0.010	1.71 (1.12; 2.60)	0.013
Receiving LTOCS										
Never	311	78.8, 12.5, 8.7	47.9, 22.5, 29.6	<0.001	Ref.		Ref.		Ref.	
Ever	189	70.4, 20.1, 9.5	39.2, 22.2, 38.6	<0.001	1.43 (0.99; 2.06)	0.057	1.33 (0.90; 1.96)	0.151	1.35 (0.91; 1.99)	0.131
					Anti-IgE					
Overall										
Never	174	64.9; 17.8; 17.2	32.8; 33.9; 33.3	<0.001	Ref.		Ref.		Ref.	
Ever	67	55.2; 23.9; 20.9	32.8; 20.9; 46.3	0.005	1.00 (0.55; 1.82)	0.991	0.85 (0.45; 1.63)	0.634	0.72 (0.37; 1.42)	0.344
Not receiving LTOCS										
Never	116	56.9, 23.3, 19.8	25.9, 38.8, 35.3	<0.001	Ref.		Ref.		Ref.	
Ever	44	54.5, 22.7, 22.7	27.3, 22.7, 50.0	0.026	0.93 (0.42; 2.03)	0.930	0.88 (0.39; 2.00)	0.769	0.84 (0.35; 1.97)	0.686
Receiving LTOCS										
Never	58	81.0, 6.9, 12.1	46.6, 24.1, 29.3	<0.001	Ref.		Ref.		Ref.	
Ever	23	56.5, 26.1, 17.4	43.5, 17.4, 39.1	0.158	1.13 (0.43; 2.99)	0.802	0.64 (0.19; 2.14)	0.474	0.55 (0.15; 2.01)	0.363
					Anti-IL5/5R					
Overall										
Never	438	72.8; 18.7; 8.4	42.9; 25.3; 31.7	<0.001	Ref.		Ref.		Ref.	
Ever	331	68.6; 20.8; 10.6	29.3; 25.7; 45.0	<0.001	1.81 (1.34; 2.46)	<0.001	1.80 (1.31; 2.48)	<0.001	1.86 (1.35; 2.57)	<0.001
Not receiving LTOCS										
Never	188	66.0, 25.0, 9.0	36.7, 29.3, 34.0	<0.001	Ref.		Ref.		Ref.	
Ever	168	64.9, 22.6, 12.5	20.2, 28.0, 51.8	<0.001	2.28 (1.41; 3.69)	0.001	2.45 (1.48; 4.07)	0.001	2.51 (1.50; 4.19)	<0.001
Receiving LTOCS										
Never	250	78.0, 14.0, 8.0	47.6, 22.4, 30.0	<0.001	Ref.		Ref.		Ref.	
Ever	163	72.4, 19.0, 8.6	38.7, 23.3, 38.0	<0.001	1.44 (0.96; 2.15)	0.074	1.39 (0.92; 2.11)	0.122	1.46 (0.96; 2.23)	0.079

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 26 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic status by comorbidity and LTOCS status: Pre-biologics Uncontrolled, Partly controlled, Well controlled (%)	Post-biologics Uncontrolled, Partly controlled, Well controlled (%)	p*	Comparison of odds of being well controlled between patients with and without comorbidity**, by LTOCS status: Crude Odds ratio (95% CI)	p	Adjusting for baseline value Odds ratio (95% CI)	p	Adjusting for baseline value, age, and gender Odds ratio (95% CI)	p
Eczema/atopic dermatitis					**All biologics**					
Overall										
Never	923	67.8; 19.7; 12.5	35.2; 25.4; 39.4	<0.001	Ref.		Ref.		Ref.	
Ever	118	71.2; 19.5; 9.3	39.0; 33.1; 28.0	<0.001	0.85 (0.57; 1.26)	0.421	0.89 (0.59; 1.35)	0.582	0.90 (0.60; 1.37)	0.636
Not receiving LTOCS										
Never	459	59.5; 24.4; 16.1	26.4; 28.1; 45.5	<0.001	Ref.		Ref.		Ref.	
Ever	82	73.2; 18.3; 8.5	32.9; 39.0; 28.0	<0.001	0.89 (0.54; 1.47)	0.664	0.85 (0.51; 1.40)	0.517	0.93 (0.49; 1.75)	0.821
Receiving LTOCS										
Never	464	76.1; 15.1; 8.8	44.0; 22.6; 33.4	<0.001	Ref.		Ref.		Ref.	
Ever	36	66.7; 22.2; 11.1	52.8; 19.4; 27.8	0.261	0.73 (0.4, 1.21)	0.221	0.87 (0.51; 1.48)	0.613	0.89 (0.52; 1.51)	0.661
					Anti-IgE					
Overall										
Never	206	60.2; 19.9; 19.9	31.6; 29.1; 39.3	<0.001	Ref.		Ref.		Ref.	
Ever	35	74.3; 17.1; 8.6	40.0; 37.1; 22.9	0.032	0.69 (0.33; 1.44)	0.327	0.86 (0.40; 1.86)	0.698	0.94 (0.43; 2.06)	0.875
Not receiving LTOCS										
Never	133	52.6; 24.1; 23.3	24.8; 32.3; 42.9	<0.001	Ref.		Ref.		Ref.	
Ever	27	74.1; 18.5; 7.4	33.3; 44.4; 22.2	0.040	0.66 (0.27; 1.61)	0.361	0.86 (0.34; 2.15)	0.744	0.92 (0.36; 2.37)	0.865
Receiving LTOCS										
Never	73	74.0; 12.3; 13.7	43.8; 23.3; 32.9	<0.001	Ref.		Ref.		Ref.	
Ever	8	75.0; 12.5; 12.5	62.5; 12.5; 25.0	NA	0.47 (0.10; 2.11)	0.323	0.38 (0.06; 2.31)	0.293	0.49 (0.08; 3.6)	0.456
					Anti-IL5/5R					
Overall										
Never	693	70.9; 1938; 9.4	36.7; 24.8; 38.5	<0.001	Ref.		Ref.		Ref.	
Ever	74	71.6; 18.9; 9.5	41.9; 31.1; 27.0	0.002	0.80 (0.49; 1.31)	0.376	0.79 (0.47; 1.32)	0.373	0.78 (0.46; 1.30)	0.341
Not receiving LTOCS										
Never	306	63.7; 25.2; 11.1	27.8; 27.5; 44.8	<0.001	Ref.		Ref.		Ref.	
Ever	48	77.1; 14.6; 8.3	37.5; 35.4; 27.1	0.001	0.64 (0.34; 1.21)	0.170	0.75 (0.39; 1.47)	0.410	0.73 (0.37; 1.42)	0.353
Receiving LTOCS										
Never	387	76.5; 15.5; 8.0	43.7; 22.7; 33.6	<0.001	Ref.		Ref.		Ref.	
Ever	26	61.5; 26.9; 11.5	50.0; 23.1; 26.9	0.550	0.77 (0.35; 1.72)	0.530	0.61 (0.26; 1.44)	0.260	0.62 (0.26; 1.46)	0.269

*McNemar test (nominal symmetry test).
**Logistic regression models.

Table 27. Association between potentially T2-related comorbidities and change in long-term OCS daily dose in mg pre- to post-biologics in patients who used long-term OCS at biologic initiation: within groups before/after paired comparisons, and across group differences between changes.

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity status				Post-biologic differences (on a log10 scale) between patients with and without comorbidity**					
		Pre-biologics	Post-biologics	Change	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
		mean (SD)	mean (SD)	mean (SD)		Difference (95% CI)	p	Difference (95% CI)	p	Difference (95% CI)	p
All biologics											
Any T2-related comorbidity											
Never	223	13.1 (10.2)	11.2 (10.3)	-1.9 (7.5)	<0.001	Ref.		Ref.		Ref.	
Ever	310	12.4 (10.3)	10.6 (9.4)	-1.9 (6.9)	<0.001	-0.03 (-0.08; 0.03)	0.311	0.00 (-0.03; 0.04)	0.812	0.00 (-0.03; 0.04)	0.808
Allergic rhinitis											
Never	332	12.5 (10.2)	10.4 (9.9)	-2.2 (7.4)	<0.001	Ref.		Ref.		Ref.	
Ever	140	13.3 (10.9)	11.5 (9.8)	-1.8 (7.7)	0.003	0.03 (-0.03; 0.10)	0.265	0.04 (-0.01; 0.09)	0.112	0.04 (-0.01; 0.09)	0.112
Chronic rhinosinusitis											
Never	382	12.6 (10.0)	10.3 (9.3)	-2.3 (7.2)	<0.001	Ref.		Ref.		Ref.	
Ever	115	12.9 (11.6)	12.0 (11.2)	-0.9 (7.7)	0.154	0.04 (-0.02; 0.10)	0.227	0.05 (0.01; 0.10)	0.031	0.05 (0.00; 0.10)	0.031
Nasal polyposis											
Never	332	13.1 (10.7)	11.4 (10.4)	-1.7 (7.1)	<0.001	Ref.		Ref.		Ref.	
Ever	196	12.0 (9.3)	9.8 (8.3)	-2.2 (7.2)	<0.001	-0.06 (-0.12; -0.01)	0.024	-0.03 (-0.07; 0.01)	0.125	-0.03 (-0.07; 0.01)	0.132
Eczema/atopic dermatitis											
Never	485	12.8 (10.2)	10.9 (9.8)	-1.9 (7.0)	<0.001	Ref.		Ref.		Ref.	
Ever	42	10.5 (10.1)	8.8 (9.0)	-1.7 (8.9)	0.116	-0.09 (-0.19; 0.00)	0.061	-0.02 (-0.09; 0.05)	0.571	-0.02 (-0.10; 0.05)	0.511

*Paired Wilcoxon tests.

**ANCOVA models. Post-and pre-biologic daily doses were log-transformed after adding 1 unit to the raw values.

Table 27 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity status				Post-biologic differences (on a log10 scale) between patients with and without comorbidity**					
		Pre-biologics mean (SD)	Post-biologics mean (SD)	Change mean (SD)	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
						Difference (95% CI)	p	Difference (95% CI)	p	Difference (95% CI)	p
Anti-IgE											
Any T2-related comorbidity											
Never	40	16.7 (15.2)	14.7 (15.3)	-2.0 (5.9)	0.022	Ref.		Ref.		Ref.	
Ever	45	14.7 (12.8)	14.7 (12.2)	0.0 (6.2)	0.554	0.01 (-0.13; 0.15)	0.913	0.06 (-0.01; 0.12)	0.073	0.06 (-0.01; 0.12)	0.093
Allergic rhinitis											
Never	48	15.2 (14.8)	13.5 (14.8)	-1.7 (6.0)	0.032	Ref.		Ref.		Ref.	
Ever	28	15.9 (13.4)	15.9 (12.2)	0.0 (7.2)	1.000	0.10 (-0.06; 0.25)	0.213	0.07 (-0.00; 0.15)	0.054	0.07 (-0.00; 0.15)	0.055
Chronic rhinosinusitis											
Never	55	15.6 (14.6)	13.7 (13.7)	-1.9 (6.2)	0.016	Ref.		Ref.		Ref.	
Ever	19	15.2 (13.9)	16.6 (15.1)	1.3 (7.0)	1.000	0.06 (-0.11; 0.23)	0.518	0.07 (-0.02; 0.15)	0.132	0.07 (-0.02; 0.15)	0.133
Nasal polyposis											
Never	65	16.8 (14.8)	15.4 (14.6)	-1.4 (6.7)	0.025	Ref.		Ref.		Ref.	
Ever	19	11.4 (9.8)	12.0 (9.9)	+0.6 (3.6)	1.000	-0.07 (-0.23; 0.10)	0.429	0.05 (-0.02; 0.13)	0.178	0.06 (-0.03; 0.14)	0.177
Eczema/atopic dermatitis											
Never	74	15.9 (14.0)	15.0 (13.6)	-0.9 (6.5)	0.120	Ref.		Ref.		Ref.	
Ever	9	10.1 (11.5)	8.6 (11.9)	-1.5 (2.4)	0.181	-0.25 (-0.46; -0.03)	0.026	-0.09 (-0.20; 0.02)	0.112	-0.10 (-0.21; 0.01)	0.088

*Paired Wilcoxon tests.

**ANCOVA models. Post-and pre-biologic daily doses were log-transformed after adding 1 unit to the raw values.

Table 27 (cont'd).

Patient characteristics	N	Comparison of pre- and post-biologic values by comorbidity status				Post-biologic differences (on a log10 scale) between patients with and without comorbidity**					
		Pre-biologics mean (SD)	Post-biologics mean (SD)	Change mean (SD)	p*	Crude		Adjusting for baseline value		Adjusting for baseline value, age, and gender	
						Difference (95% CI)	p	Difference (95% CI)	p	Difference (95% CI)	p
Anti-IL5/5R											
Any T2-related comorbidity											
Never	181	12.2 (8.4)	10.0 (8.0)	-2.1 (7.2)	<0.001	Ref.		Ref.		Ref.	
Ever	258	12.0 (9.8)	9.8 (8.6)	-2.3 (7.0)	<0.001	-0.02 (-0.08; 0.03)	0.402	0.00 (-0.04; 0.05)	0.993	0.00 (-0.05; 0.05)	0.999
Allergic rhinitis											
Never	278	11.9 (9.0)	9.5 (8.2)	-2.4 (7.3)	<0.001	Ref.		Ref.		Ref.	
Ever	109	12.7 (10.3)	10.5 (8.9)	-2.3 (7.9)	0.002	0.02 (-0.04; 0.09)	0.476	0.03 (-0.03; 0.08)	0.290	0.03 (-0.02; 0.08)	0.280
Chronic rhinosinusitis											
Never	323	12.1 (8.8)	9.5 (7.8)	-2.6 (7.0)	<0.001	Ref.		Ref.		Ref.	
Ever	92	12.3 (11.2)	11.0 (10.2)	-1.4 (7.9)	0.098	0.03 (-0.04; 0.10)	0.391	0.05 (-0.01; 0.10)	0.084	0.05 (-0.01; 0.10)	0.086
Nasal polyposis											
Never	261	12.0 (9.1)	10.0 (8.4)	-2.0 (6.8)	<0.001	Ref.		Ref.		Ref.	
Ever	174	12.1 (9.3)	9.6 (8.2)	-2.5 (7.5)	<0.001	-0.4 (-0.10; 0.02)	0.179	-0.03 (-0.07; 0.02)	0.222	-0.03 (-0.07; 0.02)	0.222
Eczema/atopic dermatitis											
Never	406	12.2 (9.2)	10.0 (8.4)	-2.2 (6.8)	<0.001	Ref.		Ref.		Ref.	
Ever	29	11.1 (10.4)	9.1 (8.7)	-2.0 (10.6)	0.343	-0.05 (-0.16; 0.06)	0.376	-0.01 (-0.10; 0.08)	0.885	-0.01 (-0.10; 0.08)	0.829

*Paired Wilcoxon tests.

**ANCOVA models. Post-and pre-biologic daily doses were log-transformed after adding 1 unit to the raw values.

8.0 Summary and Discussion

This study used the large, multi-country cohort of severe asthma adult patients included in ISAR to investigate the impact of comorbidity in severe asthma. We investigated the prevalence and patterns of comorbidities, and assessed the association between T2-related comorbidities and asthma-related outcome status post-biologic initiation.

Overall, the prevalence of having at least one comorbidity was 92%. The estimates for having at least one potentially T2-related comorbidity, at least one potentially OCS-related comorbidity, and at least one comorbidity mimicking/exacerbating asthma were 69%, 67%, and 55%, respectively. The most frequent comorbidities were allergic rhinitis (49%), gastro-esophageal reflux disease (44%), obesity (42%), chronic rhinosinusitis (with or without nasal polyposis; 38%), hypertension (23%), sleep apnea (22%), and nasal polyposis (21%). The median count of comorbidities of any type was 3 (Q1-Q3: 1-5). More than half (55%) of the patients had at least 3 comorbidities of any type. By categories, the proportions of patients with at least 3 comorbidities were 12.5%, 23.2%, and 3.9% for potentially T2-related, potentially OCS-related, and mimicking/exacerbating asthma categories, respectively. Comorbidities co-occurred across categories, with 33% of patients having at least one comorbidity of each category. Only 2.8% of patients had comorbidities restricted to the mimicking/exacerbating asthma category, 11% of patients had comorbidities restricted to the potentially T2-related category, and 11% of patients had comorbidities restricted to the potentially OCS-related category.

The prevalence of comorbidities varied by age and gender. Patients with chronic rhinosinusitis, obesity, hypertension, sleep apnea, dyslipidemia, anxiety/depression, osteoporosis, diabetes, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, and bronchiectasis were older than patients without these comorbidities. In general, the prevalence of comorbidities was higher in women than in men, except for nasal polyposis and sleep apnea that were more frequent in men than in women. Smoking status was also associated with the prevalence of most studied comorbidities, with potentially T2-related comorbidities being more frequent in non-smokers and other comorbidities being more frequent in ever smokers (both past and present).

Adjusting for age, gender, and country, we found that older age at asthma onset was associated with increased odds of chronic rhinosinusitis and nasal polyposis, and decreased odds of allergic rhinitis and eczema/atopic dermatitis, whereas no significant associations

were found between age at asthma onset and non T2-related comorbidities. Blood biomarkers were associated with potentially T2-related comorbidities with higher blood eosinophil counts, higher IgE concentrations, and higher FeNO test results being associated with increased odds of potentially T2-related comorbidity. On the contrary, lower biomarker measures were associated with higher odds of several non T2-related comorbidities.

Asthma-related outcomes at enrolment were also associated with comorbidities. Notably, several comorbidities were associated with higher odds of receiving long-term OCS and higher exacerbation rates. Osteoporosis had the strongest association with receiving long-term OCS, and gastro-esophageal reflux disease and osteoporosis had the strongest associations with exacerbation rates. Patients with potentially T2-related comorbidities tended to have better lung function, whereas several non T2-related comorbidities were associated with poorer lung function, specifically hypertension, osteoporosis, diabetes, chronic obstructive pulmonary disease, bronchiectasis, and vocal cord dysfunction/laryngeal spasms. Finally, patients with chronic rhinosinusitis, obesity, hypertension, sleep apnea, anxiety/depression, osteoporosis, diabetes, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, and vocal cord dysfunction/laryngeal spasms had higher odds of having uncontrolled asthma at enrolment, whereas no comorbidity was significantly associated with better asthma control.

We further evaluated whether presence of potentially T2-related comorbidities had an impact on response to biologics. Conditioning on asthma-related outcomes at biologic initiation, a history of allergic rhinitis, chronic rhinosinusitis, or nasal polyposis was associated with a greater reduction in exacerbation rates. Allergic rhinitis and chronic rhinosinusitis were associated with larger improvement in lung function, as measured through FEV_1 percent predicted, in patients initiating anti-IL5/5R. Allergic rhinitis, chronic rhinosinusitis, and nasal polyposis were all associated with higher odds of being well or partly controlled post-biologic initiation. The association was restricted to patients initiating anti-IL5/5R for chronic rhinosinusitis and nasal polyposis. Chronic rhinosinusitis was the only comorbidity having a significant impact on the size of long-term OCS reduction, with larger reduction in patients without chronic rhinosinusitis than in patients with. Finally, eczema/atopic dermatitis did not seem to have an impact on response to biologics for exacerbation rates, lung function, or long-term OCS daily dose but seemed to negatively impact response in terms of asthma control.

In 2021, Cheng et al. (27) explored data from placebo-controlled and real-world studies and reported that the burden of comorbidities or the type of comorbidities present in patients initiating anti-IgE therapy did not affect the improvement in exacerbation rates and FEV_1. In

this report, T2 and non-T2 comorbidities were pulled together. Amongst T2-related comorbidities, only allergic rhinitis was analysed individually. In our study, we found that allergic rhinitis was associated with a greater improvement in FEV_1 percent predicted, but only in patients initiating anti-IL5/5R. The effectiveness of anti-IL5/5R in patients with severe asthma and chronic rhinosinusitis and/or nasal polyps was shown on nasal symptoms and asthma control (28) and enhanced efficacy was previously reported in patients with nasal polyposis compared to patients without (29-32). Our study strengthened this evidence using a large, multicentre international patient population, and extended it to some degree to patients with allergic rhinitis.

9.0 Limitations

Our study did come with several limitations pertaining to real-world studies. Missing data were common both for comorbidities and asthma-related clinical variables. Not all countries collected information all 30 comorbidities of interest, and for collected comorbidities a proportion of patients had missing information which varied by country and specific comorbidities. This was a source of potential under-reporting when assessing the prevalence of having at least one comorbidity and when counting comorbidities. However, sensitivity analyses excluding patients with fewer collected information led to estimates of similar magnitudes, probably due to the fact that most common comorbidities contributing most to comorbidity counts generally had fewer missing data. Despite potential under-reporting, our study showed that comorbidities were present in high frequency in severe asthma patients and that multi-comorbidity was common.

The heterogeneity by country was substantial, highlighting potential bias due to the way data was collected: through case report form or electronic medical records, through specific fields allowing missing information or not, or free-text-fields. However, no clear pattern by data source was observed, with the exception of the UK where estimates were generally very low for comorbidities extracted from free-text fields. Variation by countries could also be due to whether the data was reported by allergists or pulmonologists.

Clinical variables were also not available for all patients, some of the missing data being due to lack of spirometry data during the COVID-19 pandemic. However, the sample sizes used for our analysis were generally large and allowed the detection of significant associations between the presence of comorbidities and several clinical characteristics.

Finally, the presence of comorbidities was assessed using all available visits to maximise data availability. While this is unlikely to have an impact for T2-related comorbidities which tend to be lifelong conditions, it is possible that it diluted the association between non T2-related comorbidities and demographic/clinical characteristics at enrolment since they may have occurred after enrolment. However, the median timeframe of visits was only one year and this has potentially only slightly diluted the associations.

10.0 Conclusion

In the real world, comorbidities are highly frequent in adults with severe asthma and multi-comorbidity is common. The presence of comorbidity is generally associated with poorer asthma-related outcomes. However, patients with allergic rhinitis, chronic rhinosinusitis and nasal polyposis tend to experience an enhanced response to biologics in terms of exacerbation rates (all three comorbidities), lung function (allergic rhinitis and chronic rhinosinusitis), and asthma control (all three comorbidities). The impact of these comorbidities on biologic response is globally more apparent in patients initiating anti-IL5/5R than in patients initiating anti-IgE. Overall, the PRISM study highlights the importance of systemic evaluation for comorbidities and a multidisciplinary approach to their management in patients with severe asthma.

11.0 Advisory Group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC). Other members of the committee, as listed in the following table, have formed the Advisory Group.

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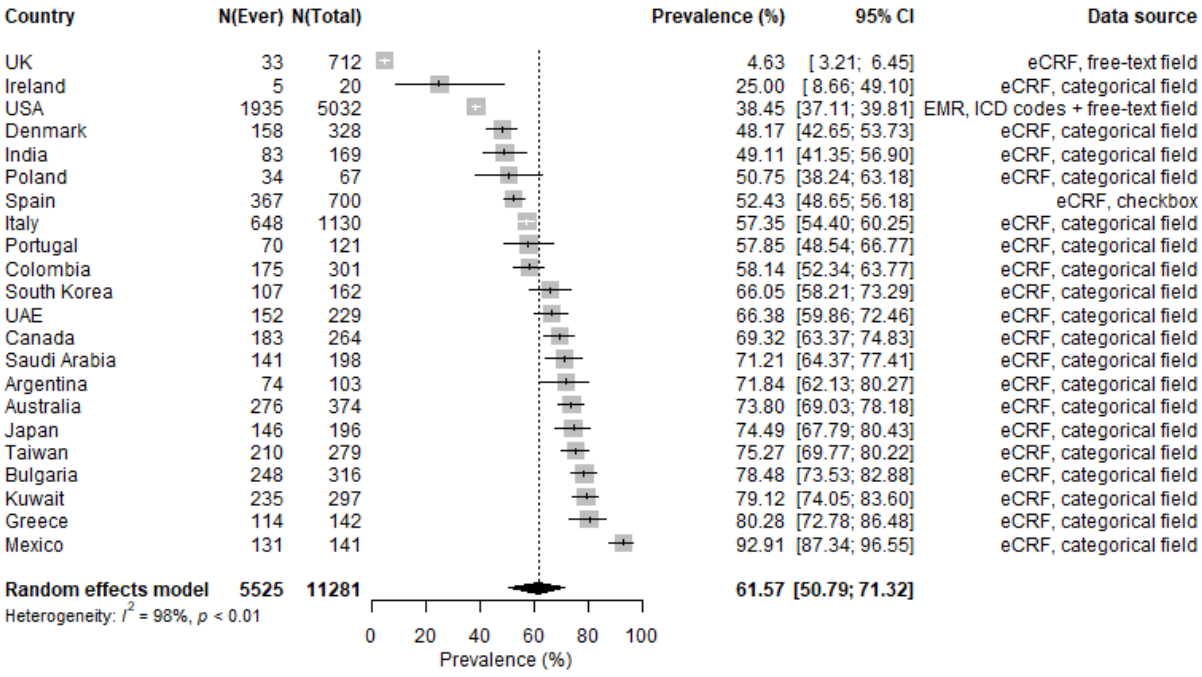
32 Nolasco S, Crimi C, Pelaia C, Benfante A, Caiaffa MF, Calabrese C, et al. Benralizumab Effectiveness in Severe Eosinophilic Asthma with and without Chronic Rhinosinusitis with Nasal Polyps: A Real-World Multicenter Study. J Allergy Clin Immunol Pract 2021;9(12):4371–80.

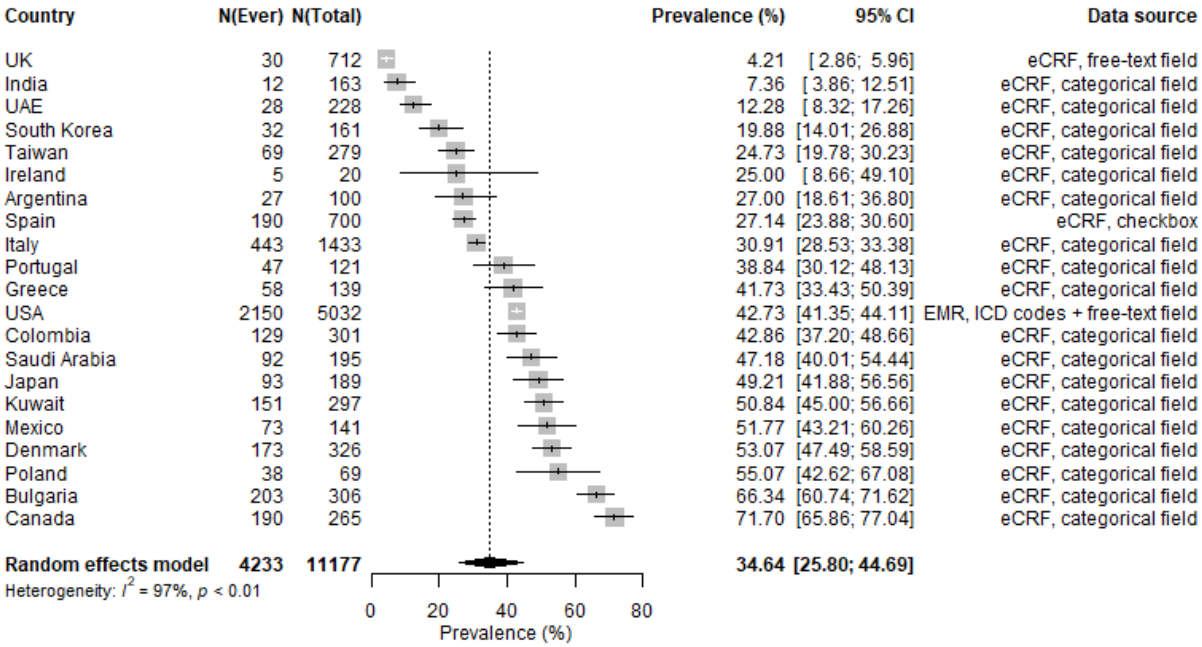
14.0 Appendices

14.1 Appendix 1: Country-specific prevalence estimates for 30 comorbid conditions and random effects model pooled estimates.

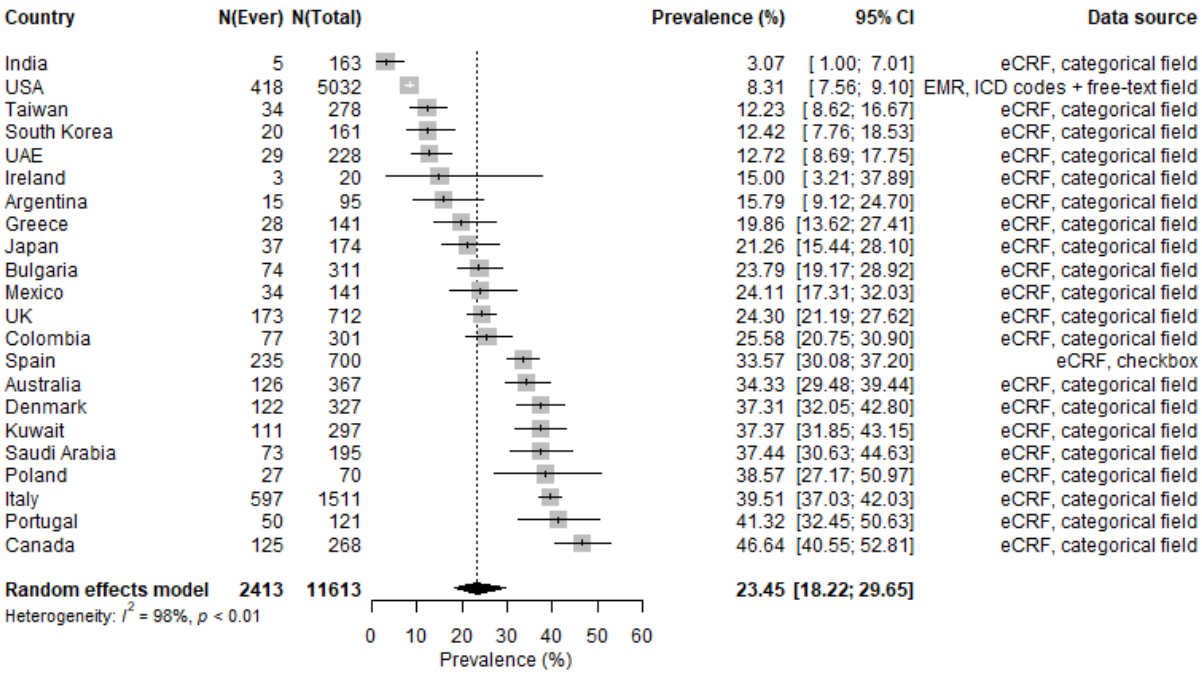
1) Allergic rhinitis



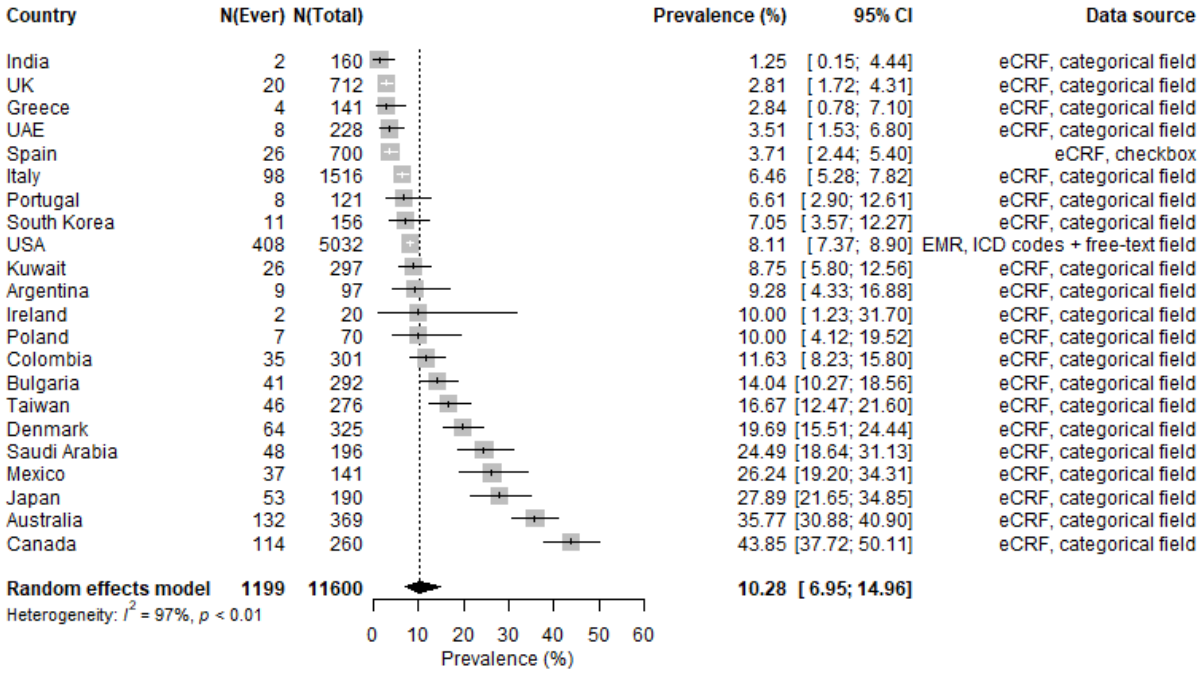
2) Chronic rhinosinusitis



3) Nasal polyposis



4) Eczema/atopic dermatitis



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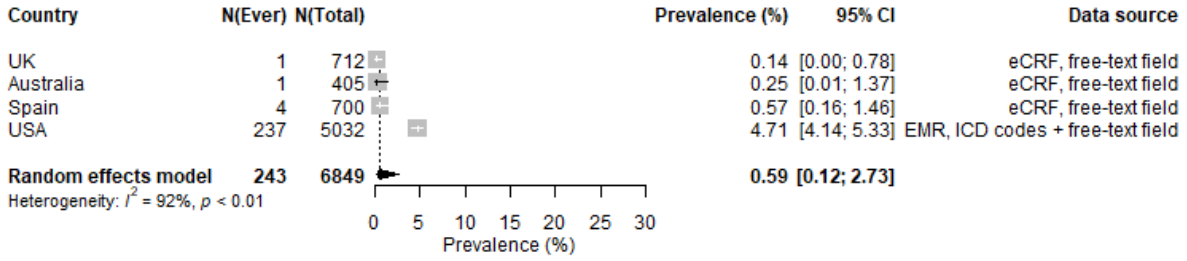
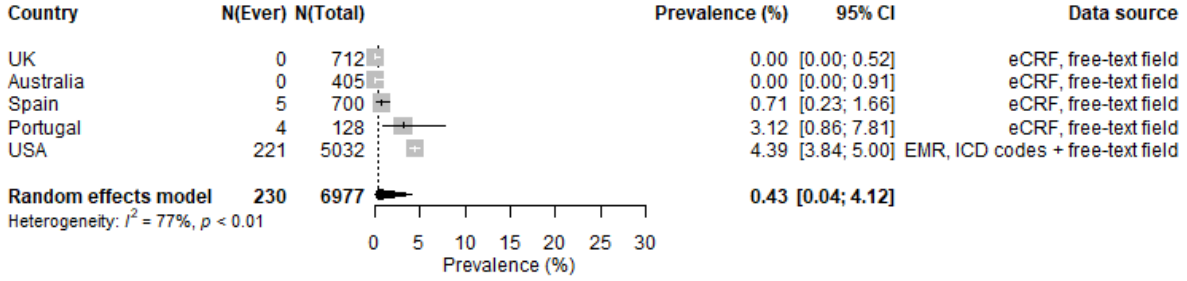
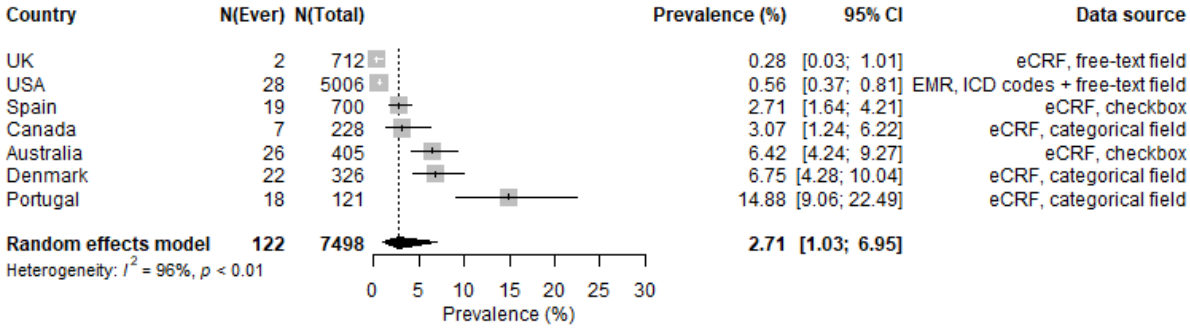


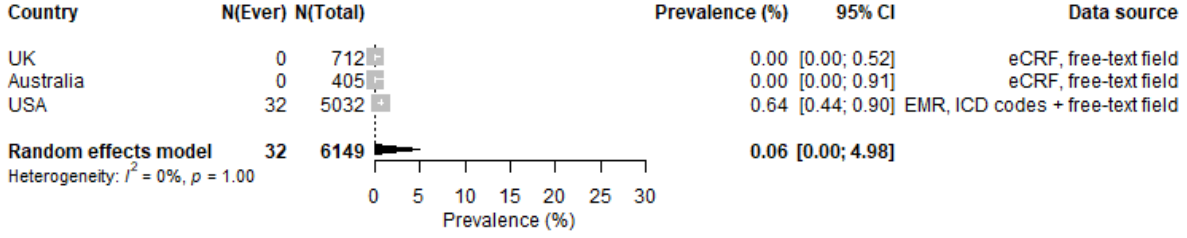
6) Food allergy



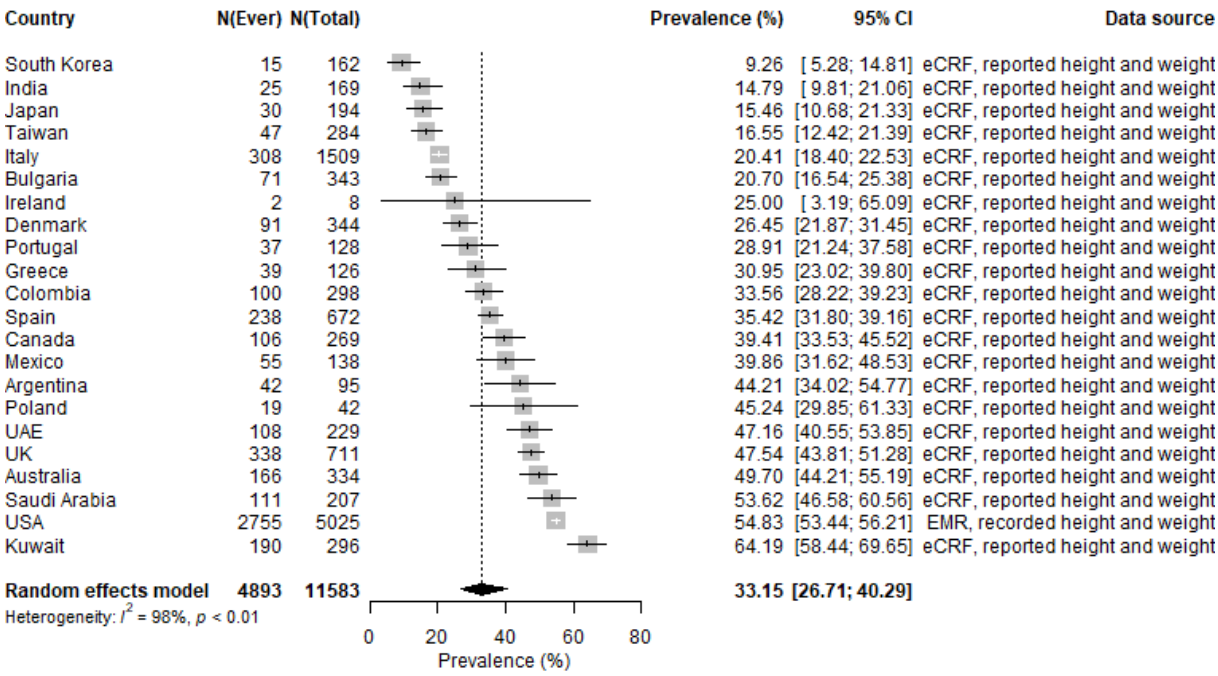
7) Aspirin sensitivity



8) Eosinophilic esophagitis



9) Obesity



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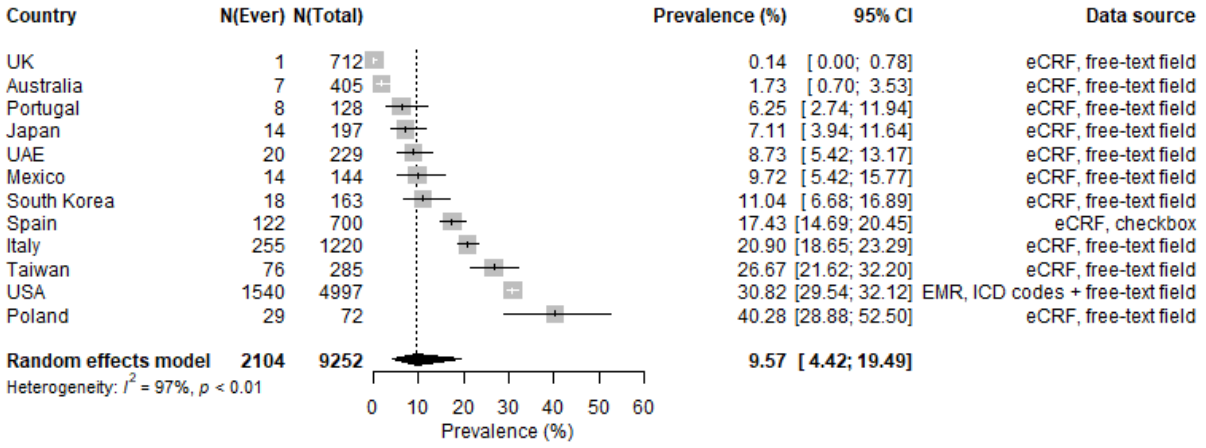
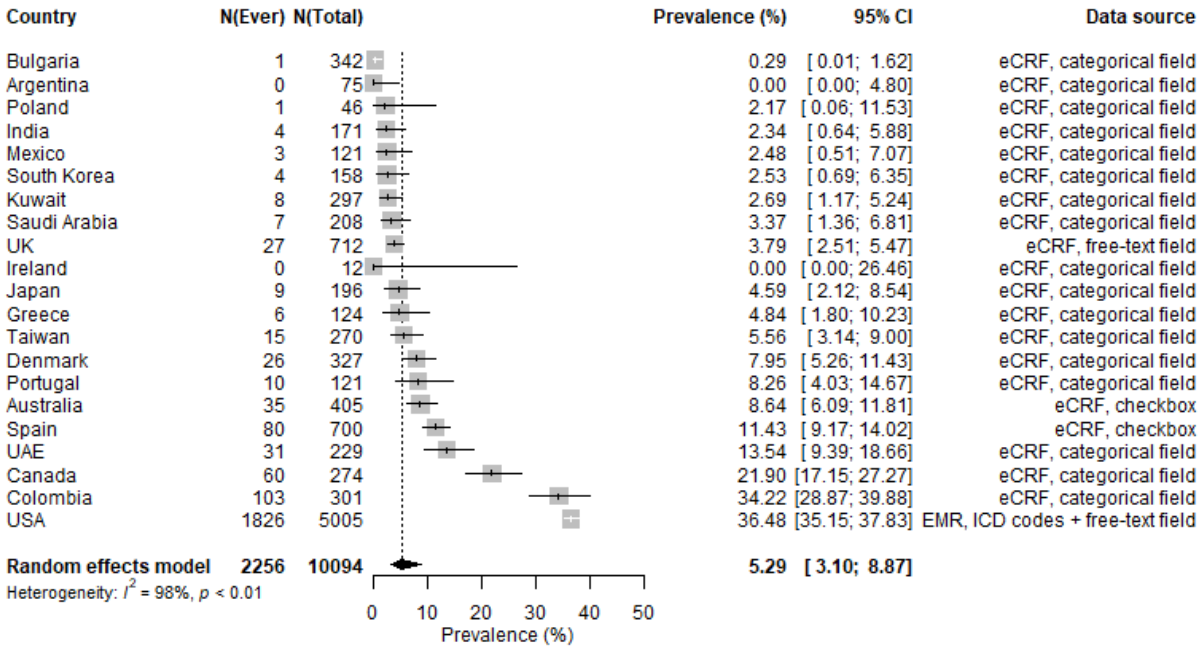
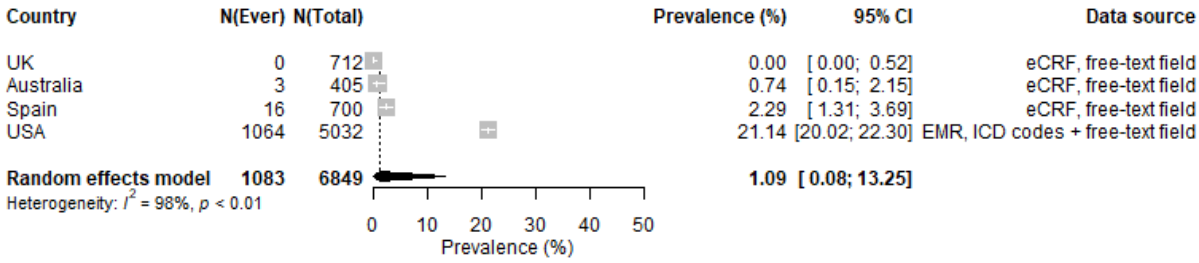


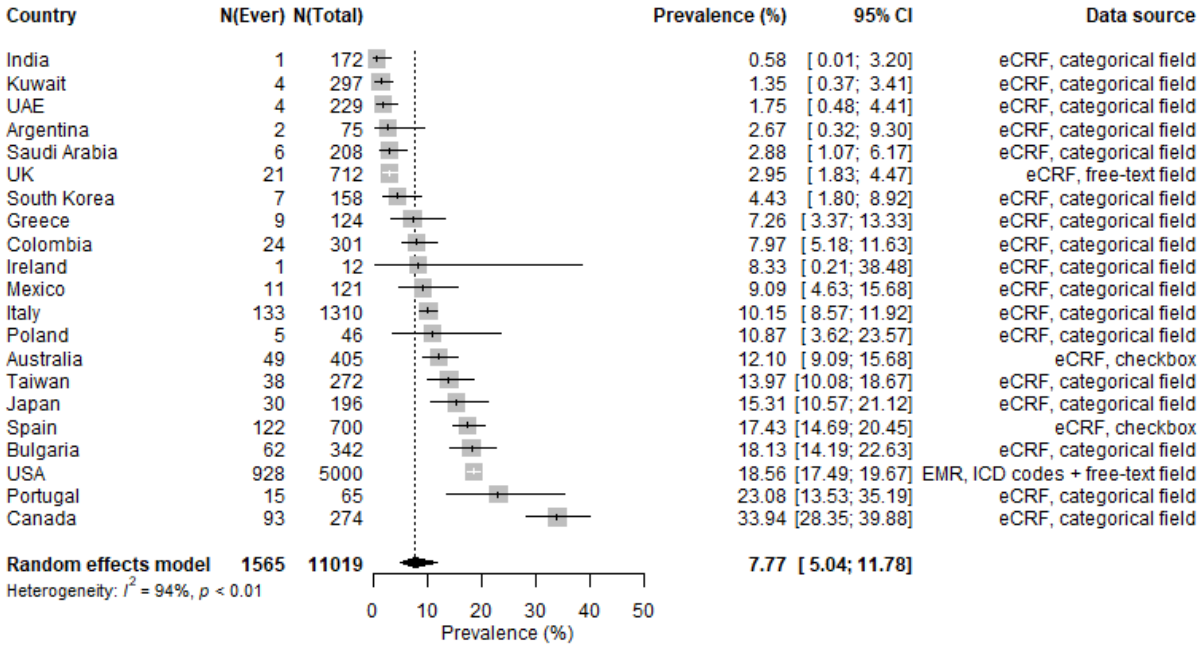
11) Sleep apnea



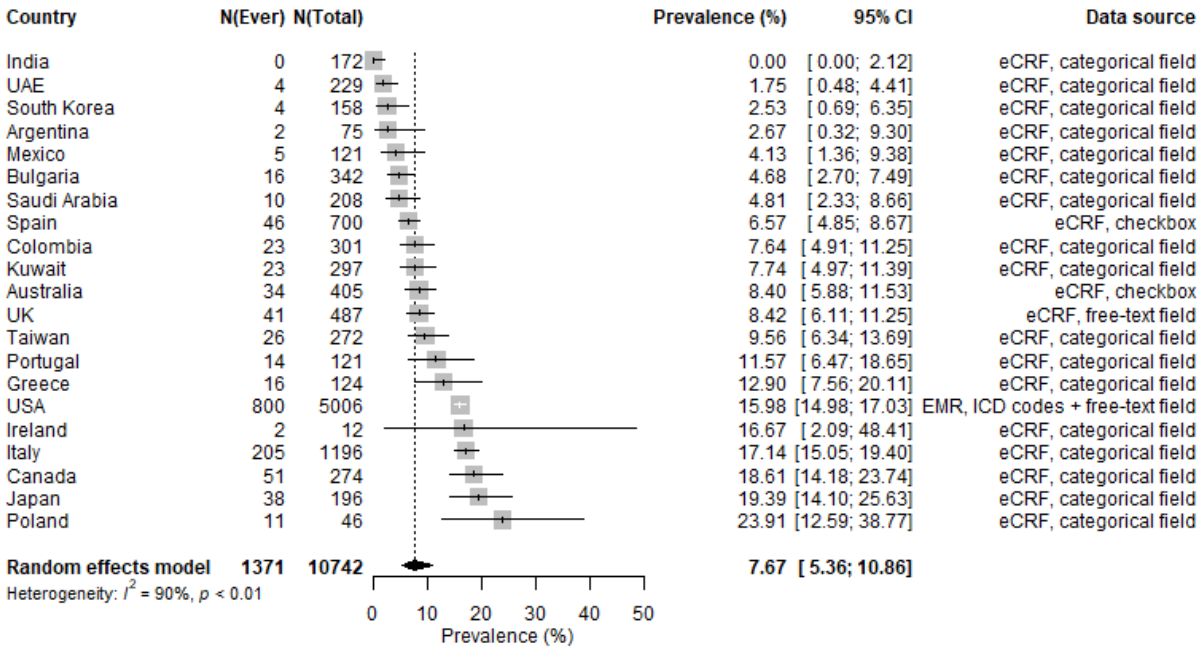
12) Dyslipidemia



13) Anxiety/depression



14) Osteoporosis



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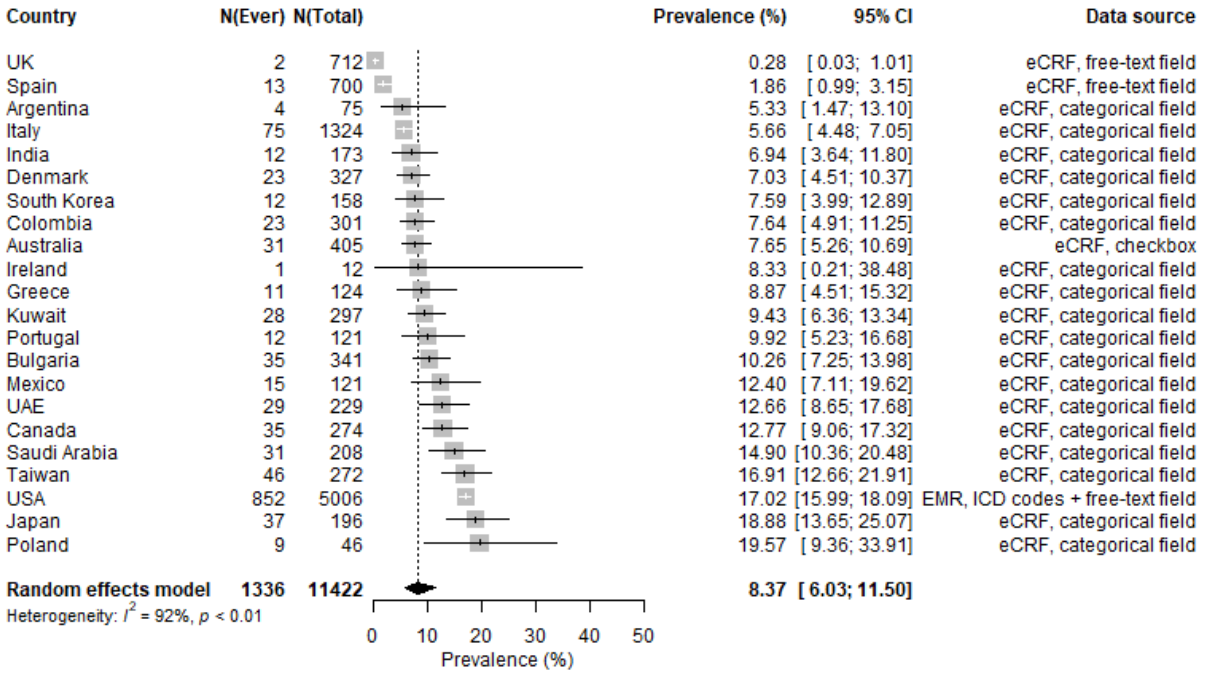
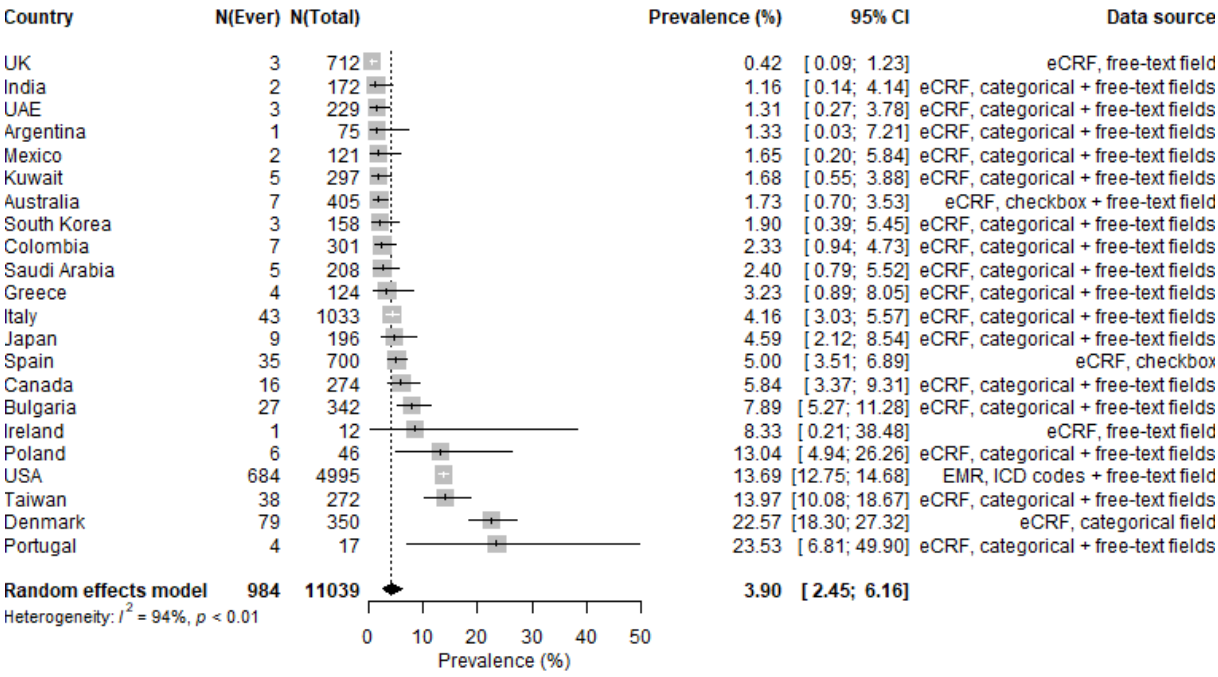
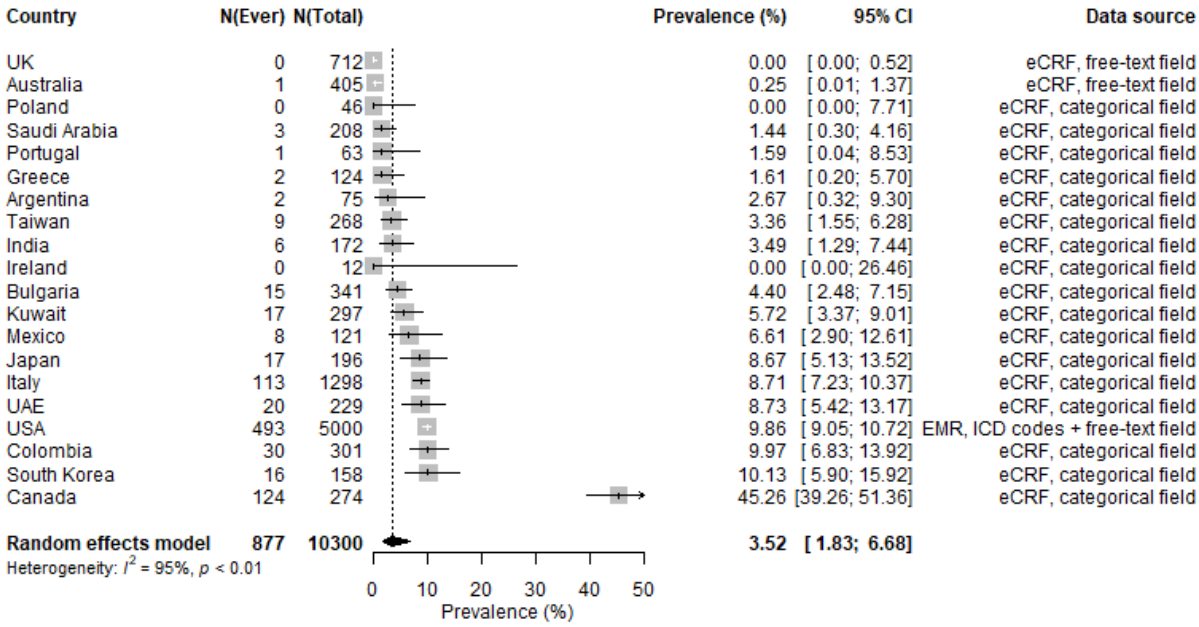


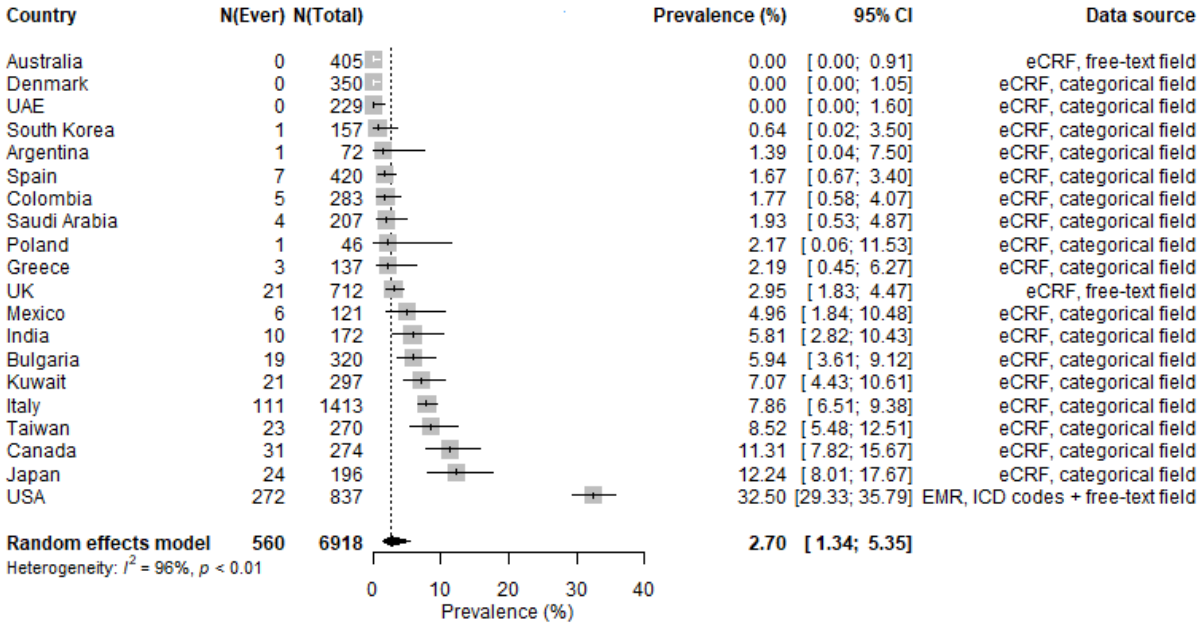
16) Coronary heart disease



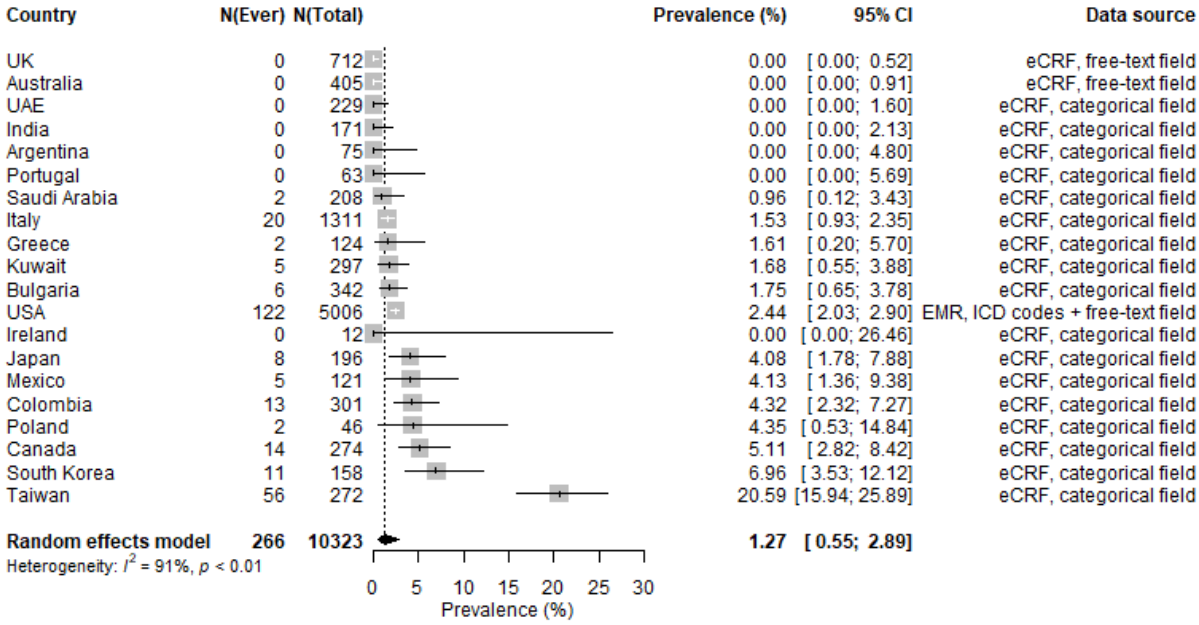
17) Pneumonia



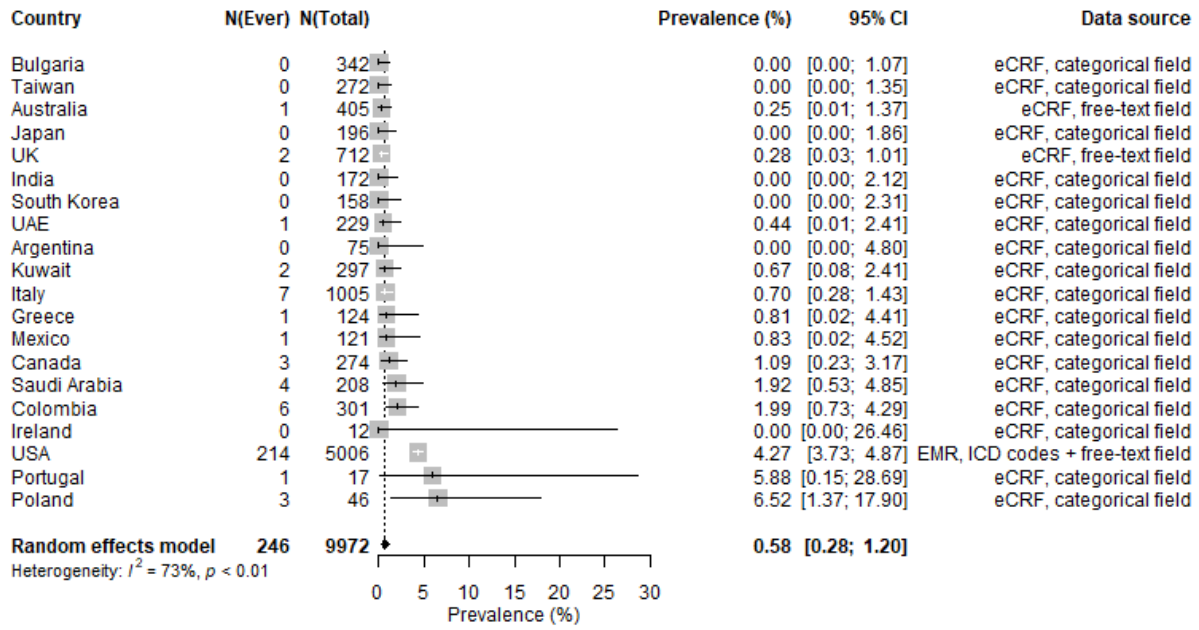
18) Other significant infections



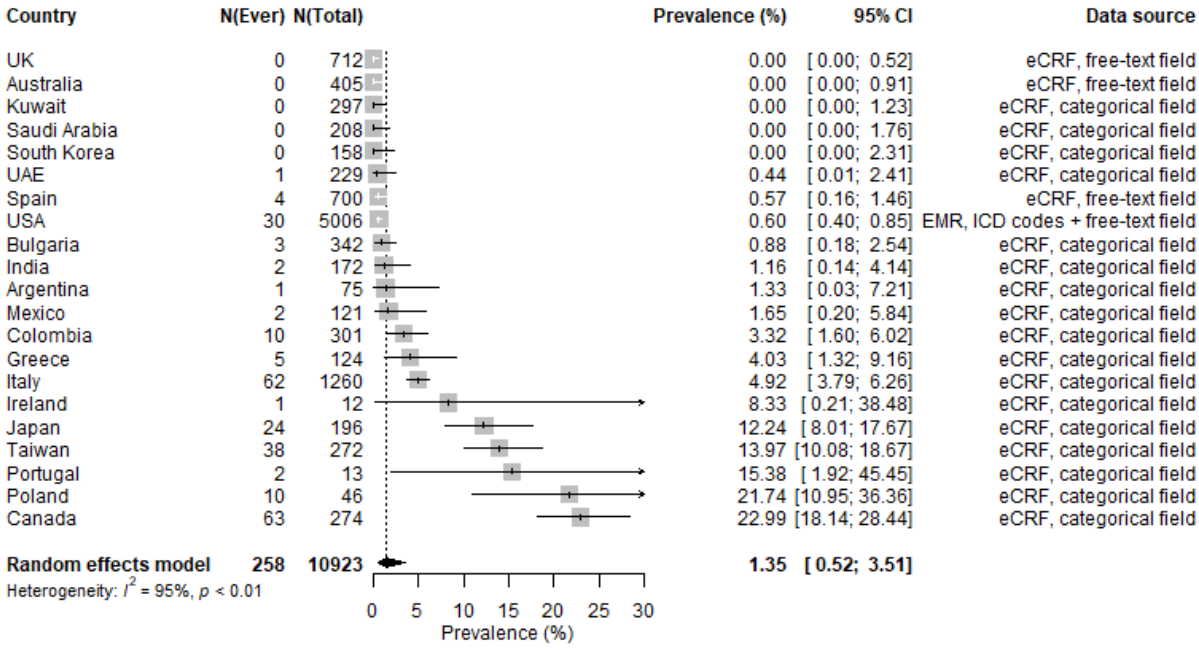
19) Peptic ulcer



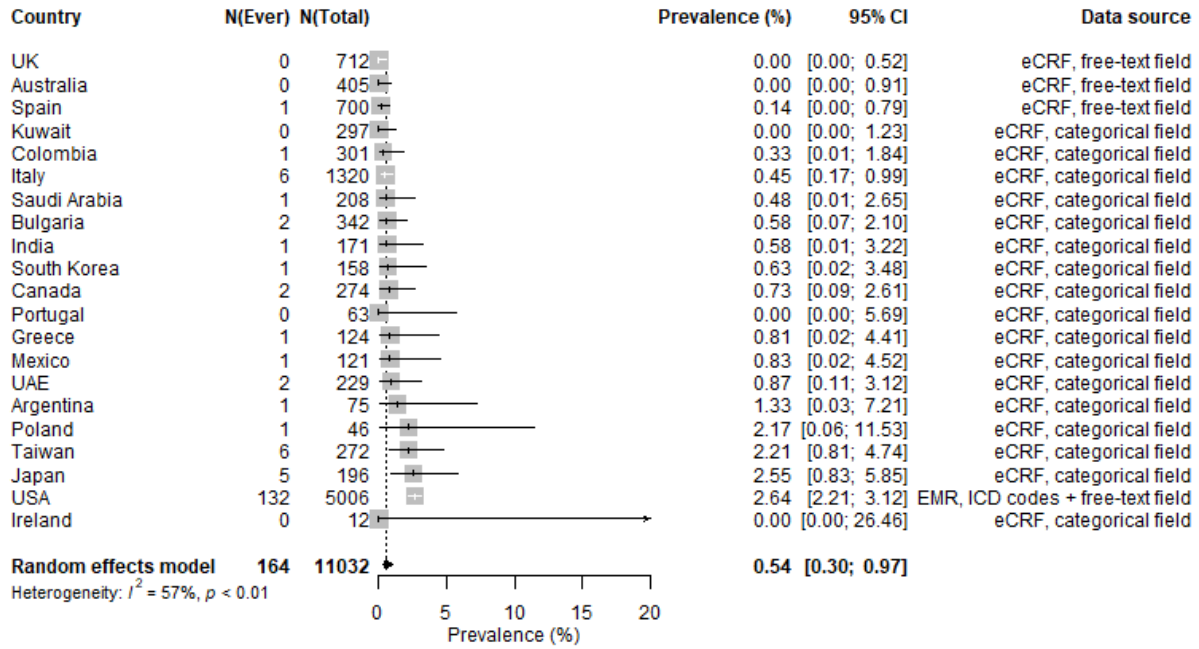
20) Pulmonary embolism/venous thromboembolism



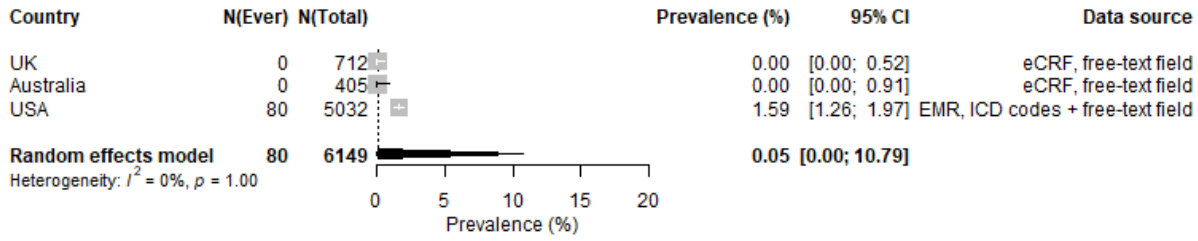
21) Cataract



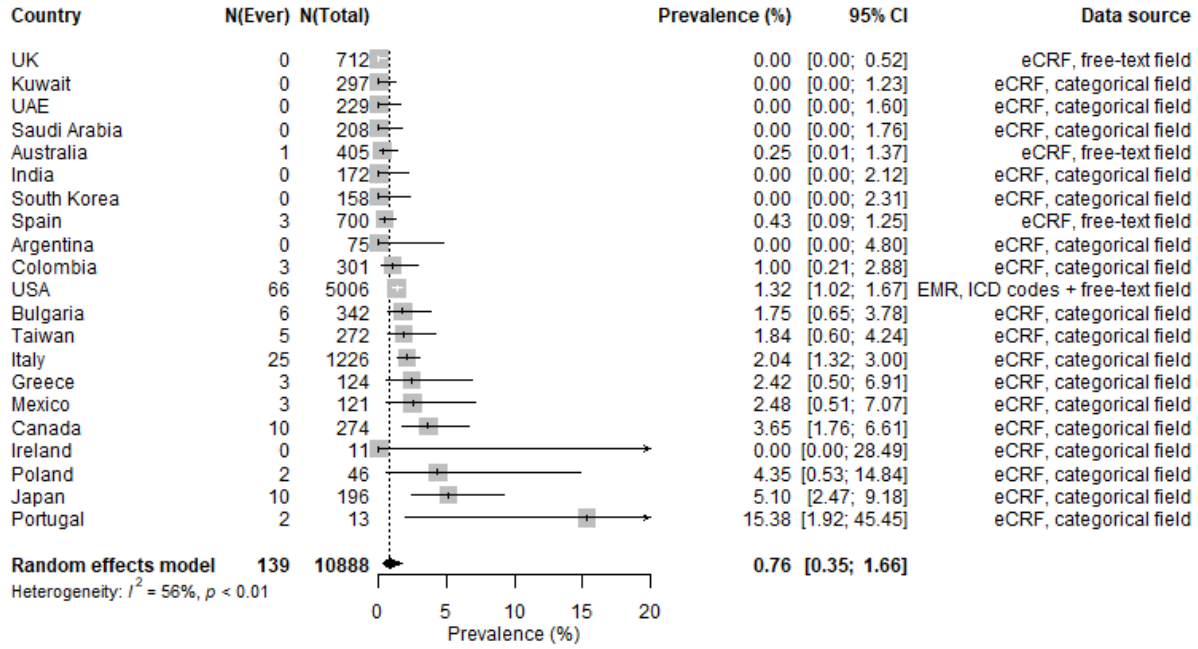
22) Chronic kidney disease



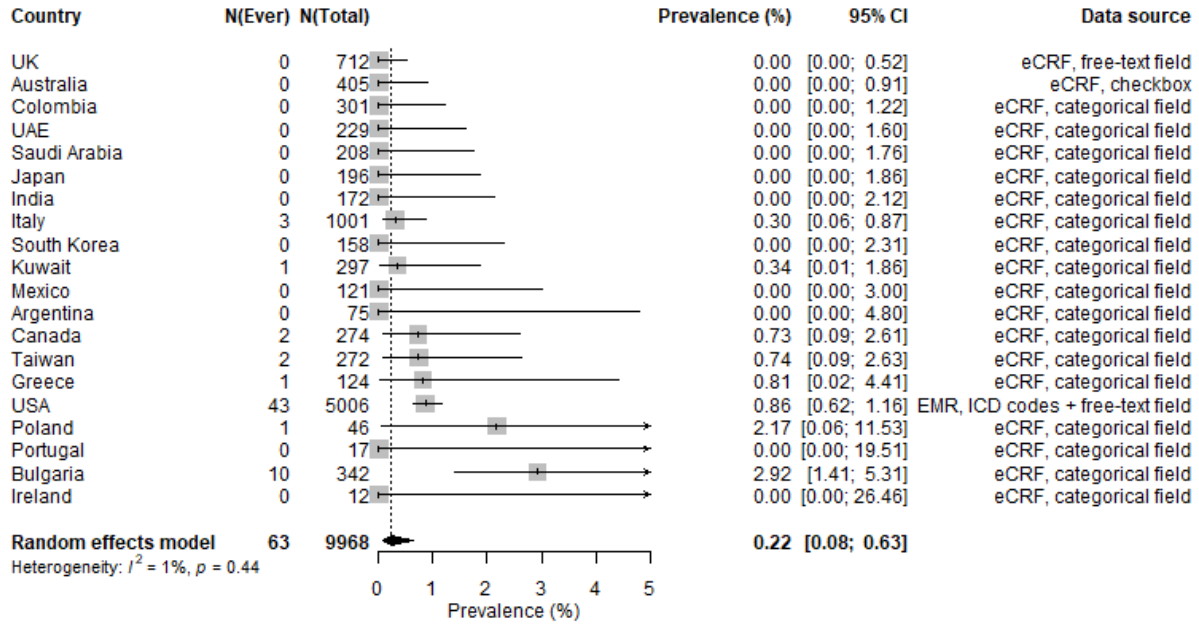
23) Adrenal insufficiency



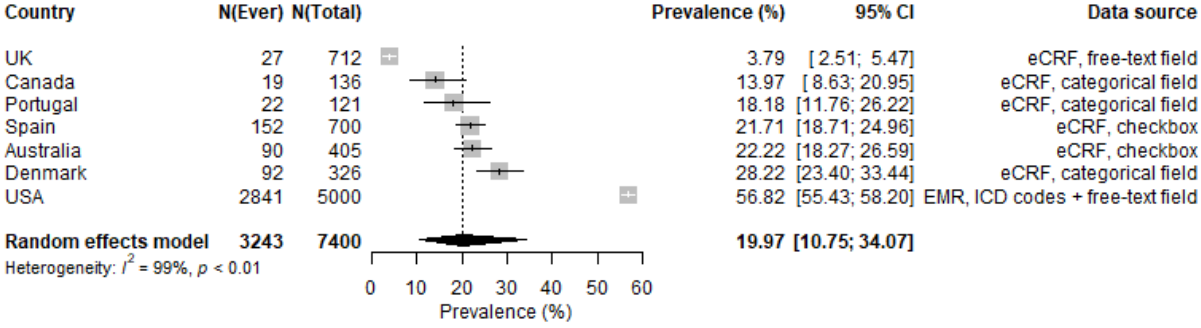
24) Glaucoma



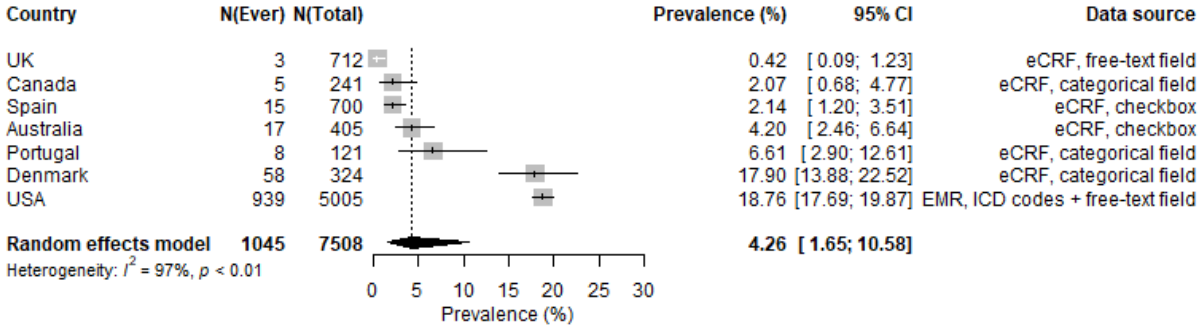
25) Cerebrovascular accident



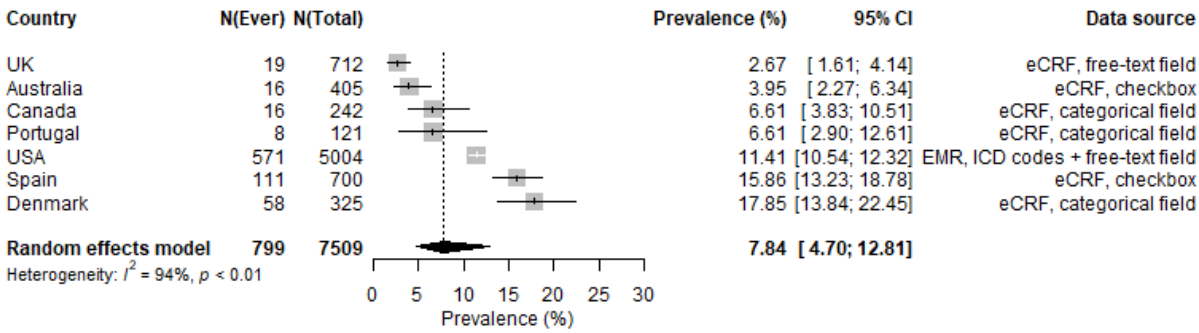
26) Gastro-esophageal reflux disease



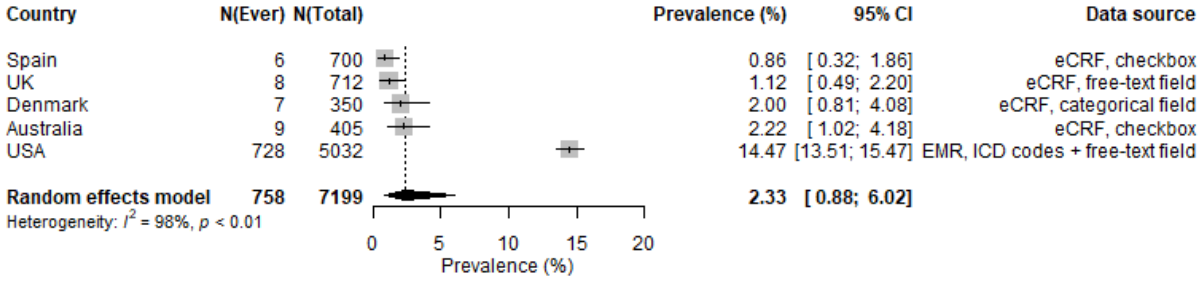
27) Chronic obstructive pulmonary disease



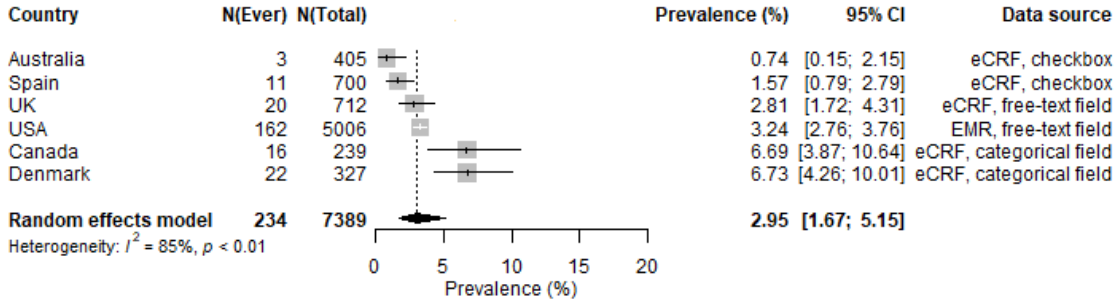
28) Bronchiectasis



29) Vocal cord dysfunction/laryngeal spasms

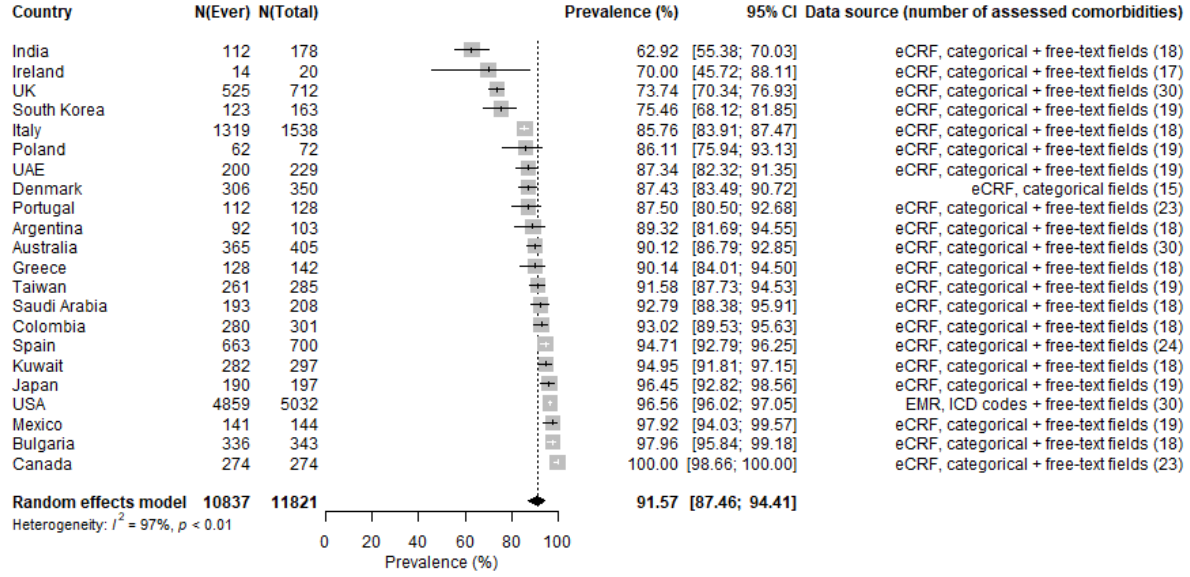


30) Dysfunctional breathing

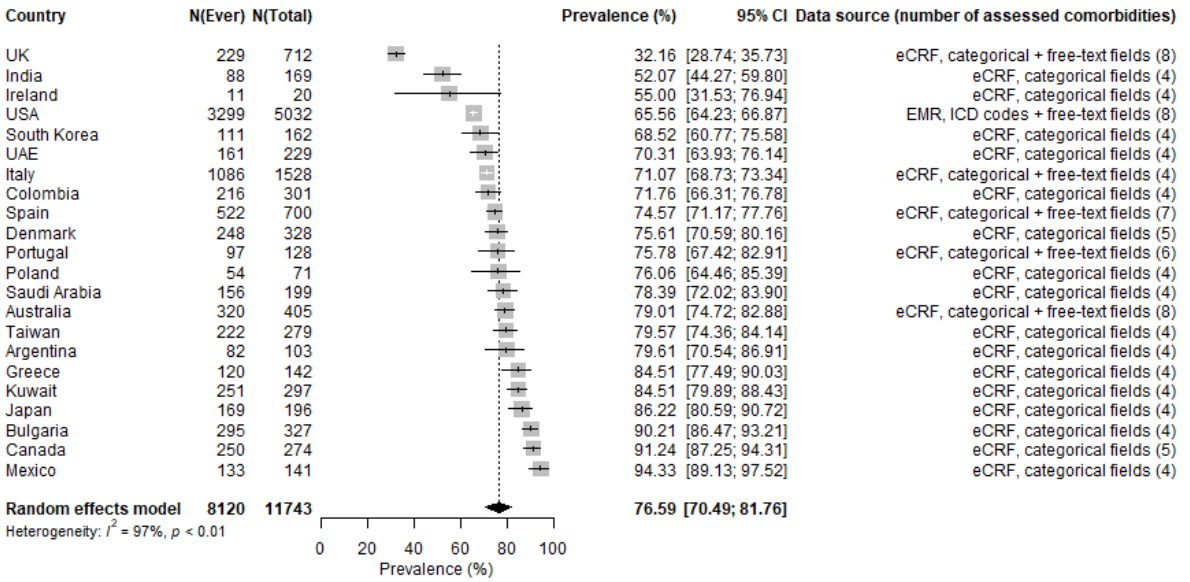


14.2 Appendix 2: Country-specific prevalence estimates random effects model pooled estimates for having at least one comorbidity, overall and by categories.

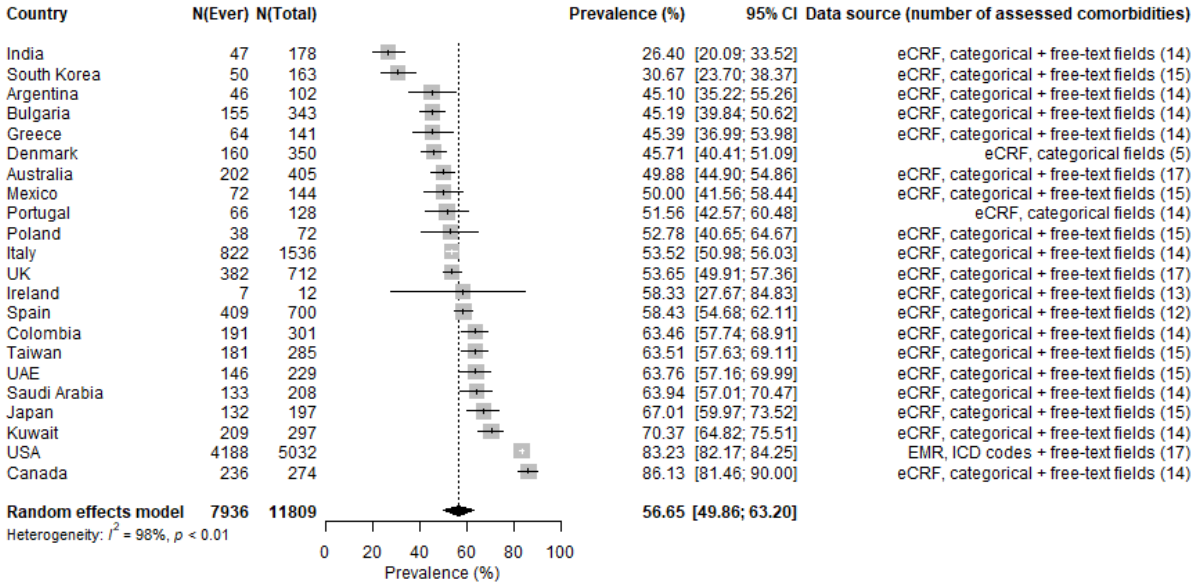
1) Any comorbidity of any type



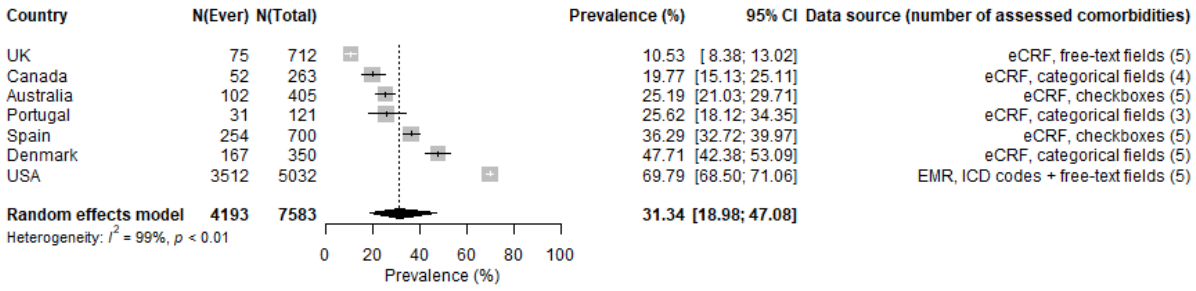
2) Any potentially T2-related comorbidity



3) Any potentially OCS-related comorbidity



4) Any comorbidity mimicking/exacerbating asthma



15.0 List of Tables and Figures