Study Report

Assessing the impact of earlier access to biologics on remission and natural course of asthma (GLEAM)

An examination of the Association Between the Timing of Biologic Therapy Initiation, Disease Progression, and Remission Probability in Severe Asthma

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TITLE	**Assessing the impact of earlier access to biologics on remission and natural course of asthma (GLEAM)**
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Study aims and objectives	**Study aims:** To evaluate the impact of early intervention with biologic therapies on the natural course of the disease in patients with severe asthma. **Study objectives:** **Objective 1**: To describe the timing of biologic therapy initiation using various definitions of time to initiation. **Objective 2**: To assess whether the timing of biologic therapy initiation is an explanatory factor in altering the natural history of asthma, including remission, biomarkers and individual clinical outcomes.
Countries of study	Argentina, Belgium, Brazil, Bulgaria, Canada, Colombia, Denmark, Estonia, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, UAE, UK, USA
Data source	ISAR, CHRONICLE, OPCRD
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADEPT	Anonymised Data Ethics & Protocol Transparency
ANOVA	Analysis of variance
BACS	Biologic Accessibility Criteria Score
BEC	Blood eosinophil count
BMI	Body mass index
FAO	Fixed airway obstruction
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HD	High dose
IgE	Immunoglobulin E
ICS	Inhaled corticosteroids
IL-4, -5, -13	Interleukin-4, -5, -13
IQR	Inter-quartile range
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
LTOCS	Long-Term Oral Corticosteroid
MD	Medium dose
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
PEFR	Peak flow rate
ppFEV1	Percent predicted FEV1
ppPEFR	Percent predicted peak flow rate
R	R software from the R Project for Statistical Computing
RCT	Randomised clinical trial
STATA	Stata software suite
FDA	U.S. Food and Drug Administration
EMA	European Medicines Agency

SD	Standard deviation
YLD	Years lived with disability

1.0 Executive Summary

The study aimed to evaluate the association between earlier intervention with biologic therapies and the course of severe asthma, including the probability of remission. The central hypothesis was that earlier access to biologics could alter the effectiveness of biologic treatments for severe asthma and improve the chance of remission.

Data from the International Severe Asthma Registry (ISAR), CHRONICLE US severe asthma registry, and the Optimum Patient Care Research Database (OPCRD) were used. The timing of biologic initiation was described using proxies: duration of asthma, duration of severe asthma, duration of lung function impairment/obstruction, duration of frequent exacerbations, and total pre-biologic oral corticosteroid (OCS) dose, derived via algorithms. Outcome variables were remission (defined across 2, 3, and 4 domains), exacerbations, asthma control, lung function, biomarkers (BEC, FeNO), and long-term OCS (LTOCS) use.

The proxies chosen to represent time to biologic initiation gave a good range of exposures and the measures were not strongly correlated in the three different data sources, suggesting that they may be measuring different aspects of disease progression at the point of biologic initiation that the proxies identified in this study was capturing.

Across all proxies, a longer duration was associated with less favourable levels of all clinical outcomes and lower probability of achieving remission at one-year post-biologic initiation, even after adjusting for baseline health status.

The odds of achieving remission at one-year post-biologic initiation decreased with increasing duration of asthma, duration of severe asthma, time since lung function impairment, time since frequent exacerbations, and cumulative OCS dose.

Exacerbation rates post-biologic initiation were higher in patients with longer pre-biologic durations across all proxies. Additionally, improvements in lung function diminished as the duration of the proxies increased, and the odds of achieving well or partly controlled asthma were lower with longer durations across all proxies.

The odds of being a non-user of LTOCS post-biologic were reduced in patients with greater duration of the proxies, suggesting that earlier initiation of biologics may be associated with reduced risks of OCS related comorbidities.

Notably, proxies indicating more severe disease, such as the duration of severe asthma, time since frequent exacerbations, and cumulative OCS dose, showed stronger negative effects on outcomes compared to the duration of asthma overall. This reinforces the hypothesis that

early initiation of biologics, once severe asthma is identified, is vital to maximize treatment benefits, as it may help prevent irreversible airway remodelling and increase the likelihood of reducing or discontinuing LTOCS, thereby mitigating associated comorbidities. The utility of the different proxies for indicating the need to start biologic therapy may be related to their availability in real world data (duration of severe asthma being the most widely available). However, longer duration across all of the proxies appeared to indicate that the benefits plateaued if biologic treatment was not initiated at the earliest opportunity.

The study also observed positive correlations between easier access to biologics (higher Biologic Accessibility Scores) and a greater likelihood of achieving positive outcomes, including remission, fewer exacerbations, better lung function, and reduced LTOCS use.

While some differences between data sources were observed, the overall direction of effects was similar across the three data sources. The study therefore draws credibility from the inclusion of a large number of severe asthma patients from a range of different sources.

2.0 Background

Severe asthma represents a significant subset of the asthma population, characterised by its resistance to standard treatment options. Defined by the Global Initiative for Asthma (GINA) as asthma that either remains uncontrolled despite good adherence to high-dose treatments or requires such treatments to achieve adequate control, severe asthma affects 6.1% of all patients with asthma globally and generates a significantly higher per-patient economic burden than non-severe asthma[1,2]. Asthma accounts for over 1% of global Years Lived with Disability (YLDs), and its management is complex and multifaceted. Its disproportionate contribution to asthma morbidity significantly impacts healthcare systems, underlining the need for effective intervention strategies[3,4]. The weight of long-term side-effects of OCS, including obesity, diabetes, osteoporosis and fragility fractures, cataracts, hypertension, and adrenal suppression makes it necessary to strengthen the evidence regarding the timely initiation of biological therapies[2]. Biologic therapies, immunomodulatory drugs tailored to target specific components of inflammatory processes, have emerged as a breakthrough in severe asthma management over the last decades[5,6]. This cohort of therapies, which includes monoclonal antibodies against various cytokines, their receptors, and immunoglobulin E (IgE), have demonstrated efficacy in reducing exacerbation rates, improving or preserving lung function, reducing/ceasing maintenance OCS use, increasing the likelihood of remission and enhancing the quality of life of patients with specific inflammatory phenotypes[6-10,23]. Medicine regulatory bodies including the Food & Drug Administration (FDA) and European Medicines Agency (EMA) have approved several biologics for therapeutic use in asthma, each predicated on evidence from clinical trials demonstrating their benefits in asthma patients[11,12]. However, RCTs usually include long-term severe asthma patients, thus, have not assessed the effect of the lag between diagnosis of severe asthma and the initiation of biologics in terms of clinical outcomes and/or remission.

Despite these advancements, managing severe asthma remains challenging due to the heterogeneous nature of the disease and variability in access, use and patient response to biological treatments[7,13-15]. This variability in response necessitates an exploration of factors that could predict and enhance treatment efficacy, particularly in the timing and selection of biologic therapies. The FULL BEAM study, as published in the American Journal of Respiratory and Critical Care Medicine, supports the hypothesis that early intervention with biologic therapy achieves better outcomes, including achieving remission[16,24]. Early intervention is hypothesized to mitigate against the development of irreversible airway

remodelling, a critical determinant in long-term outcomes for severe asthma patients. This aligns with findings from other immune-mediated diseases, where early intervention can slow progression and improve remission rates[17]. Despite these findings, FULL BEAM left some important questions still to answer, including the effect of delayed biologic initiation and the specific patient subgroups that might benefit most from early intervention and whether remission is maintained over time. These gaps underscore the need for further research to refine our understanding of how early intervention can be effectively implemented in routine clinical practice to maximize patient outcomes.

Understanding the optimal timing for initiating biologic therapies in severe asthma remains a crucial question that could significantly improve real-world clinical outcomes and reduce the socioeconomic burden of this disease. While previous studies have investigated the impact of asthma duration on biologic therapy initiation, there is a consensus that further investigation is needed to define what constitutes 'early' in the context of biologic initiation, and exactly how “timing” can be classified and approximated[18]. There are several possible factors that could influence the definition of 'early' versus 'late' initiation, such as the onset of severe asthma (early vs. later in life), and the predominant level of disease activity (poor lung function vs. severe exacerbations). Reaching an expert consensus on the definitions and proxies for timing and starting treatment is essential to guide research and develop tailored therapies for severe asthma. One source of variation lies in the eligibility criteria that are related to timely phenotyping and reimbursement criteria for initiating a biologic, between countries. Such differences can result in delays to treatment initiation for patients with similar disease manifestations (phenotypes)[19].

The International Severe Asthma Registry (ISAR) is a unique asset through which the effects of biologic therapy timing on disease progression and outcomes can be assessed. However, to enhance our understanding further, integrating data from the OPCRD[25] and CHRONICLE[22] will increase our study population, and provide the capability for additional proxies for severe asthma duration.

3.0 Study Aims and Objectives

Study Aims

To evaluate the association between early intervention with biologic therapies and clinical outcomes in patients with severe asthma.

Hypothesis: Earlier access to biologics changes the natural course of the disease of severe asthma and chance of remission.

Study Objectives

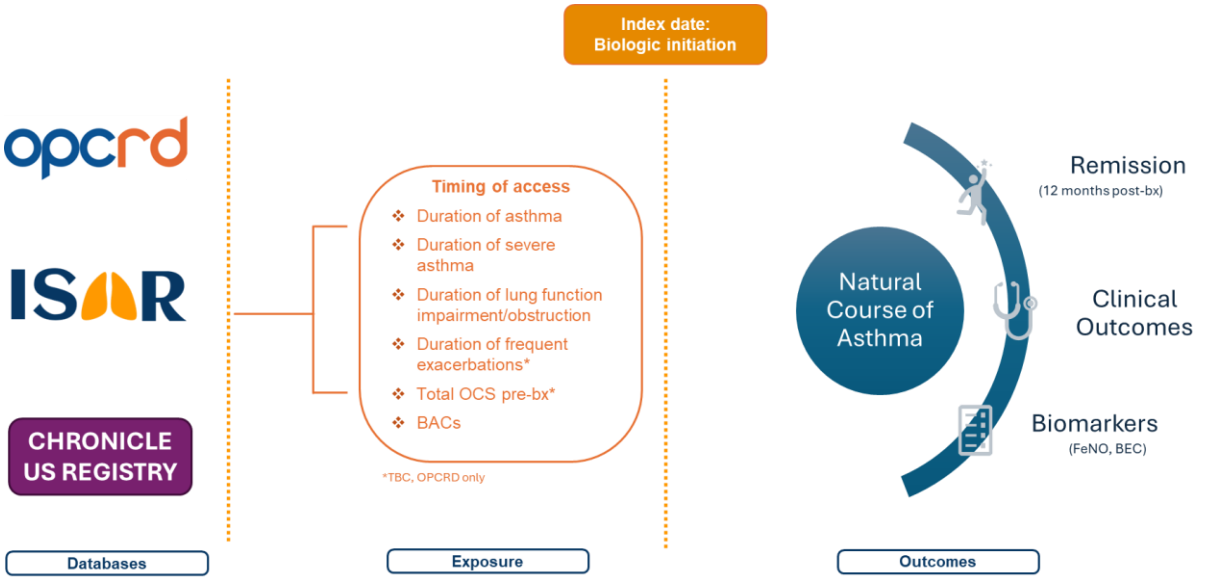
Objective 1:
To describe the timing of biologic therapy initiation using various proxies of time to initiation.

Objective 2:
To assess whether the timing of biologic therapy initiation is associated with the course of the disease in patients with severe asthma, including remission, biomarkers and individual clinical outcomes.

4.0 Materials and Methods

Overall Study Design

Figure 1. Study design



BEC: Blood Eosinophil Count, OCS: Oral Corticosteroids, FeNO: Fractional Exhaled Nitric Oxide, LABA: Long Acting Beta Agonist, ICS: Inhaled Corticosteroid, BACs: Biologic Accessibility Score
* Only available for OPCRD

A historical cohort study using data from the International Severe Asthma Registry (ISAR), CHRONICLE US severe asthma registry, and Optimum Patient Care Research Database (OPCRD) (see further details below). Data from records prior to initiation of a first biologic were used to derive the "time" of access to a biologic, by various proxy measures. Clinical outcomes related to the course of disease were assessed prior to biologic initiation and at 1 year post biologic initiation.

Study Population and Data Source(s)

The study population consists of severe asthma patients included in any of the three data sources and meeting the eligibility criteria. Patients were included in all analyses for which they had sufficient non-missing data. One site contributing data to ISAR also contributed data to CHRONICLE. The investigator flagged patients who were included in both registries (N=9). For these nine patients, data from CHRONICLE were not used. Probabilistic linkage based on biologic initiation date, age, sex and height was used to identify potential duplicates between the UK component of ISAR and OPCRD. No duplicates were detected.

The International Severe Asthma Registry (ISAR) is a global cooperative project designed to collect ongoing data from patients with severe asthma. To be included in this registry, patients must be 18 years of age or older, visit a participating centre, and have a diagnosis of severe asthma[20]. Additionally, they need to have provided appropriate consent for their data to be used in ISAR research. Severe asthma is characterised either by its lack of control despite therapeutic efforts, or by the necessity for comprehensive treatment as described in steps 4 and 5 of the GINA guidelines[2]. Data collection began in 2018. The data is comprised of relevant information collected from patients at each visit and extracted medical records.

OPCRD

The Optimum Patient Care Research Database (OPCRD) collects and analyses anonymised primary care records from UK patients. Eligibility requires relevant medical histories from participating practices. The OPCRD captures data that reflect real-world treatment patterns, outcomes, and healthcare interactions in line with clinical guidelines. Since its inception in 2008, the OPCRD has compiled records from 26 million patients.

Patients with severe asthma prescribed with a biologics were identified as follows:

- Prescription of an asthma-licensed biologics and at least one year of data pre-biologic initiation date, AND
- Using all available data pre-biologic initiation date:
    - Ever prescribed high ICS dose and a 2nd controller, and/or
    - Medium ICS dose plus LABA with 2 or more exacerbations in a year, poor asthma control, and/or percent predicted FEV_1 or PEFR < 80%, AND
- ICS prescription in the year preceding biologic initiation, AND
- OCS prescription (LTOCS and/or OCS bursts) in the year preceding biologic initiation.

CHRONICLE

CHRONICLE is a non-interventional, US, severe asthma registry that has collected data since February 2018. Adult (18 years or older) patients receiving a biologic or those who remain uncontrolled despite high-dosage inhaled corticosteroids and additional controllers are included in the registry. At inception, ISAR and CHRONICLE aligned on a core set of variables to allow for merging of a large study dataset. CHRONICLE collects clinical outcome and patient reported outcomes every six months.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Documented initiation of biologic therapy
- Age 18 years or older at the time of biologic initiation
- Record of biologic initiation date
- Data available for computing at least one proxy
- For objective 2 only: data available for at least one outcome

Exclusion Criteria

- There were no exclusion criteria

5.0 Study Variables

Demographic variables

The following variables were used to describe patients at baseline (time of biologic initiation or in the year prior to biologic initiation).

Table 1 - Variables used to describe patients in the study

Label	Details
Biologic Start Date	Date of initiation of first biologics
Age	Age at biologic initiation
Sex	Male/Female
BMI	In kg/m^2, record closest to biologic initiation
Ethnicity	Caucasian/Asian/African/Mixed/Other
Smoking status	Current/Ex-/Never smoker at biologic initiation
Age at asthma onset	ISAR: as reported by patients as age when asthma symptoms started and/or being diagnosed with asthma CHRONICLE: as reported by patients as age at time of first asthma diagnosis OPCRD: estimated using the first recording of an asthma diagnostic code. High confidence was considered when there were lifelong records, the asthma diagnosis code was dated from prior to practice join date, an asthma diagnostic code was first recorded after 5 years from joining the practice, or an asthma diagnostic code was first recorded within the fourth or fifth year of joining the practice with prescription of inhaler treatment in the 90 days following this record. Lower confidence was considered when an asthma diagnostic code was first recorded in the first 3 years of joining the practice as there was evidence of recording pre-existing asthma, or when an asthma diagnostic code was first recorded within the fourth and fifth year when there was no inhaler treatment prescription in the 90 days following this record.
Allergies - serum allergen or skin prick test	Positive/Negative Positive if positive test for at least one allergen. Negative if at least one test conducted and none are positive.

	OPCRD: because only a few serum test results were available and skin prick test results were not available, this variable was not computed.
Asthma control	Closest to biologic initiation, and maximum one year before biologic initiation. Categorized according to GINA 2020: uncontrolled/partly controlled/well controlled. When GINA symptom control score was not directly available, conversion from other tools were performed sequentially as follows: 1) If ACT available: well controlled if Total ACT >19; partly controlled if Total ACT >15 and <=19; uncontrolled if Total ACT <=15 2) If ACQ available: well controlled if Mean ACQ <=0.75; partly controlled if Mean ACQ >0.75 and <1.5; uncontrolled if Mean ACQ >=1.5 3) If RCP3Q available: well controlled if RCP3Q = 0; partly controlled if RCP3Q = 1; uncontrolled if RCP3Q = 2 or 3
Exacerbations	Number of asthma exacerbations requiring rescue steroids in the year before biologic initiation. A minimum of 48 weeks of data was required.
Percent predicted FEV1 or PEFR	Most recent percent predicted FEV1 (or PEFR when FEV1 not available) at biologic initiation, and maximum one year before biologic initiation.
FEV1/FVC ratio post bronchodilator	Most recent percent predicted FEV1/FVC ratio at biologic initiation, and maximum one year before biologic initiation.
Impaired or obstructed lung function	Yes/No Yes if percent predicted FEV1 or PEFR < 80% and/or FEV1/FVC < 0.70.
Baseline BEC	Highest blood eosinophil count up to biologic initiation (cells/mcL)
Baseline IgE	Latest serum total IgE concentration up to biologic initiation (IU/mL)
Baseline FeNO	Latest FeNO concentration up to biologic initiation (ppb)
Allergic rhinitis (AR)	Ever/Never
Chronic rhinosinusitis (CRS)	Ever/Never
Nasal polyps (NP)	Ever/Never
Atopic dermatitis / eczema	Ever/Never
Long-term OCS use	Yes/No In the year preceding biologic initiation.

	LTOCS is defined as chronic use of daily (or every other day) use of OCS for at least 90 days.
Long-term OCS daily dose	In the year preceding biologic initiation. In prednisolone-equivalent mg/day.
Biologic class	Anti-IgE/Anti-IL5/5R/Anti-IL4alpha/Anti-TSLP
Biologic name	Omalizumab/Benralizumab/Mepolizumab/ Reslizumab/Dupilumab/Tezepelumab
ICS use	Yes/No In the year preceding biologic initiation
LABA use	Yes/No In the year preceding biologic initiation
LAMA use	Yes/No In the year preceding biologic initiation
LTRA use	Yes/No In the year preceding biologic initiation
Theophylline use	Yes/No In the year preceding biologic initiation
Macrolide use	Yes/No In the year preceding biologic initiation

Proxies of time to initiation of biologics

The following variables were derived and used as proxies to describe the time to initiation of biologics:

Duration of asthma.

Time from reported asthma onset date or age to biologic initiation.

Duration of lung function impairment / obstruction

Time from earliest of:

- Earliest pre-bx percent predicted FEV1 or PEFR <80% (lung impairment);
- Earliest pre-bx, FEV1/FVC <0.70 (Fixed airway obstruction (FAO) as per GOLD criteria);

to biologic initiation.

Duration of severe asthma

Time from earliest of:

- Earliest high dose ICS with additional controllers (LABA, LAMA, LTRA, and/or theophylline);

- Earliest medium dose ICS + LABA and poor symptom control (uncontrolled, partly controlled);
- Earliest medium dose ICS + LABA and 2 or more severe exacerbations (requiring OCS);
- Earliest medium dose ICS + LABA and percent predicted FEV1 <80%;

to biologic initiation.

Duration of frequent exacerbations

Time from date of earliest frequent (2+) acute OCS prescriptions within a 24 month period to biologic initiation (the date of the second of these OCS prescriptions is used to define the start of frequent exacerbations).

Non-time based proxies

Total pre-biologic asthma-related OCS dose (g) (both long-term and rescue oral corticosteroids).

Biologic accessibility score (BACS)[13]

The highest BACS (easiest access) for the country (assessed across all available biologics in 2021).

The quality and availability of data used to compute the above proxies vary by data sources due to varying ways of collecting relevant data. The pros and cons are summarized in the below table.

Table 2. Pros and cons of each data source for computing time to biologic initiation proxies.

Proxy	ISAR	CHRONICLE	OPCRD
Duration of asthma	Pros: largely available Cons: age/date at asthma onset reported by patients (potential recall bias)	Pros: largely available Cons: age/date at asthma onset reported by patients (potential recall bias)	Pros: EMR data derived (see table 1) Cons: potential underestimation when estimated with lower

			confidence (see table 1)
Duration of lung function impairment / obstruction	Pros: spirometry results available Cons: limited retrospective data prior to biologic initiation/registry enrollment	Pros: spirometry results available Cons: limited retrospective data prior to biologic initiation/registry enrollment	Pros: Prospective data collected from when patient joined GP practices (often many years prior to initiating biologics) Cons: Spirometry data limited to a proportion of patients
Duration of severe asthma	Pros: - Cons: start date of ICS dose often missing and mostly collected for the current dose at registry enrollment (eg, if currently on high ICS dose, start date of medium dose will not be available)	Pros: specific data collection field on "best estimated date when high ICS dose plus a second controller was initiated" Cons: Start date of medium ICS + LABA with additional criterion mostly not available	Pros: Prospective prescription data collected from when patient joined GP practices (often many years prior to initiating biologics) Cons: -
Duration of frequent exacerbations	Not assessable as exacerbation data are collected only in the year preceding registry enrolment, which is most often date of biologic initiation		
Total pre-biologic asthma-related OCS dose	Not assessable as OCS-related data are collected only in the year preceding registry enrolment, which is most often date of biologic initiation		
BACS	Not applicable: BACS are country-level scores.		

Primary Outcome Variables

- **Remission** using the FULL BEAM[16] definitions
  - **2-domain**
    - No severe exacerbations in the 12 months post biologic initiation date **AND**

        - No LTOCS use or LTOCS use stopped in the 12 months post biologic initiation
    - **3-domain**
        - 2-domain **AND** asthma control score indicating good control 12 months post biologic initiation date (ACT>15, ACQ <1.5, RCP 0 or 1, aligning with GINA partly or well-controlled categorisation) OR
        - 2-domain **AND** no lung function impairment (percent predicted FEV1 or PEFR ≥80%)
    - **4-domain**
        - 2-domain **AND** partly or well-controlled asthma **AND** no lung function impairment

Secondary outcome variables

- **Exacerbations** – numbers in the years post initiation of biologics
- **Asthma control** – latest in the year prior to initiation of biologics and nearest available to 1 year post initiation of biologics
- **Post bronchodilator FEV_1** – latest in the year prior to initiation of biologics and nearest available to 1 year post initiation of biologics. If post bronchodilator results were not available then pre-bronchodilator results were used. In OPCRD peak flow rate (PEFR) was used if FEV_1 was not available.
- **Percent predicted FEV_1 or PEFR**
- **Blood eosinophil count (BEC)** – Highest ever prior to biologic initiation and nearest to 1 year post biologic initiation
- **Fractional exhaled nitric oxide (FeNO)** – Latest prior to biologic initiation and nearest to 1 year post biologic initiation
- **LTOCS daily dose** – mean daily dose for the 1 year prior to and 1 year post initiation of biologics

6.0 Statistical Analysis

Sample Size

All biologics patients with sufficient data to define at least one of the timing proxies were included in Objective 1. For Objective 2, patients also needed to have sufficient data for at least one of the outcomes, and corresponding pre-biologic values for the adjusted results.

Descriptive analysis

Descriptive analysis was conducted for each data source and for the combined dataset.

Patient characteristics were summarised using means (SD), medians (IQR), or numbers (percent of non-missing values).

The distributions of values for each proxy, for patients with sufficient data to calculate these, were plotted as cumulative distributions (proportion of patients initiating biologics by increasing durations of the proxies). Numbers of patients with available data for each proxy (and proportions of the patients in their respective data sources) were also tabulated. Correlations between the proxies were examined to determine whether these were different ways of providing the same (if highly correlated) or different (if poorly correlated) information as each other.

Main analysis

Associations between the proxies of timing and outcomes were analysed using regression, for each data source separately and for the combined dataset. Binary outcomes used logistic regression, count outcomes such as exacerbations used negative binomial regression, and continuous variables with a Gaussian distribution used linear regression. Continuous variables with a highly skewed distribution were dichotomised for the purposes of analysing associations with the proxies (e.g. LTOCS use ≤ 5mg/day or >5 mg/day) and analysed with logistic regression.

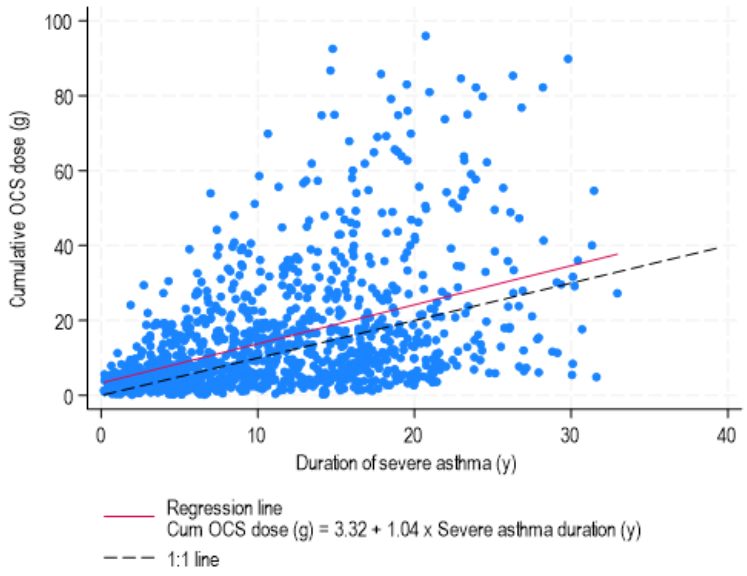
All regression models included country as a random effect when ISAR data was included, and country nested within data-source (OPCRD, ISAR or CHRONICLE) as random effects when multiple data sources were included. Adjusted models were additionally adjusted for age at biologic initiation, sex and for the baseline level of the relevant outcome. Age and sex were

available for all eligible patients and are potential direct confounders in a large range of health conditions. Additionally, they could serve as a marker for unknown or unmeasured confounders. Baseline level of relevant outcomes are main confounders as clinical characteristics before treatment initiation are associated with clinical characteristics after treatment initiation and potentially with time to biologic initiation. Other potential confounders were not considered for these association analyses.

In general, the associations between the outcomes and 10 year increments of the proxies are presented. However, in some cases it was not convenient to present the effects of 10 year increments of all proxies on the same scales so 1 year increments of some proxies have been used (as noted on the relevant forest plots). For ease of comparing the effects of 10 year increments, the data are also tabulated (with 10 year increments of all proxies) below the graphs.

Note that, on average, a 1 year increase in duration of severe asthma corresponded with 1g increase in cumulative OCS dose in OPCRD, so the associations with 10g increments of OCS are presented in the tables to compare with 10 year increments of the other proxies.

Figure 2. Association between cumulative OCS dose and duration of severe asthma in OPCRD



Biologic accessibility scores (BACS)

BACS were only available at the level of countries. The score varies between different biologics within each country. The most easily available biologic (highest BACS) within each country has been used to represent the ease of accessing biologics in that country. As BACS are not available at the individual level, correlations with the mean levels of the other proxies in each setting (country x data source) were tested. For objective 2, correlations between BACS and the proportion of patients with a positive outcome in each setting were tested. Pearsons correlations were weighted using the inverse of the variance of each estimate. This applies greater weight to settings for which the proportion of patients with a positive outcome can be estimated more accurately (settings with a large sample size and/or proportions close to one or zero).

Software

The analyses were conducted using R and Stata v18 (College Station, Texas).

Significance testing

P values ≤0.05 were considered statistically significant unless otherwise stated.

7.0 Results

Overall Patient Population/Study cohort

Patients were included in Objective 1 if they met the inclusion criteria and had sufficient information available to define at least one of the proxies of timing described in Section 5. Patients were included in Objective 2 if they were included in Objective 1 and had outcome data (in both the years pre- and post- biologic initiation) for at least one of the outcomes described in Section 5.

Table 3. Patient flow for inclusion in the study

	Data source			
	CHRONICLE (N=3,020)	**ISAR (N=12,220)**	**OPCRD (N=1,223)**	**Total (N=16,463)**
Sequential exclusions - Objective 1				
Missing biologic initiation date	10 (0.3%)	1,248 (10.2%)	0 (0.0%)	1,258 (7.6%)
Missing age	2 (0.1%)	41 (0.3%)	0 (0.0%)	43 (0.3%)
Age <18	33 (1.1%)	271 (2.2%)	43 (3.5%)	347 (2.1%)
Missing sex	0 (0.0%)	3 (0.0%)	2 (0.2%)	5 (0.0%)
No proxy available for time to biologic initiation	0 (0.0%)	129 (1.1%)	0 (0.0%)	129 (0.8%)
Included in objective 1	**2,975 (98.5%)**	**10,528 (86.2%)**	**1,178 (96.3%)**	**14,681 (89.2%)**
Sequential exclusions - Objective 2				
No pre- and post- outcomes data	15 (0.5%)	4,056 (33.2%)	169 (13.8%)	4,240 (25.8%)
Included in objective 2	**2,960 (98.0%)**	**6,472 (53.0%)**	**1,009 (82.5%)**	**10,441 (63.4%)**

Demographic and Clinical Characteristics

Characteristics of the patients included in Objective 1 are shown in Appendix 1. Characteristics of the patients included in Objective 2 (association between proxies and outcomes) are shown in Table 4 (below).

Table 4. Baseline characteristics of patients included in objective 2

	CHRONICLE (N=2,960)	**ISAR (N=6,472)**	**OPCRD (N=1,009)**	**Total (N=10,441)**
Biologic initiation date (median)	06dec2018 (min-max: 06jun2003-09jan2024)	01nov2019 (min-max: 01jan2004-05jul2024)	03mar2021 (min-max: 29mar2007-10apr2024)	15aug2019 (min-max: 06jun2003-05jul2024)

Age (years)	53.3 (13.9)	53.7 (14.2)	51.4 (15.4)	53.4 (14.3)
Female	1,984 (67.0%)	3,970 (61.3%)	610 (60.5%)	6,564 (62.9%)
Body mass index (kg/m^2) at biologic initiation	33.2 (8.7)	28.1 (6.3)	30.9 (7.6)	29.9 (7.5)
Underweight (BMI<18.5)	20 (0.7%)	118 (1.9%)	14 (1.4%)	152 (1.5%)
Normal weight (BMI 18.5 to <25)	404 (13.8%)	2,040 (32.2%)	202 (20.2%)	2,646 (25.8%)
Overweight (BMI 25 to <30)	768 (26.3%)	2,150 (34.0%)	310 (31.0%)	3,228 (31.5%)
Obese (BMI >=30)	1,729 (59.2%)	2,024 (32.0%)	474 (47.4%)	4,227 (41.2%)
Ethnicity				
Caucasian	2,217 (77.6%)	4,578 (81.4%)	886 (87.8%)	7,681 (81.0%)
Asian	53 (1.9%)	394 (7.0%)	63 (6.2%)	510 (5.4%)
African	506 (17.7%)	108 (1.9%)	13 (1.3%)	627 (6.6%)
Mixed	0 (0.0%)	224 (4.0%)	8 (0.8%)	232 (2.4%)
Other	80 (2.8%)	319 (5.7%)	39 (3.9%)	438 (4.6%)
Smoking status at biologic initiation				
Never smoker	1,907 (64.5%)	4,190 (65.8%)	609 (60.4%)	6,706 (64.9%)
Ex-smoker	889 (30.1%)	1,981 (31.1%)	330 (32.7%)	3,200 (31.0%)
Current smoker	161 (5.4%)	200 (3.1%)	70 (6.9%)	431 (4.2%)
Age at asthma onset (years)	30 [10, 48]	31 [15, 46]	28 [9, 42]	30 [12, 46]
Allergen test results				
Negative	2,349 (79.4%)	1,619 (44.3%)	0 (0.0%)	3,968 (60.0%)
Positive	611 (20.6%)	2,036 (55.7%)	0 (0.0%)	2,647 (40.0%)
Asthma control				
Uncontrolled	231 (73.1%)	1,515 (62.2%)	289 (66.1%)	2,035 (63.8%)
Partly controlled	57 (18.0%)	544 (22.3%)	107 (24.5%)	708 (22.2%)
Well controlled	28 (8.9%)	376 (15.4%)	41 (9.4%)	445 (14.0%)
Exacerbations in past year	1.6 (1.6)	2.6 (2.9)	3.3 (2.7)	2.6 (2.8)
0	153 (30.7%)	1,185 (27.1%)	97 (9.6%)	1,435 (24.4%)
1-2	221 (44.4%)	1,500 (34.3%)	390 (38.7%)	2,111 (35.9%)
3-4	94 (18.9%)	922 (21.1%)	249 (24.7%)	1,265 (21.5%)
5+	30 (6.0%)	760 (17.4%)	273 (27.1%)	1,063 (18.1%)
Percent predicted FEV1/PEFR	77.2 (21.9)	75.0 (22.3)	71.3 (21.4)	74.9 (22.2)
<60%	134 (23.0%)	1,137 (25.5%)	139 (30.2%)	1,410 (25.6%)
>=60 - <80%	191 (32.8%)	1,468 (32.9%)	155 (33.7%)	1,814 (32.9%)
>=80%	257 (44.2%)	1,859 (41.6%)	166 (36.1%)	2,282 (41.4%)
FEV1/FVC ratio	0.74 [0.65, 0.81]	0.69 [0.59, 0.77]	0.69 [0.59, 0.78]	0.69 [0.60, 0.77]
<0.5	29 (4.9%)	499 (11.0%)	23 (11.5%)	551 (10.4%)
>=0.5 - <0.7	190 (32.4%)	1,917 (42.3%)	79 (39.5%)	2,186 (41.1%)
>=0.7	367 (62.6%)	2,117 (46.7%)	98 (49.0%)	2,582 (48.5%)
Lung function impairment/obstruction[1]	482 (65.6%)	3,713 (77.2%)	707 (92.2%)	4,902 (77.7%)
Highest blood eosinophil count (cells/µL)	310 [154, 580]	500 [270, 820]	700 [460, 1100]	500 [265, 830]
<100	131 (13.0%)	256 (4.9%)	5 (0.5%)	392 (5.4%)
100- <300	345 (34.4%)	1,122 (21.3%)	83 (8.6%)	1,550 (21.4%)

300- <500	217 (21.6%)	1,196 (22.7%)	171 (17.6%)	1,584 (21.9%)
>=500	311 (31.0%)	2,695 (51.1%)	710 (73.3%)	3,716 (51.3%)
Latest total serum IgE (IU/mL)	137 [43, 375]	169 [64, 438]	336 [84, 835]	166 [60, 440]
<75	385 (35.9%)	1,179 (28.6%)	53 (23.1%)	1,617 (29.8%)
>=75	686 (64.1%)	2,945 (71.4%)	176 (76.9%)	3,807 (70.2%)
Latest FeNO (ppb)	22 [12, 50]	34 [17, 65]	38 [21, 60]	33 [16, 64]
<25	185 (52.3%)	1,332 (38.2%)	6 (42.9%)	1,523 (39.5%)
>=25	169 (47.7%)	2,151 (61.8%)	8 (57.1%)	2,328 (60.5%)
Allergic rhinitis	1,928 (65.1%)	3,062 (55.7%)	546 (54.1%)	5,536 (58.5%)
Chronic rhinosinusitis	706 (23.9%)	3,585 (56.1%)	355 (35.2%)	4,646 (44.8%)
Nasal polyposis	311 (10.5%)	2,302 (36.0%)	225 (22.3%)	2,838 (27.4%)
Eczema/atopic dermatitis	166 (5.6%)	932 (14.9%)	250 (24.8%)	1,348 (13.2%)
LTOCS user in past year	605 (20.4%)	1,934 (34.9%)	343 (34.0%)	2,882 (30.3%)
LTOCS average daily dose in past year (mg)[2]	0.7 (3.2)	2.5 (6.3)	2.5 (5.1)	2.0 (5.4)
LTOCS average daily dose in past year in users (mg)[2]	7.2 (7.7)	8.7 (9.1)	7.5 (6.3)	8.3 (8.5)
Biologic class				
Anti-IL4Ralpha	409 (13.8%)	972 (15.0%)	118 (11.7%)	1,499 (14.4%)
Anti-IL5/5R	1,204 (40.7%)	3,815 (58.9%)	597 (59.2%)	5,616 (53.8%)
Anti-IgE	1,268 (42.8%)	1,587 (24.5%)	273 (27.1%)	3,128 (30.0%)
Anti-TSLP	79 (2.7%)	98 (1.5%)	21 (2.1%)	198 (1.9%)
Biologic name				
Anti-IL4R alpha: Dupilumab	409 (13.8%)	972 (15.1%)	118 (11.7%)	1,499 (14.4%)
Anti-IL5: Mepolizumab	621 (21.0%)	2,529 (39.2%)	298 (29.5%)	3,448 (33.1%)
Anti-IL5: Reslizumab	42 (1.4%)	86 (1.3%)	2 (0.2%)	130 (1.2%)
Anti-IL5R: Benralizumab	541 (18.3%)	1,183 (18.3%)	297 (29.4%)	2,021 (19.4%)
Anti-IgE: Omalizumab	1,268 (42.8%)	1,587 (24.6%)	273 (27.1%)	3,128 (30.0%)
Anti-TSLP: Tezepelumab	79 (2.7%)	98 (1.5%)	21 (2.1%)	198 (1.9%)
ICS use in past year	1,816 (98.6%)	5,909 (98.9%)	1,009 (100.0%)	8,734 (99.0%)
LABA use in past year	1,822 (98.2%)	5,554 (94.0%)	992 (98.3%)	8,368 (95.4%)
LAMA use in past year	750 (80.5%)	3,203 (64.8%)	615 (61.0%)	4,568 (66.4%)
LTRA use in past year	1,312 (91.0%)	3,106 (63.4%)	320 (31.7%)	4,738 (64.4%)
Theophylline use in past year	47 (11.6%)	375 (10.0%)	238 (23.6%)	660 (12.8%)
Macrolide use in past year	80 (19.5%)	643 (16.9%)	11 (1.1%)	734 (14.0%)

Notes:
Mean (SD), median [IQR], or n (%) are shown
[1] FEV1 or PEFR < 80%, and/or FEV1/FVC ratio < 0.70 before biologic initiation
[2] Prednisolone equivalent

Objective 1

Availability and distributions of proxies

Duration of asthma

This was defined as the time from age of asthma onset to age at biologic initiation:

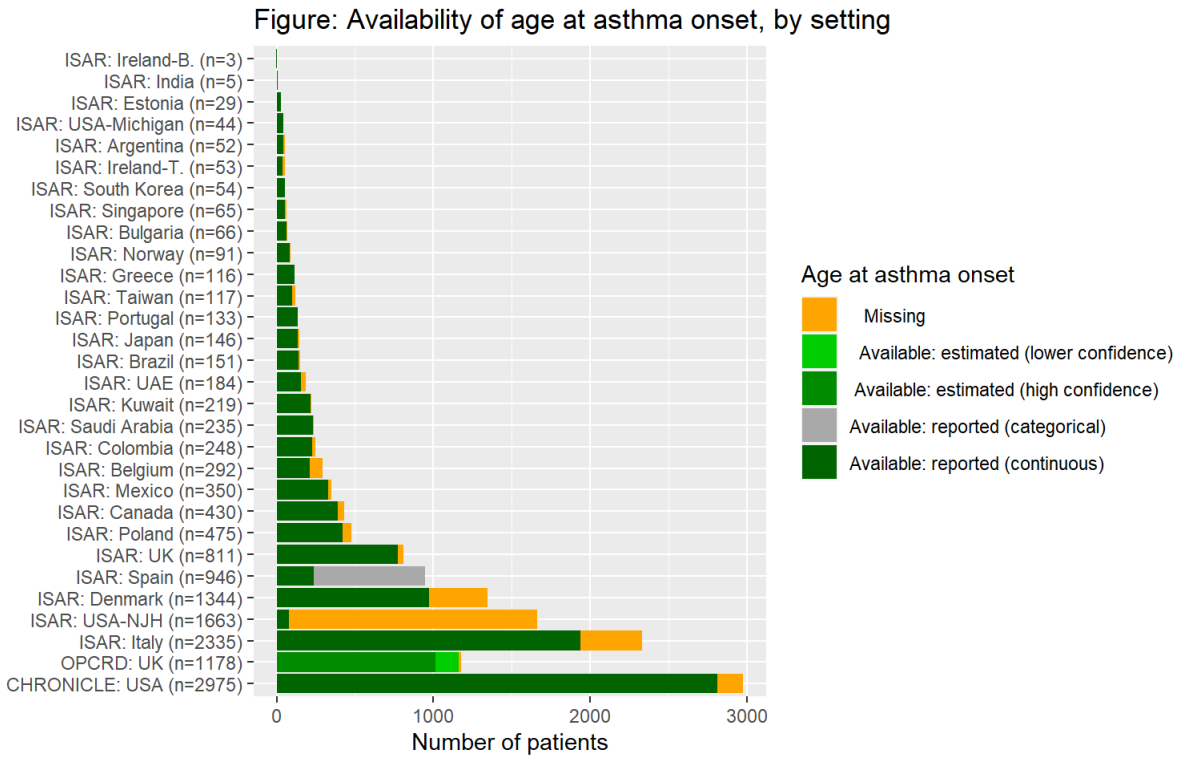
CHRONICLE – reported age of first asthma diagnosis

ISAR – reported age of first symptoms and/or asthma diagnosis

OPCRD – date of first asthma diagnostic code

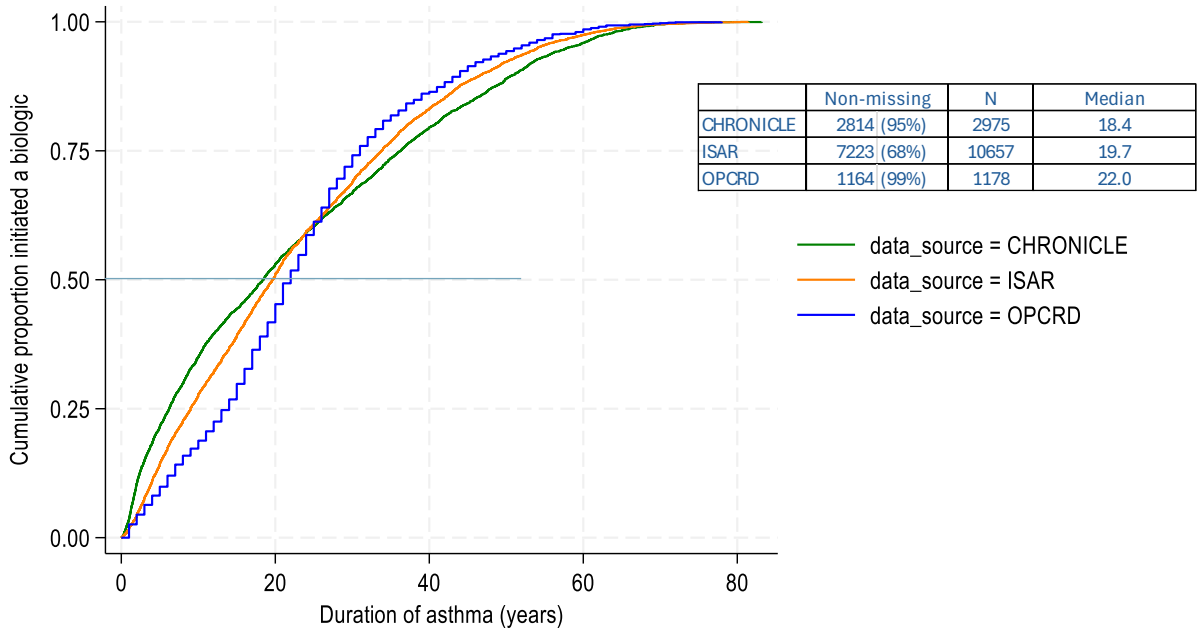
Duration of asthma was available for most patients, except those from NJH (USA).

Figure 3. Availability of data for the duration of asthma proxy



Distributions were similar in the three data sources although patients appeared to have had slightly longer asthma duration before biologic initiation in OPCRD.

Figure 4. Distributions of the duration of asthma proxy

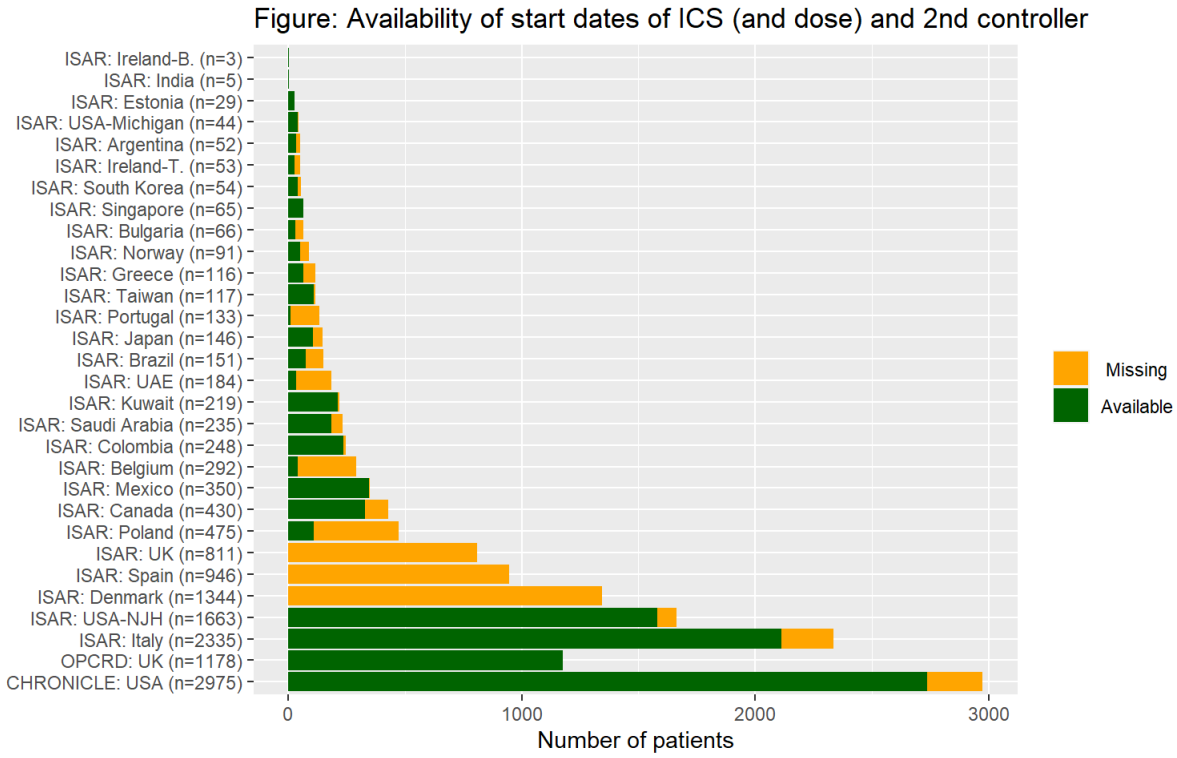


Duration of severe asthma

This was defined by the start of high dose ICS + 2nd controller, or start of medium dose ICS + LABA + at least one of: poor control, 2+ exacerbations per year, or ppFEV1/PEFR <80%.

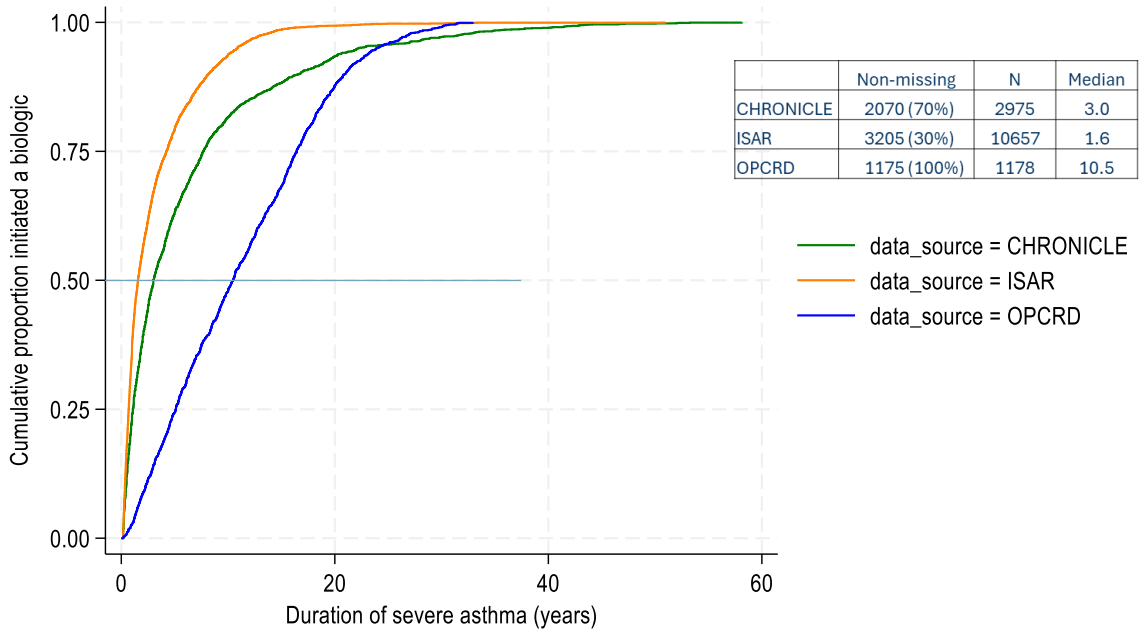
Duration of severe asthma was available for most patients in CHRONICLE and OPCRD but only for 30% of patients in ISAR, due mainly to missing information on the start dates and/or dose of ICS and a second controller.

Figure 5. Availability of data for the duration of severe asthma proxy



The estimated duration of severe asthma prior to biologic initiation tended to be shortest in ISAR and longest in OPCRD. This proxy was less available for patients in ISAR as the start of high / medium dose ISC and / or the onset of symptoms was often not available.

Figure 6. Distributions of the duration of severe asthma proxy



The duration of severe asthma (for patients where it could be determined) was most commonly defined by the initiation of high dose ICS plus a second controller.

Table 5. Indication of start of severe asthma

	CHRONICLE		ISAR		OPCRD	
High ICS dose plus 2nd controller	2,038	(98%)	2,354	(73%)	543	(46%)
Medium ICS dose plus LABA, poor control, 2+ exacerbations per year, ppFEV1/PEFR <80%	0	(0%)	26	(1%)	5	(0%)
Medium ICS dose plus LABA, poor control, 2+ exacerbations per year	1	(0%)	10	(0%)	55	(5%)
Medium ICS dose plus LABA, poor control, ppFEV1/PEFR <80%	1	(0%)	25	(1%)	16	(1%)
Medium ICS dose plus LABA, 2+ exacerbations per year, ppFEV1/PEFR <80%	2	(0%)	73	(2%)	26	(2%)
Medium ICS dose plus LABA, poor control	0	(0%)	51	(2%)	125	(11%)
Medium ICS dose plus LABA, 2+ exacerbations per year	13	(1%)	238	(7%)	239	(20%)
Medium ICS dose plus LABA, ppFEV1 or ppPEFR <80%	15	(1%)	428	(13%)	166	(14%)

The indications used to denote the start of severe asthma in individual patients are shown. For each patient, the earliest of the above indications was used to denote the start of severe asthma.

Time since lung function impairment or obstruction

Time from earliest percent predicted FEV_1 or PEFR < 80%, and/or FEV_1 / FVC ratio < 0.70 to biologic initiation.

This proxy was only available in 7, 16 and 19% of patients in CHRONICLE, ISAR and OPCRD respectively. Lack of availability was mainly due to patients not having any pre-biologic spirometry data or already having obstruction/impairment at first record, in which case the time of the start of this condition was ambiguous. If there were no records before the start of lung function impairment/obstruction these patients' data was not used.

Figure 7. Availability of data for the time with lung function impairment or obstruction proxy

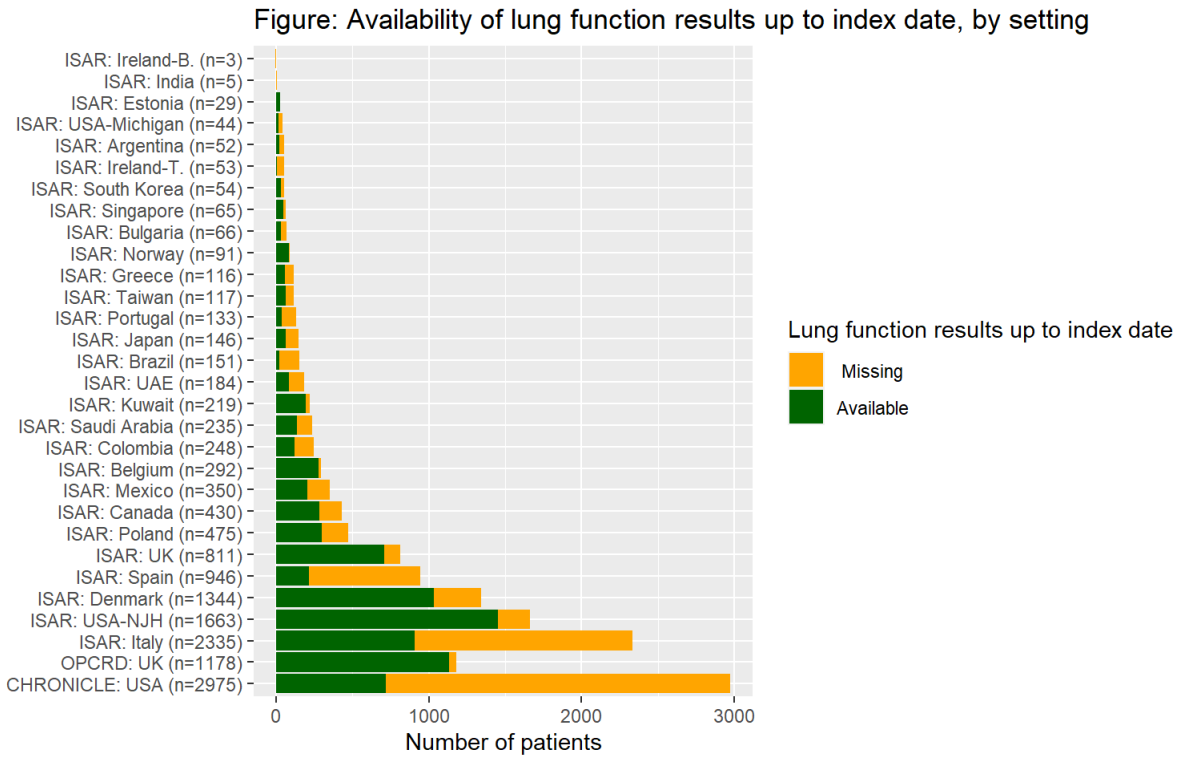
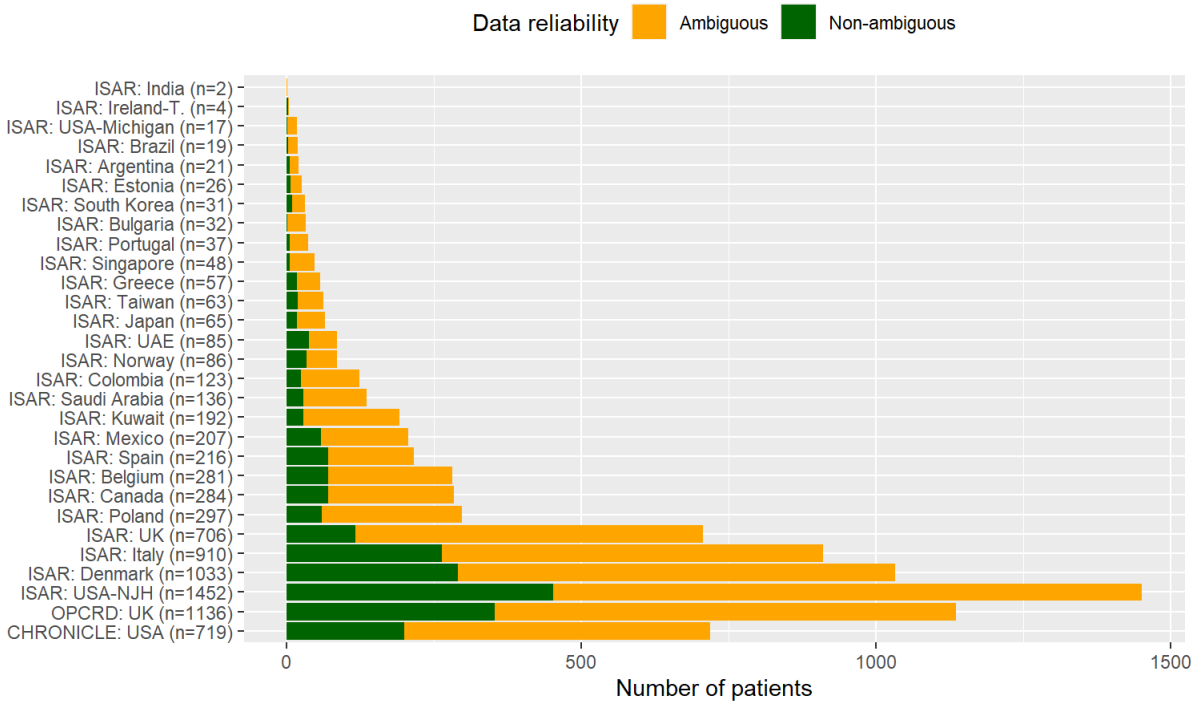


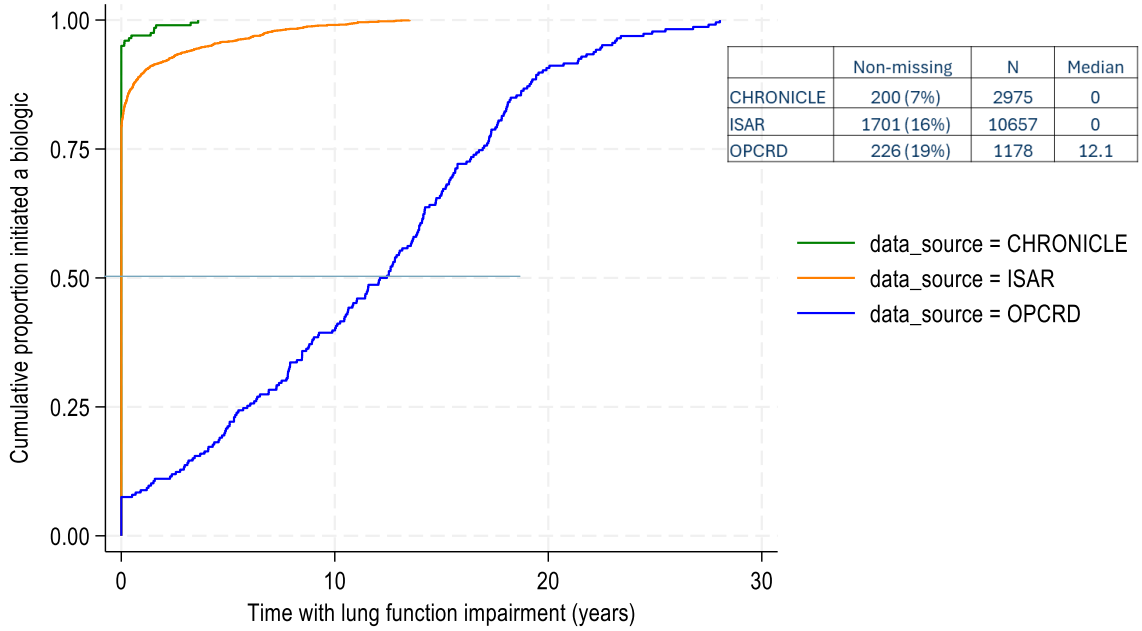
Figure: Time since lung function impairment/obstruction, by setting



In ISAR and CHRONICLE many of those patients for whom this proxy could be defined did not have lung impairment or obstruction at the time they initiated biologics (shown as having time = 0 on the plot below). However, this probably over-represents to proportion without lung function impairment at the time of biologic initiation since the time of the start of impairment or obstruction could often not be determined from the data in these two data sources. Patients with unknown time with lung function impairment or obstruction could not be included in the cumulative distributions shown.

In OPCRD, patients typically had lung function impairment or obstruction for 12 years before initiating a biologic.

Figure 8. Distributions of the time with lung function impairment or obstruction proxy

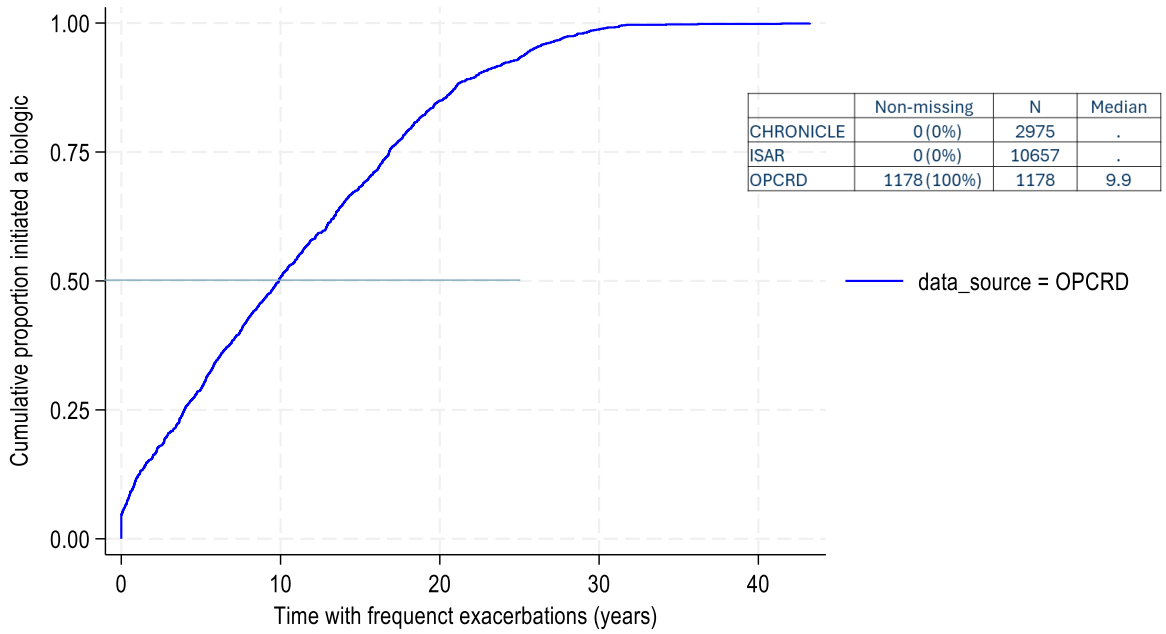


Time since frequent exacerbations

This was defined as the time from the 'first occurrence' (earliest recorded occurrence) of a second exacerbation within 24 consecutive months to biologic initiation, and was only available for OPCRD. Whilst this could miss some exacerbations before records start for individual patients, most patients have long-term records available either from the current practice or carried forward from a previous practice in OPCRD.

A wide range of times since the start of having frequent exacerbations was observed, with almost 50% of patients waiting 10 years or more from that point before starting a biologic.

Figure 9. Distribution of the time with time with frequent exacerbations proxy

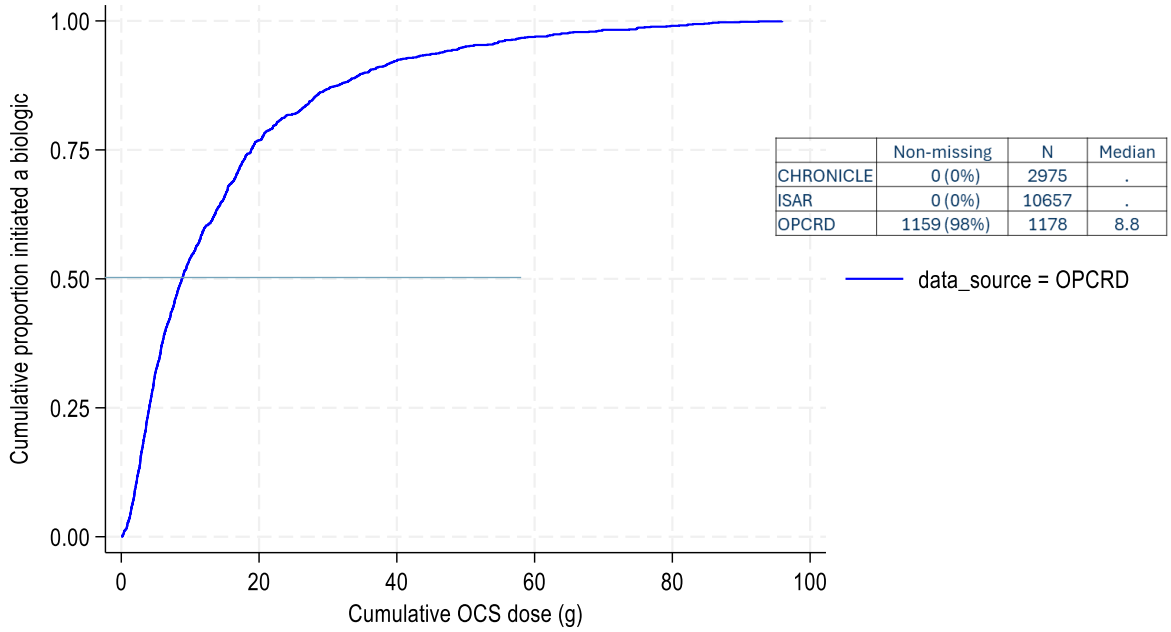


Cumulative OCS dose

The lifetime cumulative dose of oral corticosteroids (OCS) for an asthma indication (both long-term and rescue steroids) was calculated for patients in OPCRD (not available for CHRONICLE or ISAR). Whilst this could miss some OCS doses before records start for individual patients, most patients have long-term records available either from the current practice or carried forward from a previous practice in OPCRD.

The median value was a total of 8.8g (prednisone equivalent), with some patients having received over 40g before starting a biologic. Nineteen patients with values >100g total OCS dose have been removed from these data as these seem likely to contain errors.

Figure 10. Distribution of the cumulative OCS dose proxy



Correlations between proxies of timing

The proxies were all positively correlated though, in general, they were not strongly correlated with one another. Duration of severe asthma, time with frequent exacerbations and time with lung function impairment within OPCRD were the most strongly correlated variables, though the correlation between duration of severe asthma and time with lung function impairment was not as strong in ISAR and CHRONICLE (and time with frequent exacerbations was only determined for OPCRD). This may reflect the difficulty of deriving accurate start times for these proxies in ISAR and CHRONICLE because accurate data was often only available for a small number of years prior to biologic initiation.

Table 6. Correlations (r) between the proxies within CHRONICLE

	Duration of asthma	Duration of severe asthma	Lung function impairment time
Duration of asthma	1		
Duration of severe asthma	0.27	1	
Lung function impairment time	0.17	0.11	1

Table 7. Correlations (r) between the proxies within ISAR

	Duration of asthma	Duration of severe asthma	Lung function impairment time
Duration of asthma	1		
Duration of severe asthma	0.09	1	
Lung function impairment time	0.04	0.47	1

Table 8. Correlations (r) between the proxies within OPCRD

	Duration of asthma	Duration of severe asthma	Lung function impairment time	Time with frequent exacerbations*	Cumulative OCS dose*
Duration of asthma	1				
Duration of severe asthma	0.45	1			
Lung function impairment time	0.44	0.71	1		
Time with frequent exacerbations*	0.42	0.78	0.66	1	
Cumulative OCS dose*	0.20	0.46	0.35	0.44	1

* Variables only available for OPCRD

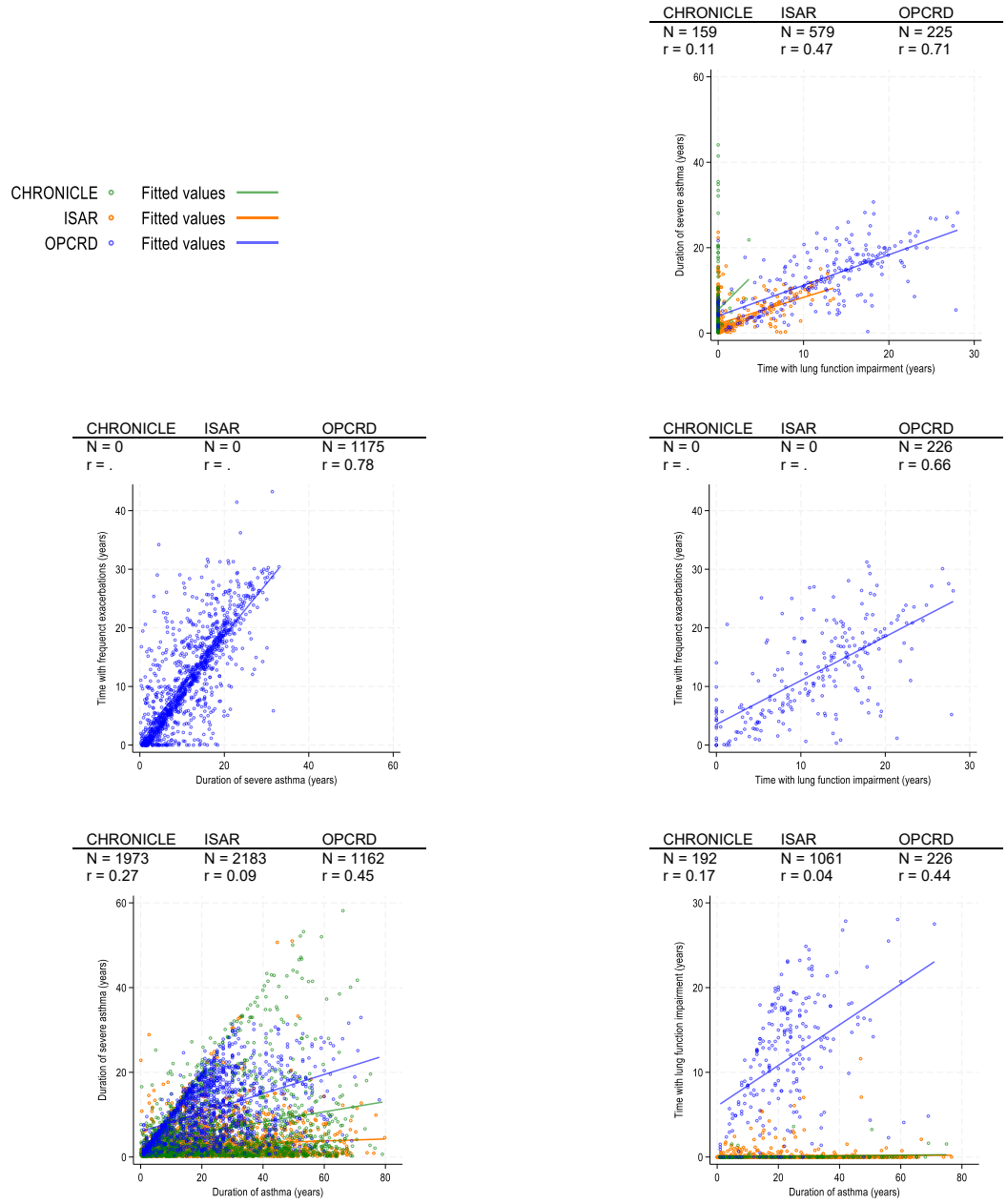
It was also notable that none of the proxies were correlated with age at biologic initiation. This was similar in all three data sources.

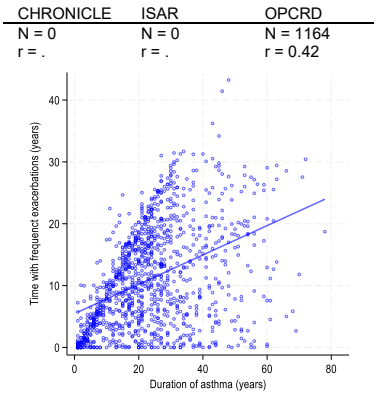
Table 9. Correlations (r) between the proxies and age at biologic initiation (all data sources combined)

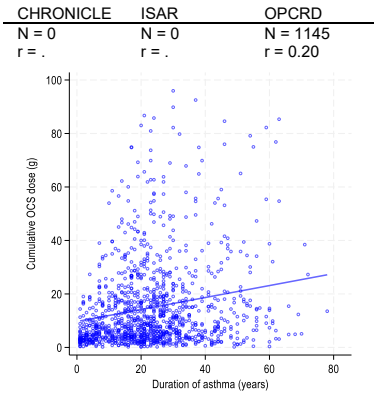
	Duration of asthma	Duration of severe asthma	Lung function impairment time	Time with frequent exacerbations*	Cumulative OCS dose*
Age at biologic initiation	0.22	0.06	0.10	0.14	0.18

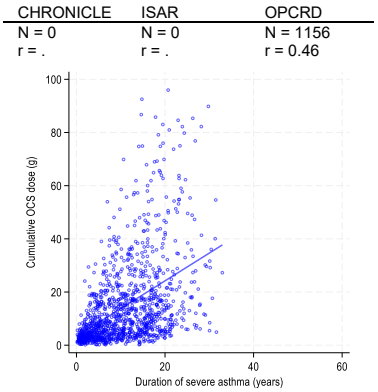
* Variables only available for OPCRD

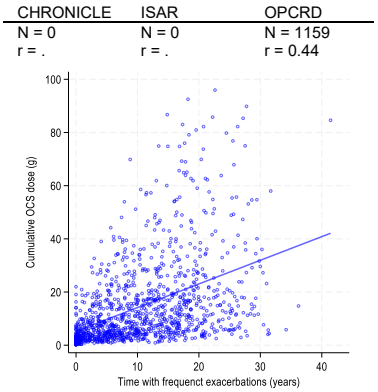
Figure 11. Scatter graphs showing the strength of association between proxies

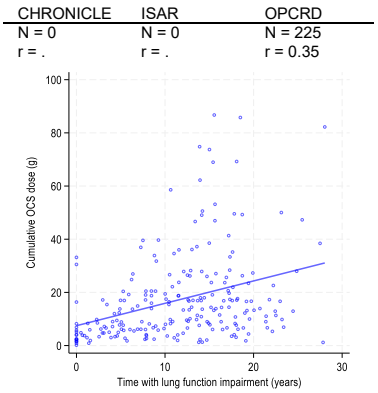






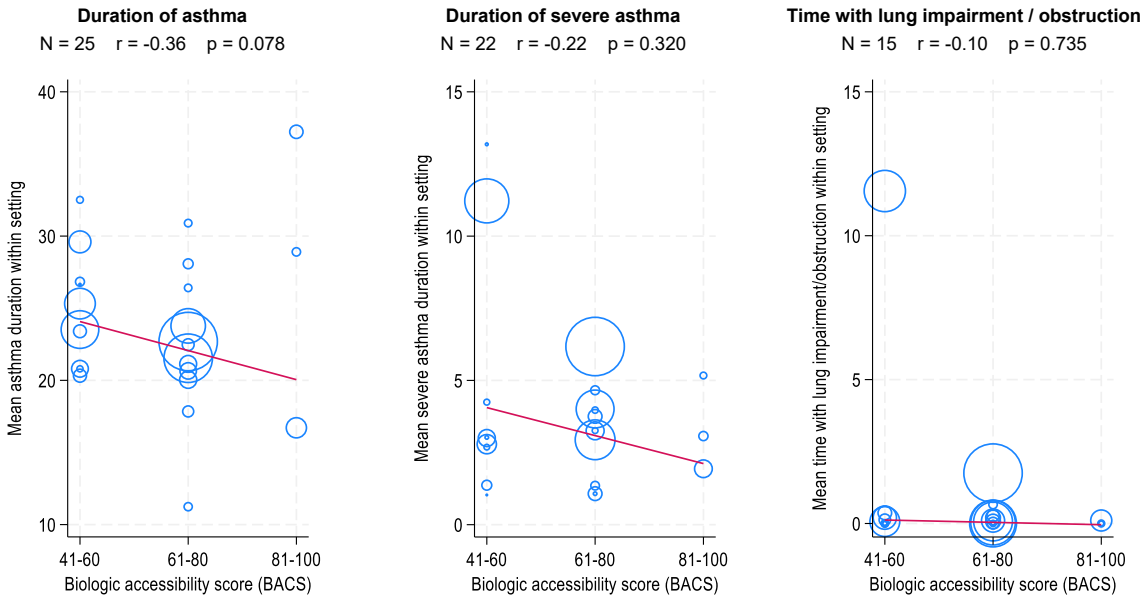






No significant correlations between BACS and the other proxies were observed. However, for the three proxies which were available across multiple settings, the correlations were all negative, consistent with patients having shorter durations of asthma, severe asthma, or lung function impairment before starting biologics in settings with easier access to biologics.

Figure 12. Correlation between BACS and other proxies



BACS - 41-60: Moderately difficult; 61-80: Neither easy nor difficult; 81-100: Easy. Setting = data-source x country/centre
Size of the circles indicates the number of patients in each setting. Correlations weighted using 1/var(mean) within each setting to apply greater weight to the results with greatest precision.

Note: time with frequent exacerbations and total OCS dose were only available in OPCRD (one setting) so there was no variation in BACS to test for a correlation.

Summary for Objective 1

The proxies chosen to represent time to biologic initiation give a good range of exposures and the measures are not strongly correlated in the three different data sources, suggesting that they may be measuring different aspects of disease progression at the point of biologic initiation. It was stated in the protocol that a selection of proxies may be made, based on their apparent usefulness from Objective 1. However, given that they were largely uncorrelated it was decided to continue to study the associations between each of the proxies and the different outcomes in Objective 2.

The scope to derive the proxies accurately for the majority of patients was more limited in the ISAR and CHRONICLE datasets as patient records do not routinely go back more than a few years before biologic initiation in these datasets. The most widely available proxies were duration of asthma (available for 95, 68 and 99% of patients in CHRONICLE, ISAR and OPCRD respectively) and duration of severe asthma (available for 70, 30 and 100% of patients in CHRONICLE, ISAR and OPCRD respectively). Time with lung function impairment was the least complete because spirometry data were usually not available from before the time when lung function impairment was suspected so it was not possible to know if the first

record showing obstruction in fact represented the start of the condition (available for 7, 16 and 19% of patients in CHRONICLE, ISAR and OPCRD respectively). Additionally, time since the start of frequent exacerbations was not directly recorded in any of the datasets but could be derived for patients in OPCRD only. Similarly, total cumulative dose of OCS was only available in OPCRD (98% of patients). The long-term recording of patients' symptoms, such as in OPCRD, would provide better opportunities to study the early development of asthma and severe asthma and to identify the most appropriate timing of intervention strategies including initiation of biologics.

Objective 2

Associations between timing proxies and outcomes

Note that all regression results in the section (unadjusted and adjusted) included data source and country nested within data sources as random effects for each analysis where multiple data sources/countries were included. Multivariable analyses were additionally adjusted for age, sex and baseline levels of the relevant outcomes, as described in footnotes of the graphs.

Remission at 1 year post biologic initiation

2-domain – no (or stop) LTOCS use **and** no exacerbations
3-domain – no (or stop) LTOCS use **and** no exacerbations **and** partly or well-controlled asthma

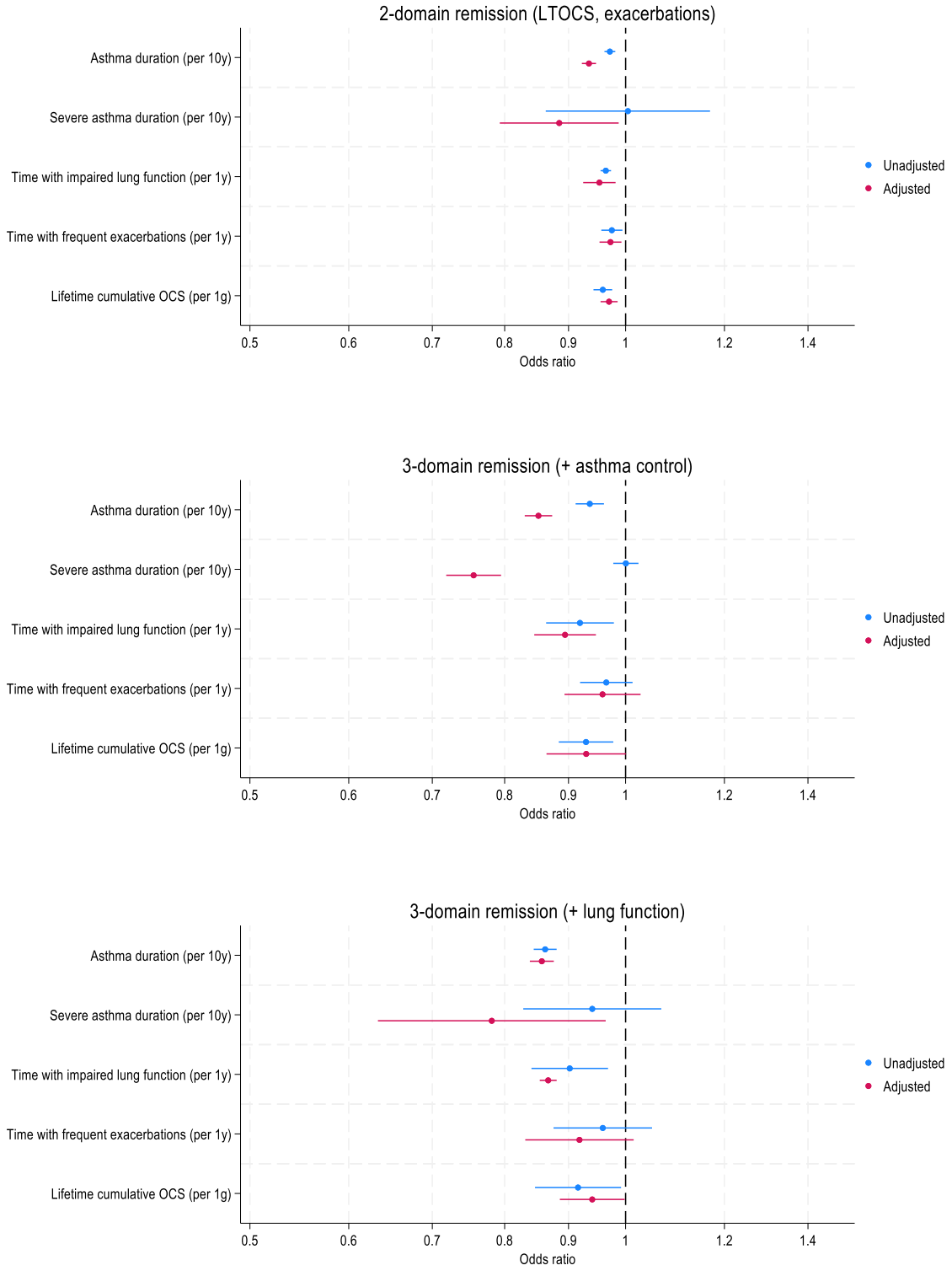
- no (or stop) LTOCS use **and** no exacerbations **and** no lung function impairment (percent predicted FEV1 or PEFR ≥80%)

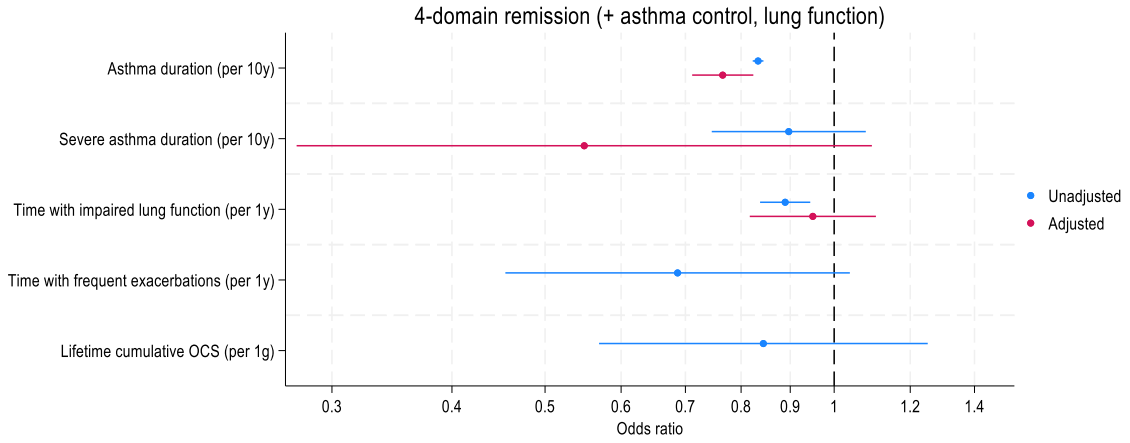
4-domain – no (or stop) LTOCS use **and** no exacerbations **and** partly or well-controlled asthma **and** no lung function impairment (percent predicted FEV1 or PEFR ≥80%)

The odds of remission 1 year post biologic initiation decreased with increasing durations of the proxies, even after adjusting for age, sex, and baseline levels of the outcomes comprising remission status. The effect of 10 years with severe asthma was greater than the effects of 10 years since the first onset of asthma. Point estimates of the effects of 10 years with lung function impairment, 10 years with frequent exacerbations, or 10 g of cumulative OCS were even greater (see Table 10). Note, although the effects are compared for a 10 year (10g) increment in duration, the same comparative order would be true comparing the effects of an

additional 1 yr with asthma *vs* 1 year with severe asthma *vs* 1 year with lung function impairment, etc.

Figure 13. Associations between the proxies and remission at 1 year post biologic initiation





Estimates for time with frequent exacerbations and lifetime cumulative OCS are from OPCRD data only.
An odds ratio <1 shows the decrease in odds of achieving remission at 1 year post biologic initiation with every n units increase in the proxy.
Adjusted odds ratios were adjusted for age at biologic initiation, sex and baseline exacerbation rate and baseline LTOCS use. Additionally, 2 and 3 domain remission were adjusted for the relevant baseline outcomes of asthma control (well/partial vs uncontrolled) and / or percent predicted FEV_1 or PEFR.
Adjusted effects of time with frequent exacerbations and cumulative dose of OCS for 4-domain remission are not shown as the odds ratios were not calculable (small sample size led to model not converging).

Note: The graphs show the odds ratio for an *n* unit increase in each of the proxies. The effects of 1 year increments of time with lung function impairment, time with frequent exacerbations, and 1g increments lifetime dose of LTOCS are shown so that the results can be included on the same graph. For comparisons of the adjusted effects of 10 year/10g increments of all proxies see Table 10 (below).

Table 10. Adjusted effects of 10y increments in the proxies (or 10g increment in cumulative OCS dose) on odds of remission at 1 year post biologic initiation

	N	OR	(95% CI)	P-value
Effects of proxies on 2 domain remission				
Duration of asthma (per 10y)	3418	0.935	(0.922, 0.947)	<0.001
Duration of severe asthma (per 10y)	2258	0.885	(0.793, 0.987)	0.029
Time with lung impairment (per 10y)	940	0.616	(0.457, 0.831)	0.002
Time with frequent exacerbations (per 10y)	968	0.756	(0.618, 0.926)	0.007
Cumulative OCS dose (per 10g)	950	0.737	(0.630, 0.863)	<0.001
Effects of proxies on 3 domain remission (asthma control)				
Duration of asthma (per 10y)	1468	0.851	(0.830, 0.873)	<0.001
Duration of severe asthma (per 10y)	865	0.756	(0.718, 0.795)	<0.001
Time with lung impairment (per 10y)	400	0.327	(0.185, 0.579)	<0.001
Time with frequent exacerbations (per 10y)	162	0.654	(0.324, 1.319)	0.235
Cumulative OCS dose (per 10g)	161	0.484	(0.232, 1.007)	0.052

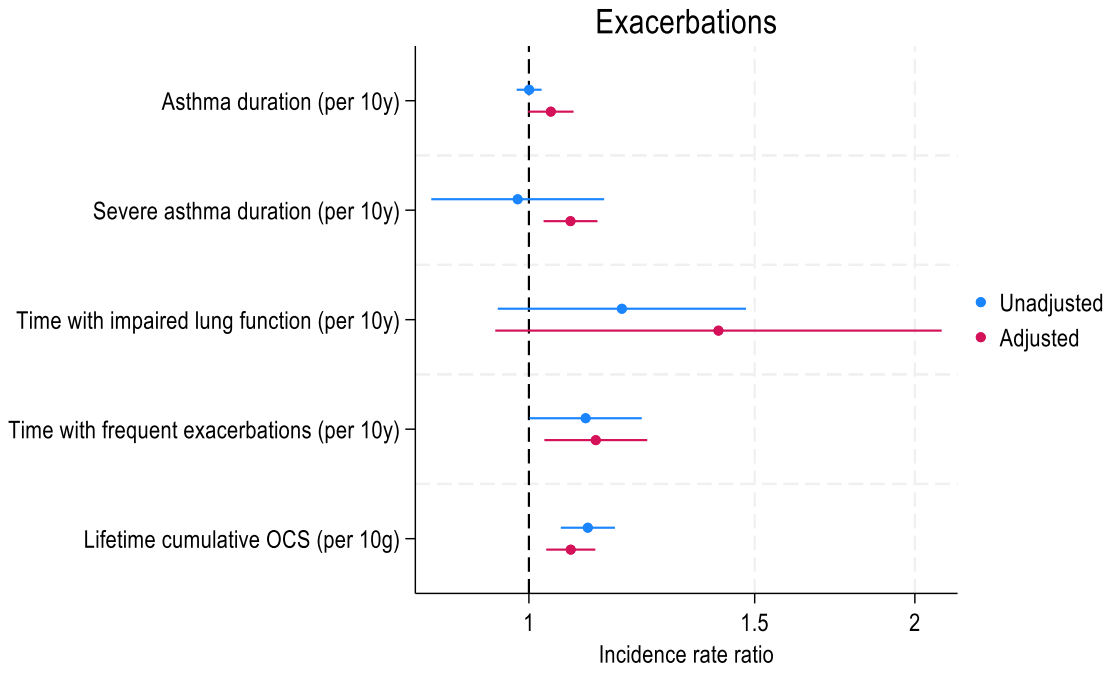
Effects of proxies on 3 domain remission (lung function)				
Duration of asthma (per 10y)	1800	0.857	(0.838, 0.876)	<0.001
Duration of severe asthma (per 10y)	903	0.781	(0.633, 0.964)	0.021
Time with lung impairment (per 10y)	618	0.240	(0.205, 0.280)	<0.001
Time with frequent exacerbations (per 10y)	179	0.427	(0.157, 1.161)	0.095
Cumulative OCS dose (per 10g)	179	0.541	(0.297, 0.983)	0.044

Effects of proxies on 4 domain remission				
Duration of asthma (per 10y)	938	0.766	(0.711, 0.824)	<0.001
Duration of severe asthma (per 10y)	476	0.549	(0.276, 1.095)	0.089
Time with lung impairment (per 10y)	297	0.600	(0.132, 2.715)	0.507
Time with frequent exacerbations (per 10y)	40	Not calculable		
Cumulative OCS dose (per 10g)	40	Not calculable		

Exacerbations

Post biologic incidence rates of exacerbations increased with increasing durations of the proxies after adjusting for pre-biologic rates. The effect of 10 years with severe asthma was greater than the effect of 10 years since first asthma onset.

Figure 14. Associations between the proxies and exacerbation rates in the first year post biologic initiation



Estimates for time with frequent exacerbations and lifetime cumulative OCS are from OPCRD data only.
An incidence rate ratio >1 shows the increase in incidence rate of exacerbations in the first year post biologic initiation with every *n* units increase in the proxy.
Adjusted IRRs were adjusted for age at biologic initiation, sex and baseline exacerbation rate.

For comparisons of the adjusted effects of 10 year/10g increments of all proxies see Table 11 (below).

Table 11. Adjusted effects of 10y increments in the proxies (or 10g increment in cumulative OCS dose) on incidence rate ratios of exacerbations in the first year post biologic initiation

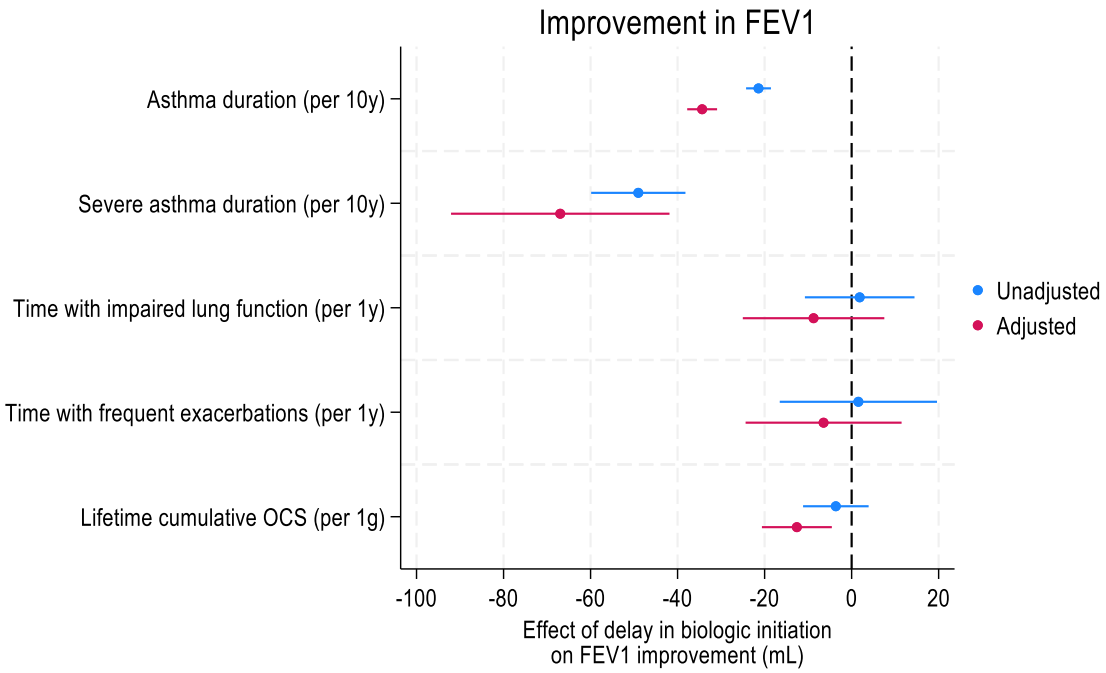
	N	IRR	(95% CI)	P-value
Effects of proxies on exacerbation rates				
Duration of asthma (per 10y)	3377	1.040	(0.999, 1.083)	0.058
Duration of severe asthma (per 10y)	2204	1.078	(1.027, 1.131)	0.002
Time with lung impairment (per 10y)	961	1.406	(0.941, 2.099)	0.096
Time with frequent exacerbations (per 10y)	887	1.128	(1.028, 1.237)	0.011
Cumulative OCS dose (per 10g)	870	1.078	(1.032, 1.127)	0.001

Lung function

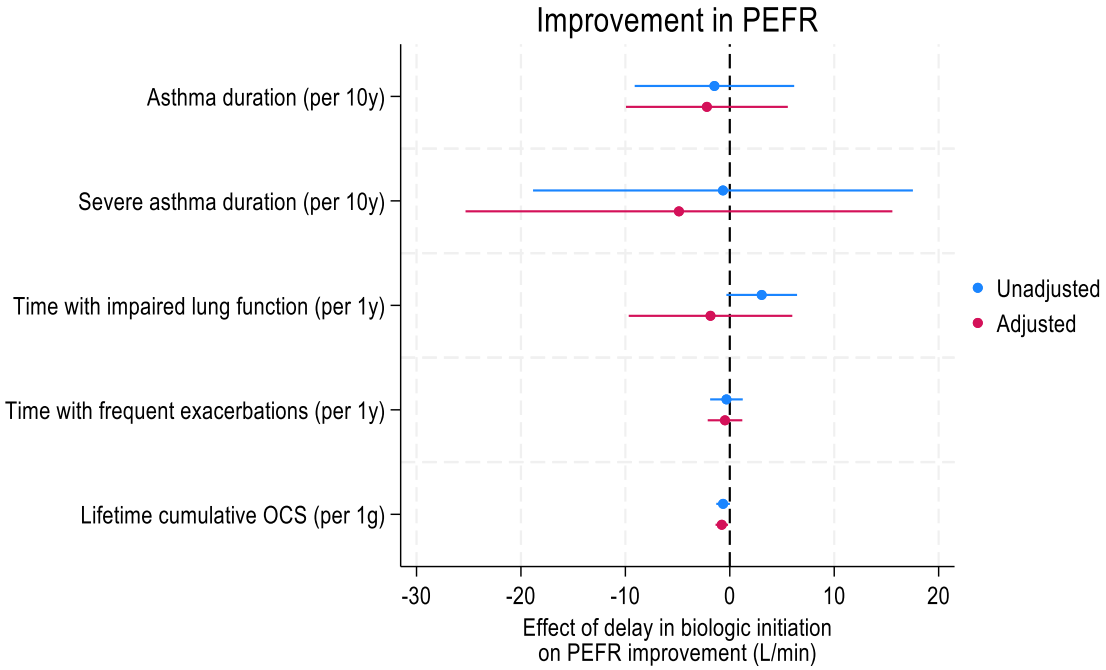
Improvements in lung function were calculated as follow-up FEV1 (nearest to 1 year post-biologic) minus baseline FEV1 (most recent in the last year prior to biologic), and similarly for improvement in PEFR and improvement in percent predicted FEV1 or PEFR.

Post-biologic improvements in lung function reduced as values of the proxies increased. This was particularly evident for the effect of longer durations of severe asthma prior to biologic initiation. The apparent effects of 10 years with asthma or 10 years with severe asthma on lung function improvement were substantial compared to the overall observed mean improvements of 115mL in FEV1, 2.0L/min in PEFR and 4.7% in percent predicted FEV1 or PEFR in this cohort of patients.

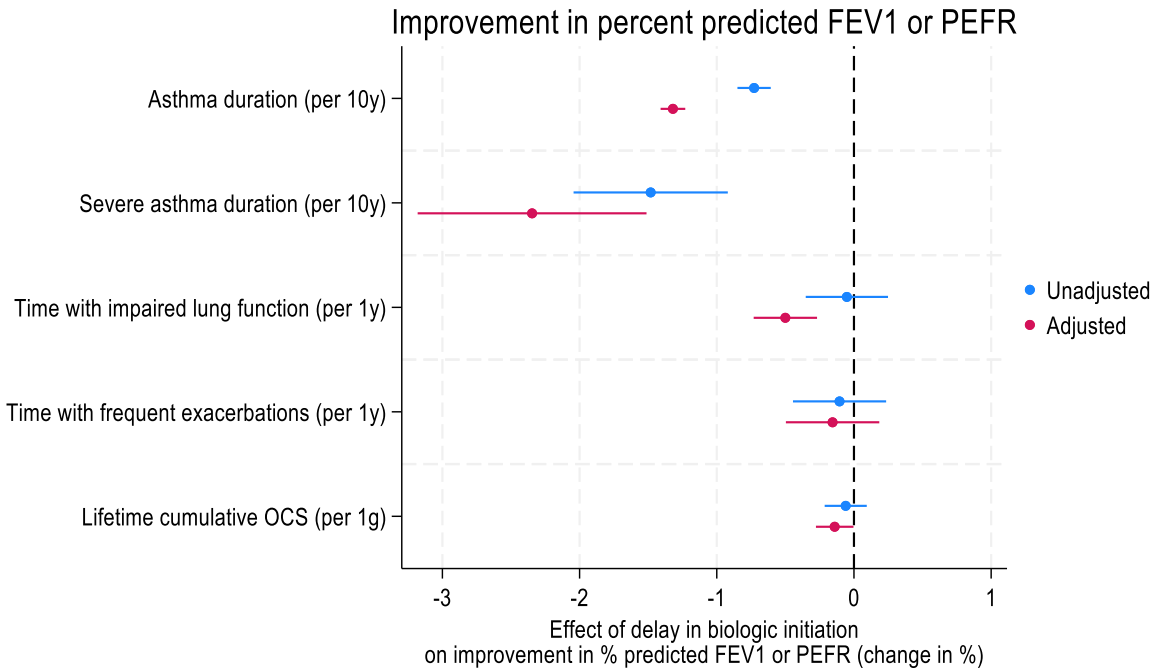
Figure 15. Associations between the proxies and lung function 1 year post biologic initiation



Estimates for time with frequent exacerbations and lifetime cumulative OCS are from OPCRD data only.
The graph shows the effects of the proxies on improvement in FEV1. A negative value indicates that longer durations of the proxies were associated with less improvement compared to baseline in FEV1 after initiation of biologics.
Adjusted effects were adjusted for age at biologic initiation, sex and baseline FEV1
Note: Overall mean improvement in FEV1 post biologic initiation was 115 mL.



Estimates for time with frequent exacerbations and lifetime cumulative OCS are from OPCRD data only.
The graph shows the effects of the proxies on improvement in peak flow rate (OPCRD only). A negative value indicates that longer durations of the proxies were associated with less improvement compared to baseline in PEFR after initiation of biologics.
Adjusted effects were adjusted for age at biologic initiation, sex and baseline PEFR.
Note: Overall mean improvement in PEFR post biologic initiation was 2.0 L/min.



Estimates for time with frequent exacerbations and lifetime cumulative OCS are from OPCRD data only.
The graph shows the effects of the proxies on improvement in percent predicted FEV1 or PEFR. A negative value indicates that longer durations of the proxies were associated with less improvement compared to baseline in percent predicted FEV1 or PEFR after initiation of biologics.
Adjusted effects were adjusted for age at biologic initiation, sex and baseline percent predicted FEV1 or PEFR.
Note: Overall mean improvement in % predicted FEV1 or PEFR was post biologic initiation was 4.7%.

Table 12. Adjusted effects of 10y increments in the proxies (or 10g increment in cumulative OCS dose) on improvements in lung function 1 year post biologic initiation

	N	Effect	(95% CI)	P-value
Effects of proxies on improvement in FEV1		delta mL		
Duration of asthma (per 10y)	2531	-34	(-38, -31)	<0.001
Duration of severe asthma (per 10y)	1434	-67	(-92, -42)	<0.001
Time with lung impairment (per 10y)	1010	-87	(-250, 75)	0.292
Time with frequent exacerbations (per 10y)	68	-64	(-244, 115)	0.475
Cumulative OCS dose (per 10g)	68	-126	(-206, -46)	0.003

Effects of proxies on improvement in PEFR		delta L/min		
Duration of asthma (per 10y)	112	-2.2	(-9.9, 5.6)	0.576
Duration of severe asthma (per 10y)	113	-4.9	(-25.3, 15.6)	0.638
Time with lung impairment (per 10y)	20	-18.5	(-96.8, 59.9)	0.623
Time with frequent exacerbations (per 10y)	113	-4.6	(-21.2, 12.0)	0.583
Cumulative OCS dose (per 10g)	113	-7.7	(-13.7, -1.7)	0.012

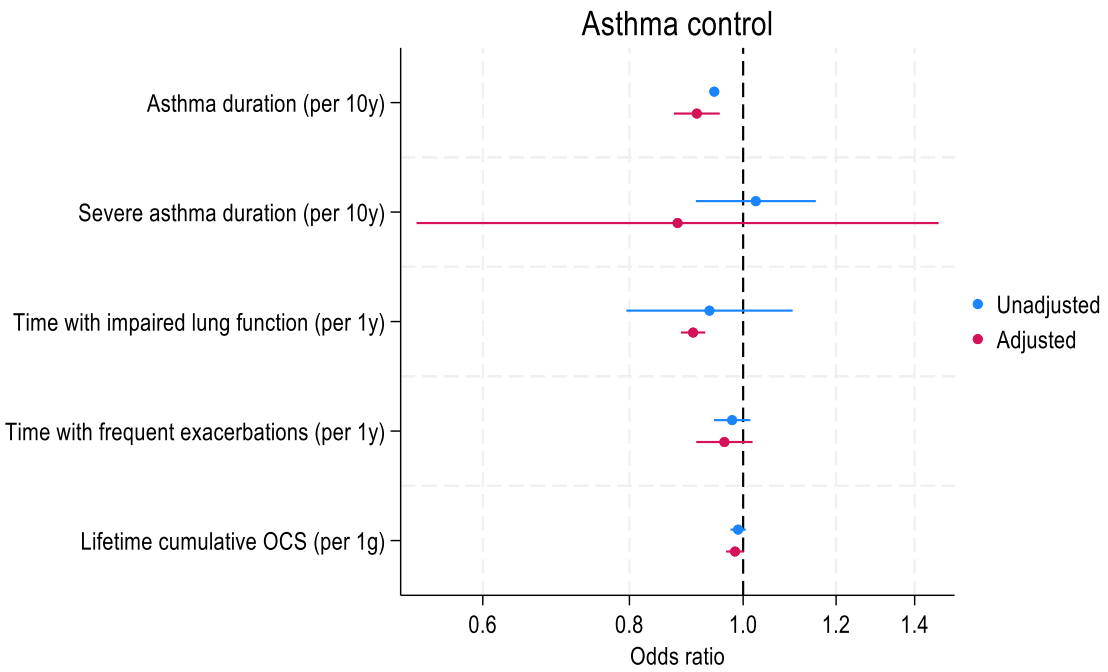
Effects of proxies on improvement in % predicted FEV1 or PEFR		delta %		
Duration of asthma (per 10y)	2602	-1.32	(-1.41, -1.23)	<0.001
Duration of severe asthma (per 10y)	1542	-2.35	(-3.18, -1.51)	<0.001
Time with lung impairment (per 10y)	1035	-5.00	(-7.31, -2.69)	<0.001
Time with frequent exacerbations (per 10y)	181	-1.56	(-4.96, 1.85)	0.368
Cumulative OCS dose (per 10g)	181	-1.41	(-2.77, -0.04)	0.044

Asthma control

Asthma control was treated as a binary outcome: partial / well controlled vs uncontrolled, in line with the treatment of asthma control for determining remission status.

The point estimates all suggested poorer odds of achieving well / partially controlled asthma post biologic treatment with longer durations of the proxies.

Figure 16. Associations between the proxies and asthma control 1 year post biologic initiation



Estimates for time with frequent exacerbations and lifetime cumulative OCS are from OPCRD data only.
Adjusted effects were adjusted for age at biologic initiation, sex and baseline asthma control (well/partial vs uncontrolled)

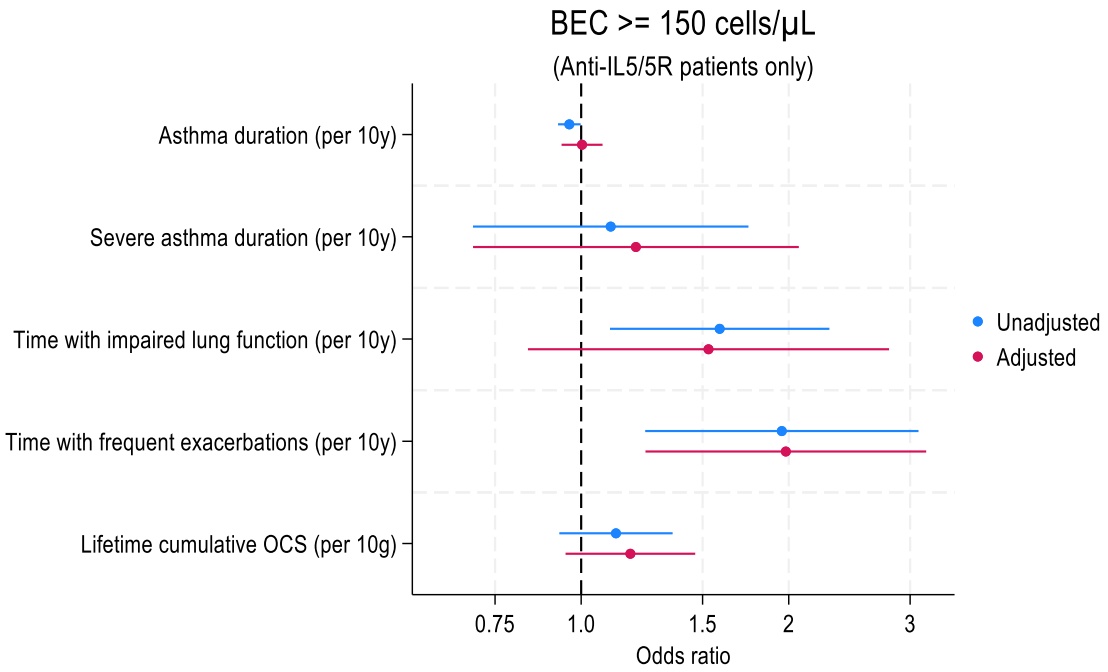
Table 13. Adjusted effects of 10y increments in the proxies (or 10g increment in cumulative OCS dose) on the odds of achieving well / partially controlled asthma 1 year post biologic initiation

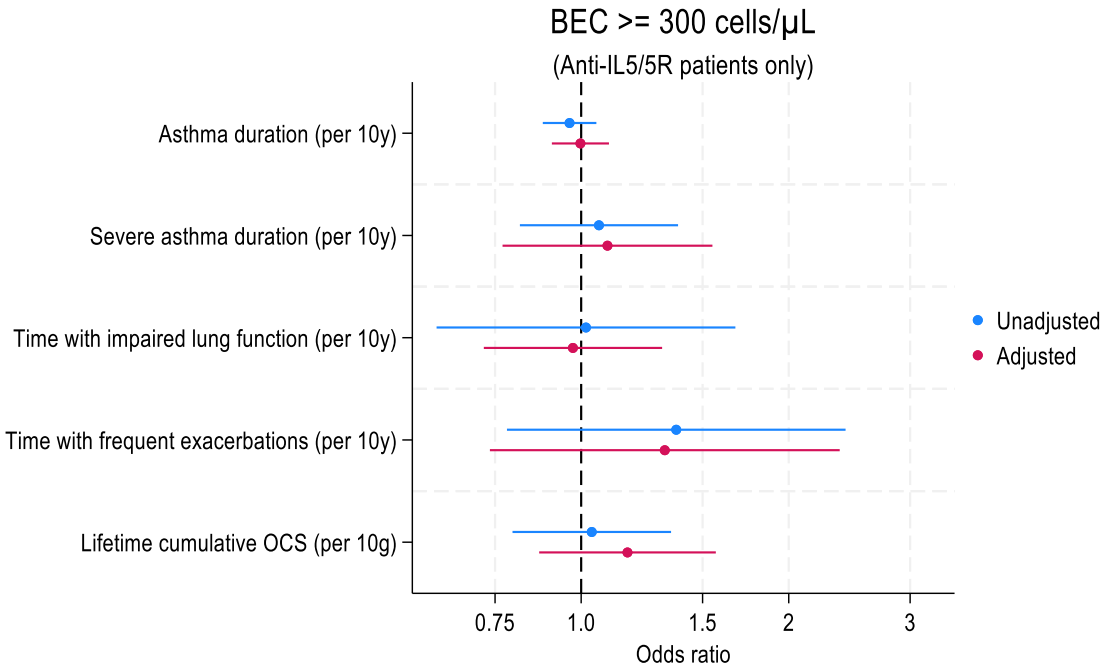
	N	OR	(95% CI)	P-value
Effects of proxies on asthma control				
Duration of asthma (per 10y)	1939	0.913	(0.873, 0.955)	<0.001
Duration of severe asthma (per 10y)	1118	0.879	(0.527, 1.468)	0.623
Time with lung impairment (per 10y)	529	0.375	(0.295, 0.476)	<0.001
Time with frequent exacerbations (per 10y)	164	0.692	(0.398, 1.203)	0.192
Cumulative OCS dose (per 10g)	163	0.853	(0.715, 1.016)	0.075

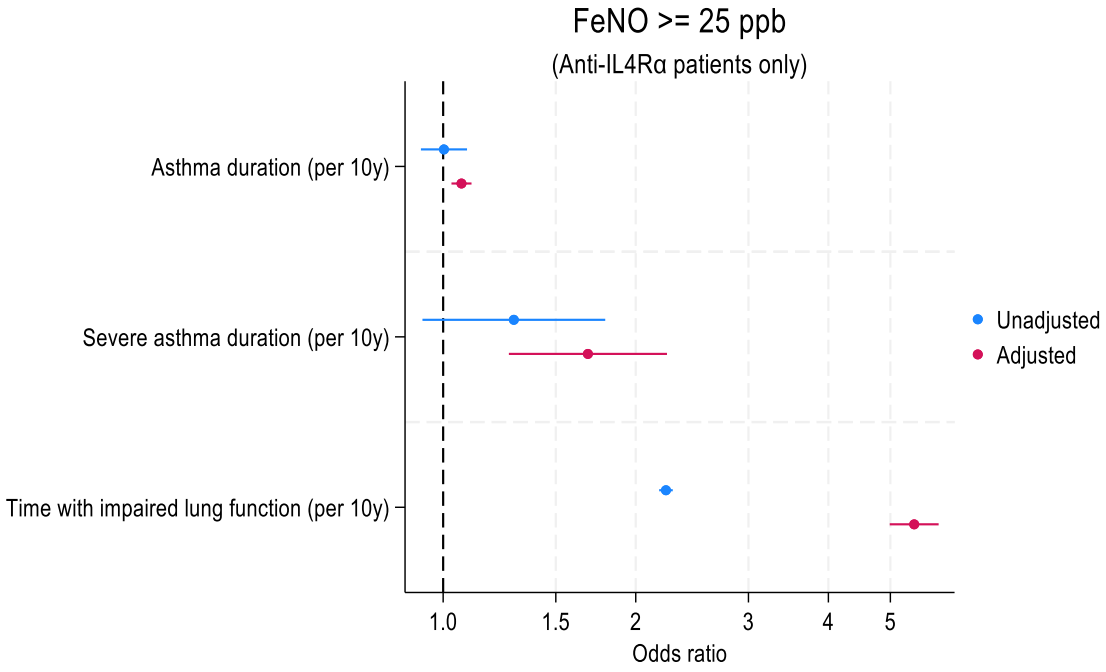
Biomarkers

The odds of having high values of the biomarkers (BEC and FeNO) 1 year post biologic initiation increased with increasing values of the proxies, although the odds of having BEC greater than or equal to the higher cut-off of 300 cells/μL were not strongly related to the duration of the proxies.

Figure 17. Associations between the proxies and biomarkers 1 year post biologic initiation







Estimates for time with frequent exacerbations and lifetime cumulative OCS are from OPCRD data only.
Adjusted effects were adjusted for age at biologic initiation, sex and baseline BEC or FeNO (as binary variables, above or below the same cut-offs).
Note: Only 2 anti-IL4Rα patients in OPCRD had follow-up FeNO data therefore proxies only available in OPCRD are not shown.

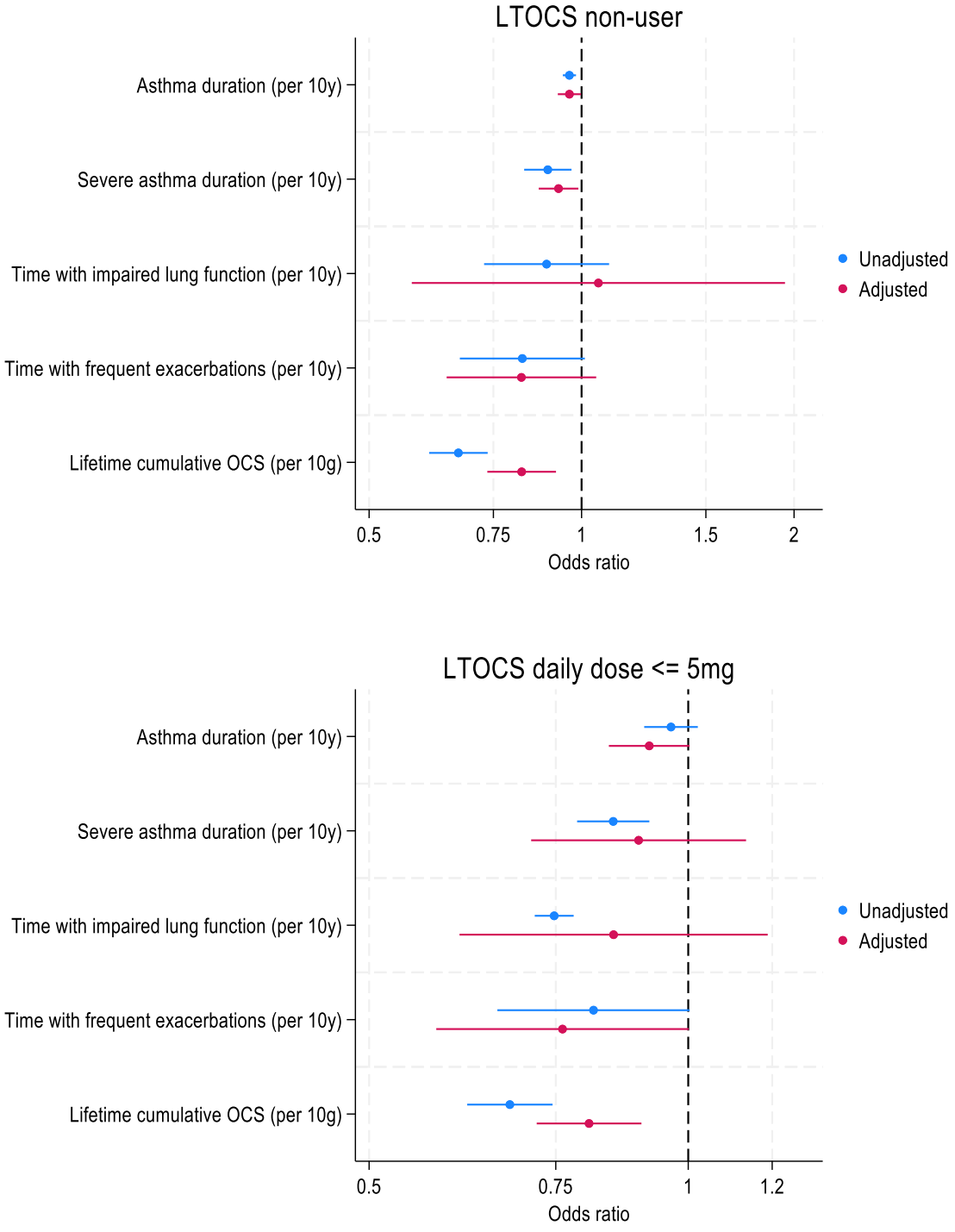
Table 14. Adjusted effects of 10y increments in the proxies (or 10g increment in cumulative OCS dose) on the odds of having high levels of the biomarkers (BEC and FeNO) 1 year post biologic initiation

	N	OR	(95% CI)	P-value
Effects of proxies on odds of BEC >=150 cells/µL				
Duration of asthma (per 10y)	2096	1.003	(0.937, 1.074)	0.935
Duration of severe asthma (per 10y)	1094	1.201	(0.697, 2.068)	0.510
Time with lung impairment (per 10y)	492	1.530	(0.837, 2.796)	0.167
Time with frequent exacerbations (per 10y)	169	1.981	(1.240, 3.165)	0.004
Cumulative OCS dose (per 10g)	164	1.179	(0.949, 1.464)	0.137
Effects of proxies on odds of BEC >=300 cells/µL				
Duration of asthma (per 10y)	2096	0.997	(0.907, 1.097)	0.959
Duration of severe asthma (per 10y)	1094	1.092	(0.769, 1.550)	0.623
Time with lung impairment (per 10y)	492	0.973	(0.722, 1.310)	0.856
Time with frequent exacerbations (per 10y)	163	1.322	(0.737, 2.371)	0.349
Cumulative OCS dose (per 10g)	158	1.167	(0.869, 1.568)	0.304
Effects of proxies on odds of FeNO >=25 ppb				
Duration of asthma (per 10y)	267	1.068	(1.030, 1.107)	<0.001
Duration of severe asthma (per 10y)	120	1.684	(1.267, 2.238)	<0.001
Time with lung impairment (per 10y)	95	5.447	(4.988, 5.949)	<0.001
Time with frequent exacerbations (per 10y)	.	.	. .	.
Cumulative OCS dose (per 10g)	.	.	. .	.

Oral corticosteroid (OCS) use

The odds of being a non-user of LTOCS at 1 year post biologic (no use or stopping within the follow-up year) were reduced in patients with greater duration of the proxies. This was particularly evident for patients with higher cumulative lifetime dose of OCS. The odds of having a daily LTOCS dose <=5 mg at follow-up followed a similar pattern. This may be related to prescribing habits of the treating physicians and/or patients with high cumulative doses being prescribed LTOCS for purposes other than to control their asthma.

Figure 18. Associations between the proxies and LTOCS use 1 year post biologic initiation



Estimates for time with frequent exacerbations and lifetime cumulative OCS are from OPCRD data only.
Adjusted effects were adjusted for age at biologic initiation, sex and baseline LTOCS use (use within the previous year (y/n) or daily dose <=5mg (y/n) within the previous year)

Table 15. Adjusted effects of 10y increments in the proxies (or 10g increment in cumulative OCS dose) on the odds of being a non-user of LTOCS or of having a daily dose of LTOCS <=5mg, 1 year post biologic initiation

	N	OR	(95% CI)	P-value
Effects of proxies on LTOCS non-use				
Duration of asthma (per 10y)	7498	0.961	(0.925, 0.998)	0.041
Duration of severe asthma (per 10y)	4872	0.928	(0.870, 0.989)	0.023
Time with lung impairment (per 10y)	1408	1.056	(0.575, 1.942)	0.860
Time with frequent exacerbations (per 10y)	1009	0.822	(0.644, 1.049)	0.115
Cumulative OCS dose (per 10g)	991	0.822	(0.735, 0.920)	0.001
Effects of proxies on LTOCS daily dose (<=5mg /day)				
Duration of asthma (per 10y)	6491	0.919	(0.842, 1.003)	0.058
Duration of severe asthma (per 10y)	4309	0.898	(0.711, 1.134)	0.365
Time with lung impairment (per 10y)	1265	0.850	(0.608, 1.188)	0.343
Time with frequent exacerbations (per 10y)	1009	0.761	(0.579, 1.001)	0.051
Cumulative OCS dose (per 10g)	991	0.806	(0.720, 0.903)	<0.001

Association between biologic accessibility score (BACS) and proportion of positive outcomes

Outcomes were dichotomised using commonly used cutoffs so that the proportion of patients achieving a positive outcome in each setting could be related to the highest BACS within that country. In principle, higher BACS (easier access) should be related to more patients achieving a positive outcome following biologic initiation.

BACS and remission

Various definitions of remission one year after biologic initiation were investigated.

2-domain – no LTOCS use **and** no exacerbations

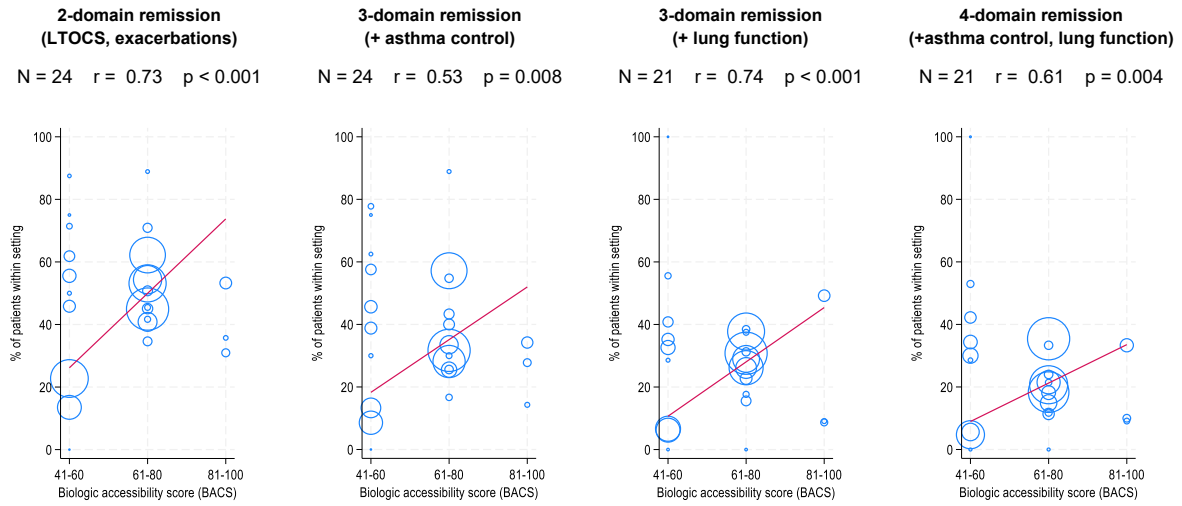
3-domain – no LTOCS use **and** no exacerbations **and** partly or well-controlled asthma

- no LTOCS use **and** no exacerbations **and** no lung function impairment (ppFEV1 or PEFR ≥80%)

4-domain – no LTOCS use **and** no exacerbations **and** partly or well-controlled asthma **and** no lung function impairment (ppFEV1 or PEFR ≥80%)

Easier access to biologics was associated with a higher probability of achieving remission.

Figure 19. Correlation between BACS and remission



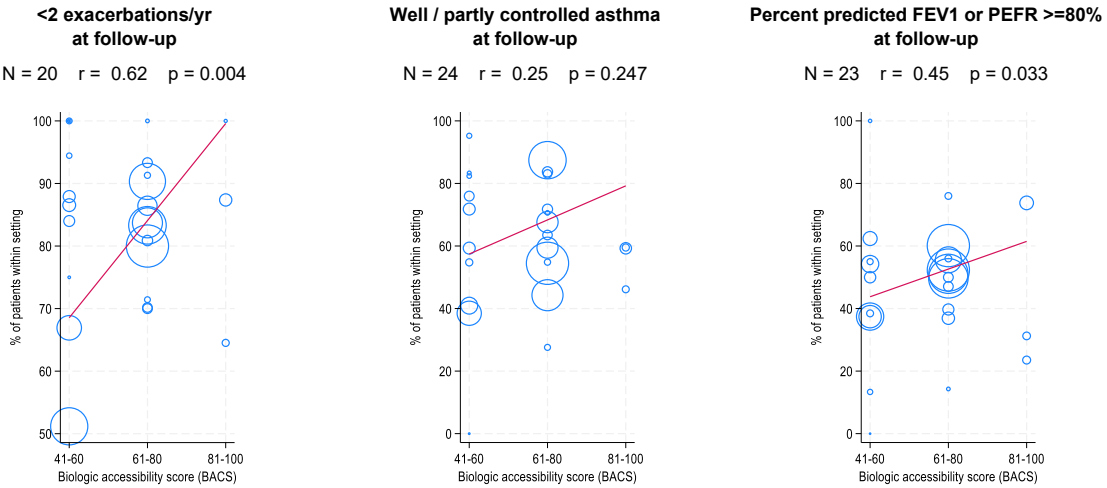
BACS - 41-60: Moderately difficult; 61-80: Neither easy nor difficult; 81-100: Easy. Setting = data-source x country/centre
Size of the circles indicates the number of patients in each setting. Correlations weighted using 1/var(proportion) within each setting to apply greater weight to the results with greatest precision.

BACS and clinical outcomes

Associations between BACS and selected clinical outcomes one year after biologic initiation were investigated.

Higher BACS were associated with a greater probability of having <2 exacerbations at follow-up and not having lung function impairment. There was also a positive association between ease of access and the probability of having partly or well controlled asthma at follow-up, though this was not statistically significant.

Figure 20. Correlation between BACS and clinical outcomes (exacerbations, asthma control and lung function impairment)

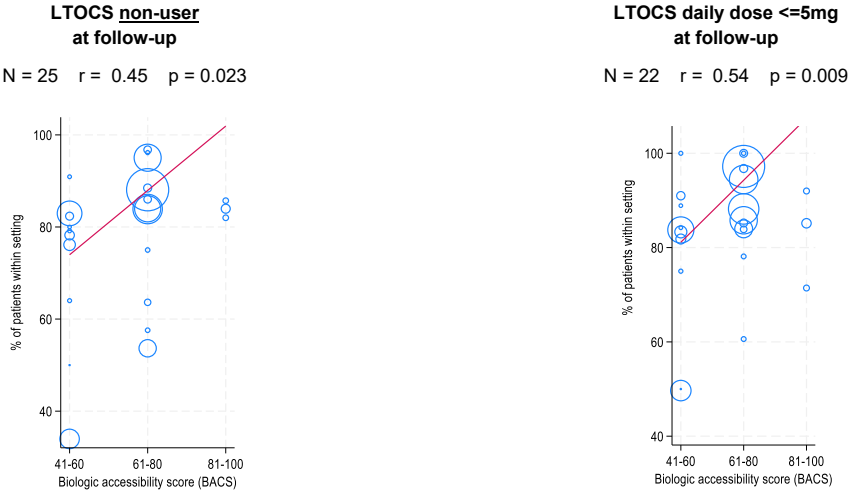


BACS - 41-60: Moderately difficult; 61-80: Neither easy nor difficult; 81-100: Easy. Setting = data-source x country/centre
Size of the circles indicates the number of patients in each setting. Correlations weighted using 1/var(proportion) within each setting to apply greater weight to the results with greatest precision.

BACS and LTOCS use

Both LTOCS use and the probability of having a mean daily dose <=5mg at follow-up were associated with ease of access to biologics with more favourable outcomes being more common in settings with easier access.

Figure 21. Correlation between BACS and LTOCS use at follow-up



BACS - 41-60: Moderately difficult; 61-80: Neither easy nor difficult; 81-100: Easy. Setting = data-source x country/centre
Size of the circles indicates the number of patients in each setting. Correlations weighted using 1/var(proportion) within each setting to apply greater weight to the results with greatest precision.

Summary for Objective 2

Overall, there was a clear pattern of longer duration of the proxies being associated with poorer outcomes, even after adjusting for baseline levels of the outcomes. For all outcomes, point estimates of the adjusted effects of 10 years with severe asthma were greater than the equivalent effect of 10 years asthma, suggesting a more rapid deterioration in reversible symptoms during the more severe stages of the disease. The negative effects of 10 years with frequent exacerbations could only be estimated for the OPCRD population but was comparable to severe asthma for exacerbations, asthma control, lung function, BEC, and LTOCS use, and stronger than severe asthma for the odds of achieving remission (comparing OPCRD only results in Appendix 2).

In general, consistent associations were seen across the three data sources (CHRONICLE, ISAR and OPCRD) (see Appendix 2). However, there were considerable differences between the results from the different data sources for time with lung function impairment, perhaps because this was unavailable or very short for many of the patients in ISAR and CHRONICLE and was only available for 19% of patients in OPCRD. These inconsistencies and small sample sizes led to wide confidence intervals in the combined sources results (presented in this section) for the effects of time with lung function impairment on outcomes. The results for the associations between the proxies and BEC were also inconsistent between the data sources, the combined results being dominated by the effects seen in OPCRD.

The cumulative OCS dose was only available for OPCRD though increasing levels of this proxy showed statistically significant associations with poorer outcomes for remission, exacerbations, lung function, and OCS use at follow-up.

The analysis of correlations of proportions of patients with good outcomes and ease of obtaining biologics (as measured by BACS) showed positive associations in all cases, as might be hypothesized. Using weighted correlations, this effect was statistically significant for remission, exacerbations, lung function and LTOCS use.

8.0 Discussion and conclusions

The proxies of asthma duration and severe asthma duration were the most widely available, being defined for 76% and 44% of patients respectively. Lung function impairment/obstruction was only available for 14% of patients, with large differences in the distribution of durations between CHRONICLE, ISAR and OPCRD. In both CHRONICLE and ISAR a large proportion of patients with data did not have impairment at the time of initiating biologics. It is possible that many of those who were excluded did have impairment, but the time of first occurrence (and hence the duration) could not be determined. Time with frequent exacerbations and total OCS dose were available for almost all patients in OPCRD but not for either of the other data sources.

OCS is not strictly time based like the other proxies, but this measure may provide an interesting integration of both duration and severity of asthma, not as well captured by any of the other proxies.

It was notable that time with severe asthma was associated with stronger effects than time with non-severe asthma. Other proxies, which suggested that severe symptoms had begun (e.g. lung function impairment or total OCS dose), were also associated with more rapidly reducing opportunity for good health outcomes compared to accrued time since asthma was first diagnosed. This supports the notion that early initiation of biologics, once high-risk or severe asthma has been detected, is vital to capitalise on the opportunity to treat asthma whilst symptoms are still largely reversible, and would be highly beneficial for the majority of patients. Earlier initiation of biologics was also associated with a greater chance of being a non-user of LTOCS one year after initiation, which would also reduce the risk of developing other OCS related comorbidities[26, 27, 28].

In general, increasing values of all of the proxies of timing or with more delay of initiating biologics were associated with poorer outcomes, or poorer probability of a good outcome, after initiating biologic therapy. This was the case even after adjusting for baseline levels of the outcomes, suggesting that this was not simply a case of poorer prognosis in patients with poorer health at the time of biologic initiation. Although the proxies did not show strong statistical correlation with each other, it appears that all were related to a worsening of severe asthma and a receding possibility of successful treatment as a patient continues with severe symptoms.

Previous studies have shown an association between longer asthma duration prior to starting biologics and the effectiveness of biologic treatment[16, 29, 30]. However, there is relatively little evidence of how opportunities for successful treatment are affected by the duration of severe asthma symptoms prior to biologic initiation. This study has shown that the chance of successful treatment with biologics lessens after a patient begins to exhibit signs of severe asthma, or conversely that greater benefit from the treatment can be achieved by earlier intervention.

In this study it was not possible to define the start point of various symptoms or treatments for many of the patients (such as the start of high dose ICS, or the start of lung function impairment), particularly in ISAR and CHRONICLE, because information about their asthma prior to being referred to a specialist was often captured retrospectively within the relevant systems or estimated. Long-term recording of patients' symptoms and treatment from their time of first being diagnosed with asthma would provide valuable information to study the most appropriate timing for treatment(s) to begin.

9.0 Limitation(s)

Pre-biologic data is limited within ISAR and CHRONICLE, which limits the possibility to determine accurately when different criteria were first reached (e.g. the earliest ever date when a patient had a pre-biologic percent predicted FEV_1 <80%). This leads to some biases as to which patients can have the proxies defined and hence which patients are included in the analyses. This does not necessarily mean there is a bias in the observed associations between proxies and outcomes. For example, we may over-represent patients with short durations of asthma in the sample but the outcomes for patients with long durations are unaffected by this. However, a narrow range of values of the proxies, particularly within ISAR and CHRONICLE can lead to wide confidence intervals for the magnitude of the effects.

The CHRONICLE, ISAR and OPCRD datasets generally showed similar effects when analysed individually and have been combined to increase the overall sample size, and hence power of the study. The study draws credibility from including a large number of severe asthma patients from a range of data sources. However, patients enter these three datasets through different criteria and the methods of recording data differ. The effects seen in one dataset are not always exactly the same in the others. Small sample sizes within each dataset limit the possibilities to study each of these populations separately in greater detail.

BACS can vary over time, as new biologics are introduced and as countries change their licensing or reimbursement criteria. The scores used in this study were from 2021, which is equal to the median date for patients initiating a biologic in OPCRD but slightly later than the median dates for the patients in ISAR and CHRONICLE (end of 2019 and end of 2018 respectively). Ease of access may have been greater or less at the time individual patients initiated their biologics. As the BACS were only available at national level it is also not possible to allow for other potential confounders in these analyses.

10.0 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, will form the Advisory Group.

No	Name	Country / Institution
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13.0 Appendices

Appendix 1: Baseline characteristics of patients included in Objective 1

	CHRONICLE (N=2,975)	ISAR (N=10,528)	OPCRD (N=1,178)	Total (N=14,681)
Biologic initiation date (median)	15dec2018 (min-max: 06jun2003-15jan2024)	31jul2019 (min-max: 01jan2004-23dec2024)	14sep2021 (min-max: 29mar2007-30aug2024)	17jul2019 (min-max: 06jun2003-23dec2024)
Age (years)	53.3 (13.9)	53.0 (14.2)	51.5 (15.5)	53.0 (14.3)
Female	1,996 (67.1%)	6,646 (63.1%)	714 (60.6%)	9,356 (63.7%)
Body mass index (kg/m^2) at biologic initiation	33.2 (8.7)	28.2 (6.3)	30.8 (7.6)	29.5 (7.3)
Underweight (BMI<18.5)	20 (0.7%)	192 (1.9%)	16 (1.4%)	228 (1.6%)
Normal weight (BMI 18.5 to <25)	408 (13.9%)	3,221 (31.6%)	240 (20.6%)	3,869 (27.0%)
Overweight (BMI 25 to <30)	775 (26.4%)	3,470 (34.0%)	357 (30.6%)	4,602 (32.2%)
Obese (BMI >=30)	1,733 (59.0%)	3,325 (32.6%)	553 (47.4%)	5,611 (39.2%)
Ethnicity				
Caucasian	2,226 (77.6%)	7,355 (79.3%)	1,032 (87.6%)	10,613 (79.7%)
Asian	54 (1.9%)	582 (6.3%)	69 (5.9%)	705 (5.3%)
African	509 (17.7%)	157 (1.7%)	18 (1.5%)	684 (5.1%)
Mixed	0 (0.0%)	466 (5.0%)	12 (1.0%)	478 (3.6%)
Other	81 (2.8%)	712 (7.7%)	47 (4.0%)	840 (6.3%)
Smoking status at biologic initiation				
Never smoker	1,915 (64.4%)	7,103 (68.7%)	695 (59.0%)	9,713 (67.1%)
Ex-smoker	893 (30.0%)	2,888 (27.9%)	408 (34.6%)	4,189 (28.9%)
Current smoker	164 (5.5%)	343 (3.3%)	75 (6.4%)	582 (4.0%)
Age at asthma onset (years)	30 [10, 48]	30 [14, 44]	27 [9, 43]	30 [12, 45]
Allergen test results				
Negative	2,361 (79.4%)	2,390 (41.9%)	0 (0.0%)	4,751 (54.7%)
Positive	614 (20.6%)	3,314 (58.1%)	0 (0.0%)	3,928 (45.3%)
Asthma control				
Uncontrolled	235 (73.0%)	2,234 (64.5%)	313 (66.2%)	2,782 (65.4%)
Partly controlled	57 (17.7%)	731 (21.1%)	114 (24.1%)	902 (21.2%)
Well controlled	30 (9.3%)	497 (14.4%)	46 (9.7%)	573 (13.5%)
Exacerbations in past year	1.6 (1.7)	2.5 (2.8)	3.3 (2.7)	2.6 (2.8)
0	156 (30.8%)	1,559 (26.5%)	110 (9.3%)	1,825 (24.1%)
1-2	223 (44.1%)	2,036 (34.6%)	459 (39.0%)	2,718 (35.9%)
3-4	96 (19.0%)	1,291 (22.0%)	298 (25.3%)	1,685 (22.3%)
5+	31 (6.1%)	994 (16.9%)	311 (26.4%)	1,336 (17.7%)
Percent predicted FEV1/PEFR	77.3 (22.0)	75.4 (22.3)	71.0 (21.8)	75.2 (22.2)
<60%	134 (22.8%)	1,485 (24.8%)	162 (30.5%)	1,781 (25.0%)
>=60 - <80%	193 (32.9%)	1,959 (32.7%)	180 (33.9%)	2,332 (32.8%)
>=80%	260 (44.3%)	2,550 (42.5%)	189 (35.6%)	2,999 (42.2%)

FEV1/FVC ratio	0.74 [0.65, 0.81]	0.69 [0.60, 0.77]	0.69 [0.59, 0.78]	0.70 [0.60, 0.78]
<0.5	29 (4.9%)	641 (10.5%)	25 (11.1%)	695 (10.0%)
>=0.5 - <0.7	191 (32.3%)	2,525 (41.3%)	89 (39.4%)	2,805 (40.4%)
>=0.7	371 (62.8%)	2,954 (48.3%)	112 (49.6%)	3,437 (49.5%)
Lung function impairment/obstruction[1]	485 (65.5%)	4,966 (76.3%)	818 (92.0%)	6,269 (77.0%)
Highest blood eosinophil count (cells/µL)	311 [154, 582]	500 [250, 830]	700 [450, 1100]	500 [260, 850]
<100	132 (13.0%)	372 (5.2%)	5 (0.4%)	509 (5.5%)
100- <300	348 (34.3%)	1,578 (22.1%)	101 (8.9%)	2,027 (21.8%)
300- <500	218 (21.5%)	1,573 (22.0%)	197 (17.4%)	1,988 (21.4%)
>=500	316 (31.2%)	3,622 (50.7%)	826 (73.2%)	4,764 (51.3%)
Latest total serum IgE (IU/mL)	137 [43, 375]	177 [66, 456]	318 [84, 880]	173 [62, 455]
<75	387 (35.9%)	1,561 (27.5%)	59 (22.7%)	2,007 (28.6%)
>=75	690 (64.1%)	4,112 (72.5%)	201 (77.3%)	5,003 (71.4%)
Latest FeNO (ppb)	22 [12, 50]	33 [17, 65]	33 [20, 51]	33 [16, 64]
<25	185 (52.1%)	1,734 (38.7%)	12 (42.9%)	1,931 (39.7%)
>=25	170 (47.9%)	2,744 (61.3%)	16 (57.1%)	2,930 (60.3%)
Allergic rhinitis	1,937 (65.1%)	5,190 (56.7%)	642 (54.5%)	7,769 (58.4%)
Chronic rhinosinusitis	707 (23.8%)	5,613 (54.2%)	413 (35.1%)	6,733 (46.4%)
Nasal polyposis	312 (10.5%)	3,615 (34.9%)	258 (21.9%)	4,185 (28.9%)
Eczema/atopic dermatitis	168 (5.6%)	1,455 (14.3%)	293 (24.9%)	1,916 (13.4%)
LTOCS user in past year	610 (20.5%)	2,278 (30.9%)	379 (32.2%)	3,267 (28.4%)
LTOCS average daily dose in past year (mg)[2]	0.7 (3.2)	2.2 (5.9)	2.4 (4.9)	1.8 (5.3)
LTOCS average daily dose in past year in users (mg)[2]	7.1 (7.6)	8.7 (9.1)	7.4 (6.2)	8.3 (8.6)
Biologic class				
Anti-IL4alpha	416 (14.0%)	1,480 (14.1%)	145 (12.3%)	2,041 (13.9%)
Anti-IL5/5R	1,209 (40.6%)	5,346 (50.8%)	689 (58.5%)	7,244 (49.3%)
Anti-IgE	1,271 (42.7%)	3,433 (32.6%)	292 (24.8%)	4,996 (34.0%)
Anti-TSLP	79 (2.7%)	269 (2.6%)	52 (4.4%)	400 (2.7%)
Biologic name				
Anti-IL4R alpha: Dupilumab	416 (14.0%)	1,480 (14.1%)	145 (12.3%)	2,041 (13.9%)
Anti-IL5: Mepolizumab	622 (20.9%)	3,455 (32.9%)	336 (28.5%)	4,413 (30.1%)
Anti-IL5: Reslizumab	42 (1.4%)	114 (1.1%)	2 (0.2%)	158 (1.1%)
Anti-IL5R: Benralizumab	545 (18.3%)	1,759 (16.7%)	351 (29.8%)	2,655 (18.1%)
Anti-IgE: Omalizumab	1,271 (42.7%)	3,433 (32.7%)	292 (24.8%)	4,996 (34.1%)
Anti-TSLP: Tezepelumab	79 (2.7%)	269 (2.6%)	52 (4.4%)	400 (2.7%)
ICS use in past year	1,826 (98.5%)	8,605 (98.5%)	1,178 (100.0%)	11,609 (98.6%)
LABA use in past year	1,833 (98.1%)	8,109 (93.6%)	1,161 (98.6%)	11,103 (94.8%)
LAMA use in past year	753 (80.0%)	4,449 (63.6%)	726 (61.6%)	5,928 (65.0%)
LTRA use in past year	1,324 (90.9%)	4,531 (63.7%)	350 (29.7%)	6,205 (63.7%)
Theophylline use in past year	47 (11.4%)	507 (9.6%)	264 (22.4%)	818 (11.9%)
Macrolide use in past year	80 (19.2%)	798 (14.9%)	11 (0.9%)	889 (12.8%)

Notes:

Mean (SD), median [IQR], or n (%) are shown

[1] FEV1 or PEFR < 80%, and/or FEV1/FVC ratio < 0.70 before biologic initiation

[2] Prednisolone equivalent

Appendix 2: Associations between proxies and outcomes for individual data sources

The tables in this appendix show the adjusted effects of the proxies on outcomes within each of the 3 data sources (CHRONICLE, ISAR and OPCRD) separately. The outcomes were adjusted for age, sex and baseline level of the outcome in each case and models for ISAR included country as a random effect.

Remission

Proxy (predictor)	Data source	N	OR	(95% CI)	P-value
Effects of proxies on 2 domain remission					
Duration of asthma (per 10y)	CHRONICLE	354	0.916	(0.813, 1.033)	0.154
	ISAR	2107	0.931	(0.863, 1.003)	0.061
	OPCRD	957	0.964	(0.862, 1.078)	0.521
Duration of severe asthma (per 10y)	CHRONICLE	337	0.895	(0.671, 1.194)	0.451
	ISAR	955	0.991	(0.720, 1.364)	0.955
	OPCRD	966	0.812	(0.648, 1.016)	0.069
Time with lung impairment (per 10y)	CHRONICLE	71	0.001	(0.000, 5.340)	0.118
	ISAR	677	0.542	(0.285, 1.030)	0.062
	OPCRD	192	0.743	(0.445, 1.243)	0.258
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	968	0.756	(0.618, 0.926)	0.007
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	950	0.737	(0.630, 0.863)	<0.001
Effects of proxies on 3 domain remission (asthma control)					
Duration of asthma (per 10y)	CHRONICLE	197	0.816	(0.670, 0.995)	0.044
	ISAR	1109	0.860	(0.808, 0.916)	<0.001
	OPCRD	162	0.785	(0.517, 1.190)	0.254
Duration of severe asthma (per 10y)	CHRONICLE	197	0.705	(0.457, 1.087)	0.113
	ISAR	506	0.786	(0.561, 1.100)	0.160
	OPCRD	162	0.780	(0.347, 1.754)	0.547
Time with lung impairment (per 10y)	CHRONICLE	43	0.001	(0.000, 10.287)	0.134
	ISAR	318	0.000	(0.000, 76.438)	0.182

	OPCRD	39	0.335	(0.079, 1.423)	0.138
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	162	0.654	(0.324, 1.319)	0.235
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	161	0.484	(0.232, 1.007)	0.052
Effects of proxies on 3 domain remission (lung function)					
Duration of asthma (per 10y)	CHRONICLE	100	0.819	(0.629, 1.066)	0.138
	ISAR	1522	0.854	(0.783, 0.931)	<0.001
	OPCRD	178	0.994	(0.740, 1.336)	0.970
Duration of severe asthma (per 10y)	CHRONICLE	99	0.736	(0.263, 2.059)	0.559
	ISAR	626	0.719	(0.376, 1.373)	0.317
	OPCRD	178	0.769	(0.355, 1.668)	0.506
Time with lung impairment (per 10y)	CHRONICLE	32	0.000	(0.000, 1285.687)	0.160
	ISAR	547	0.261	(0.099, 0.686)	0.006
	OPCRD	27	0.018	(0.000, 684.656)	0.455
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	179	0.427	(0.157, 1.161)	0.095
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	179	0.541	(0.297, 0.983)	0.044
Effects of proxies on 4 domain remission					
Duration of asthma (per 10y)	CHRONICLE	59	0.513	(0.298, 0.885)	0.016
	ISAR	811	0.786	(0.727, 0.850)	<0.001
	OPCRD	40	0.459	(0.114, 1.845)	0.273
Duration of severe asthma (per 10y)	CHRONICLE	61	1.138	(0.454, 2.850)	0.783
	ISAR	347	0.605	(0.296, 1.236)	0.168
	OPCRD	40	0.119	(0.005, 2.765)	0.185
Time with lung impairment (per 10y)	CHRONICLE	7	N/A	N/A	N/A
	ISAR	262	0.000	(0.000, 6.960)	0.092
	OPCRD	N/A	N/A	N/A	N/A
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A

	OPCRD	40	0.000	(0.000, 0.770)	0.047
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	N/A	N/A	N/A	N/A

N/A: Not applicable due to proxy not available/not computable due to lack of model convergence.

Exacerbations

Proxy (predictor)	Data source	N	IRR	(95% CI)	P-value
Effects of proxies on exacerbation rates					
Duration of asthma (per 10y)	CHRONICLE	339	1.055	(0.972, 1.144)	0.200
	ISAR	2160	1.060	(1.027, 1.094)	<0.001
	OPCRD	878	1.000	(0.949, 1.055)	0.988
Duration of severe asthma (per 10y)	CHRONICLE	323	1.086	(0.924, 1.277)	0.314
	ISAR	996	0.735	(0.505, 1.069)	0.107
	OPCRD	885	1.124	(1.014, 1.246)	0.026
Time with lung impairment (per 10y)	CHRONICLE	69	0.949	(0.117, 7.697)	0.961
	ISAR	716	2.218	(1.484, 3.314)	<0.001
	OPCRD	176	1.196	(0.949, 1.506)	0.129
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	887	1.128	(1.028, 1.237)	0.011
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	870	1.078	(1.032, 1.127)	0.001

Asthma control

Proxy (predictor)	Data source	N	OR	(95% CI)	P-value
Effects of proxies on asthma control (well/partial control)					
Duration of asthma (per 10y)	CHRONICLE	259	0.887	(0.765, 1.029)	0.112
	ISAR	1516	0.934	(0.873, 0.999)	0.048
	OPCRD	164	0.844	(0.659, 1.080)	0.177
Duration of severe asthma (per 10y)	CHRONICLE	258	1.226	(0.827, 1.816)	0.311
	ISAR	696	0.576	(0.402, 0.824)	0.003

	OPCRD	164	0.588	(0.321, 1.078)	0.086
Time with lung impairment (per 10y)	CHRONICLE	52	0.199	(0.000, 156.204)	0.635
	ISAR	437	1.322	(0.017, 100.584)	0.900
	OPCRD	40	0.338	(0.092, 1.248)	0.104
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	164	0.692	(0.398, 1.203)	0.192
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	163	0.853	(0.715, 1.016)	0.075

Lung function

Proxy (predictor)	Data source	N	Effect	(95% CI)	P-value
Effects of proxies on improvement in FEV1			delta mL		
Duration of asthma (per 10y)	CHRONICLE	210	-30	(-62, 2)	0.066
	ISAR	2253	-34	(-44, -23)	<0.001
	OPCRD	68	-77	(-153, -1)	0.046
Duration of severe asthma (per 10y)	CHRONICLE	197	-48	(-131, 36)	0.262
	ISAR	1169	-72	(-132, -13)	0.017
	OPCRD	68	-50	(-221, 122)	0.565
Time with lung impairment (per 10y)	CHRONICLE	65	34	(-844, 913)	0.938
	ISAR	930	-6	(-66, 54)	0.844
	OPCRD	15	-55	(-684, 574)	0.849
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	68	-64	(-244, 115)	0.475
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	68	-126	(-206, -46)	0.003
Effects of proxies on improvement in PEFR			delta L/min		
Duration of asthma (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	112	-2.2	(-9.9, 5.6)	0.576

Duration of severe asthma (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	113	-4.9	(-25.3, 15.6)	0.638
Time with lung impairment (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	20	-18.5	(-96.8, 59.9)	0.623
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	113	-4.6	(-21.2, 12.0)	0.583
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	113	-7.7	(-13.7, -1.7)	0.012
Effects of proxies on improvement in % predicted FEV1 or PEFR			delta %		
Duration of asthma (per 10y)	CHRONICLE	209	-1.11	(-2.23, 0.01)	0.052
	ISAR	2213	-1.33	(-1.70, -0.96)	<0.001
	OPCRD	180	-1.64	(-3.28, -0.01)	0.049
Duration of severe asthma (per 10y)	CHRONICLE	196	-1.45	(-4.16, 1.26)	0.293
	ISAR	1166	-2.59	(-4.95, -0.23)	0.031
	OPCRD	180	-1.75	(-5.96, 2.47)	0.415
Time with lung impairment (per 10y)	CHRONICLE	65	-29.70	(-85.55, 26.16)	0.292
	ISAR	930	-2.96	(-4.73, -1.19)	0.001
	OPCRD	40	-4.01	(-12.70, 4.68)	0.355
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	181	-1.56	(-4.96, 1.85)	0.368
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	181	-1.41	(-2.77, -0.04)	0.044

Biomarkers

Proxy (predictor)	Data source	N	Effect	(95% CI)	P-value
Effects of proxies on odds of BEC >=150 cells/µL (anti-IL5/5R patients)					
Duration of asthma (per 10y)	CHRONICLE	215	0.880	(0.719, 1.078)	0.216

	ISAR	1711	0.993	(0.926, 1.065)	0.841
	OPCRD	167	1.367	(1.081, 1.730)	0.009
Duration of severe asthma (per 10y)	CHRONICLE	203	0.865	(0.501, 1.493)	0.602
	ISAR	720	0.960	(0.588, 1.567)	0.869
	OPCRD	168	2.946	(1.660, 5.228)	<0.001
Time with lung impairment (per 10y)	CHRONICLE	23	.	. .	.
	ISAR	423	0.557	(0.228, 1.361)	0.199
	OPCRD	43	2.399	(0.718, 8.008)	0.155
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	169	1.981	(1.240, 3.165)	0.004
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	164	1.179	(0.949, 1.464)	0.137
Effects of proxies on odds of BEC >=300 cells/µL (anti-IL5/5R patients)					
Duration of asthma (per 10y)	CHRONICLE	215	1.033	(0.790, 1.350)	0.813
	ISAR	1711	0.961	(0.886, 1.043)	0.346
	OPCRD	163	1.504	(1.116, 2.025)	0.007
Duration of severe asthma (per 10y)	CHRONICLE	203	0.891	(0.515, 1.543)	0.680
	ISAR	720	0.962	(0.613, 1.511)	0.867
	OPCRD	163	1.958	(1.005, 3.812)	0.048
Time with lung impairment (per 10y)	CHRONICLE	17	.	. .	.
	ISAR	423	1.689	(0.738, 3.864)	0.214
	OPCRD	43	0.989	(0.282, 3.463)	0.986
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	163	1.322	(0.737, 2.371)	0.349
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	158	1.167	(0.869, 1.568)	0.304
Effects of proxies on odds of FeNO >=25 ppb (anti-IL4Rα patients)					
Duration of asthma (per 10y)	CHRONICLE	17	1.528	(0.859, 2.716)	0.149
	ISAR	250	1.059	(0.926, 1.210)	0.404

	OPCRD	0	N/A	N/A	N/A
Duration of severe asthma (per 10y)	CHRONICLE	17	2.232	(0.862, 5.778)	0.098
	ISAR	103	2.957	(1.574, 5.557)	0.001
	OPCRD	0	N/A	N/A	N/A
Time with lung impairment (per 10y)	CHRONICLE	N/A	N/A	N/A	N/A
	ISAR	91	5.302	(3.067, 9.164)	<0.001
	OPCRD	0	N/A	N/A	N/A
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	0	N/A	N/A	N/A
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	0	N/A	N/A	N/A

LTOCS use

Proxy (predictor)	Data source	N	Effect	(95% CI)	P-value
Effects of proxies on LTOCS non-use					
Duration of asthma (per 10y)	CHRONICLE	2796	0.977	(0.914, 1.045)	0.501
	ISAR	3704	0.958	(0.903, 1.016)	0.150
	OPCRD	998	0.870	(0.760, 0.995)	0.043
Duration of severe asthma (per 10y)	CHRONICLE	2053	0.923	(0.785, 1.085)	0.331
	ISAR	1812	1.104	(0.752, 1.621)	0.614
	OPCRD	1007	0.830	(0.630, 1.093)	0.184
Time with lung impairment (per 10y)	CHRONICLE	197	0.091	(0.000, 57.320)	0.466
	ISAR	1010	6.589	(1.605, 27.047)	0.009
	OPCRD	201	0.780	(0.365, 1.669)	0.522
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	1009	0.822	(0.644, 1.049)	0.115
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	991	0.822	(0.735, 0.920)	0.001

Effects of proxies on LTOCS daily dose (<=5mg /day)					
Duration of asthma (per 10y)	CHRONICLE	2218	0.849	(0.719, 1.002)	0.053
	ISAR	3275	0.960	(0.901, 1.023)	0.210
	OPCRD	998	0.828	(0.711, 0.964)	0.015
Duration of severe asthma (per 10y)	CHRONICLE	1588	0.876	(0.571, 1.342)	0.543
	ISAR	1714	1.272	(0.826, 1.959)	0.276
	OPCRD	1007	0.807	(0.589, 1.106)	0.183
Time with lung impairment (per 10y)	CHRONICLE	143	.	. .	.
	ISAR	914	1.461	(0.788, 2.710)	0.229
	OPCRD	201	0.635	(0.260, 1.548)	0.317
Time with frequent exacerbations (per 10y)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	1009	0.761	(0.579, 1.001)	0.051
Cumulative OCS dose (per 10g)	CHRONICLE	0	N/A	N/A	N/A
	ISAR	0	N/A	N/A	N/A
	OPCRD	991	0.806	(0.720, 0.903)	<0.001

14.0 List of Figures

15.0 List of Tables