Study Report C3-001

17th November 2023

Version 2.1

Contents

Study Title	DARWIN EU® - Background rates of serious adverse events to contextualise safety assessments in clinical trials and non-interventional studies in adolescent and adult patients with severe asthma.
Study Report Version identifier	V2.1
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EU PAS register number	EUPAS103936
Active substance	N/A
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Research question and objectives	**Research question:** During the evaluation of the safety results of a clinical trial in patients with severe asthma, differences in rates of serious adverse events were observed in the experimental treatment arm compared to the control arm. In order to contextualise these differences, more information is required. Therefore, a real-world non-interventional study was requested to generate background rates of selected health outcomes in patients with severe asthma. The present study is to produce background information on the occurrence of the health outcomes listed below (see Study Objectives) in adolescent and adult patients with severe asthma using recent data. **The objectives of this study are:** (i) To estimate the rate of mortality due to any cause stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022. (ii) To estimate the rate of mortality due to infections stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022. (iii) To estimate the rate of mortality due to cardiovascular events stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022. (iv) To estimate the incidence rate of serious cardiovascular events (but not necessarily leading to death) stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022

Country(-ies) of study	The Netherlands, Spain (2 data sources), Estonia and the UK.
Author	Katia Verhamme, Department of Medical Informatics, EMC Rotterdam, The Netherlands. Mail: k.verhamme@darwin-eu.org Maria de Ridder, Department of Medical Informatics, EMC Rotterdam, The Netherlands. Mail: m.deridder@darwin-eu.org John Arinze, Department of Medical Informatics, EMC Rotterdam, The Netherlands. Mail: j.arinze@darwin-eu.org

1. DESCRIPTION OF STUDY TEAM

Table 1 shows a description of the Study team by role, name, and organization.

Table 1: Description of Study Team

Study team Role	Names	Organisation
Study Project Manager/ Principal Investigator	Katia Verhamme Maria de Ridder	Erasmus MC
Data Scientist	Katia Verhamme	Erasmus MC
Epidemiologist	Katia Verhamme Ed Burn John Arinze	Erasmus MC University of Oxford Erasmus MC
Statistician	Maria de Ridder	Erasmus MC
Data Manager	Mees Mosseveld	Erasmus MC
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	Antonella Delmestri Mees Mosseveld Miguel-Angel Mayer Angela Leis JuanManuel Ramirez Raivo Koldo Talita Duarte Salles	University of Oxford – CPRD data Erasmus MC – IPCI data PSMAR - IMASIS PSMAR - IMASIS PSMAR - IMASIS University Tartu IDIAPJGol – SIDIAP data

*Data partners' role is only to execute code at their data source. These people do not have an investigator role.

2. DATA SOURCES

This study was conducted using routinely collected data from 5 databases in 4 countries (3 EU countries and United Kingdom). All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. Parc Salut Mar Barcelona (PSMAR), Hospital del Mar (IMIM) (hospital database), Spain
5. University of Tartu - Estonian Biobank, Estonia

Information on the data source(s) is described in Table 2

Table 2: Description of Data sources

Country	Name of Database	Health Care setting	Type of Data (EHR, claims, registries)	Person counts	Data lock for the last update
NL	IPCI	Primary care	EHR	2.8 million	31st December 2022
ES	SIDIAP	Primary care	EHR	8.3 million	30th June 2022
UK	CPRD GOLD	Primary care	EHR	17.0 million	20th June 2022
ES	IMASIS	Secondary care (in and outpatients)	EHR	1.0 million	31st December 2022
Estonia	Estonian Biobank – University of Tartu	Biobank	Claims data	0.2 million	31st December 2021

NL = The Netherlands, ES = Spain, UK = United Kingdom, IPCI = Integrated Primary Care Information Project; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IMASIS= Institut Municipal Assistencia Sanitaria Information System, CPRD GOLD = Clinical Practice Research Datalink GOLD, EHR = Electronic Heath record.
Nap= Not applicable

3. ABSTRACT (STAND-ALONE SUMMARY OF THE STUDY REPORT)

Title

DARWIN EU® - Background rates of serious adverse events to contextualise safety assessments in clinical trials and non-interventional studies in adolescent and adult patients with severe asthma.

Rationale and Background

During the evaluation of the safety results of a clinical trial in patients with severe asthma, differences in rates of serious adverse events were observed in the experimental treatment arm compared to the control arm. In order to contextualise these differences, a non-interventional study was requested to generate background rates of selected health outcomes in patients with severe asthma, with a disease definition that follows the conducted clinical trials. The results of this study may inform future drug-related safety assessments in severe asthma population.

This study was conducted to produce background information on the occurrence of the health outcomes listed below (see Objectives) in adolescent and adult patients with severe asthma.

Research question and Objectives

The objectives of this study were:

(i) To estimate the rate of mortality due to any cause stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022.

(ii) To estimate the rate of mortality due to fatal infections stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022.

(iii) To estimate the rate of mortality due to cardiovascular events stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022.

(iv) To estimate the incidence rate of serious cardiovascular events (but not necessarily leading to death) stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022

Research Methods

Study design

Retrospective cohort studies were conducted using routinely-collected health data from 5 databases. Based on the application of the respective inclusion and exclusion criteria, 3 retrospective cohorts were defined namely one cohort created following inclusion criteria only, the second cohort applying in-and exclusion criteria and the third cohort which consisted of patients who fulfilled inclusion criteria but were excluded because of the presence of exclusion criteria.

Population

All individuals present in the database in the period between 01/01/2015 and 31/12/2022, with at least 1 year of prior history, being diagnosed with severe asthma and fulfilling inclusion (cohort 1), inclusion and exclusion criteria (cohort 2), and individuals who were identified in cohort 1 but were excluded because of exclusion criteria (cohort 3).

Variables

Variables of interest consisted of outcomes, comorbidity, lifestyle factors, measurements, and drug exposure data.

Outcomes of interest were overall mortality and cause-specific mortality (infection-related mortality, cardiovascular-related mortality) and serious cardiovascular events (acute myocardial infarction, acute coronary syndrome/ischemic heart disease, stroke and hospitalisation for heart failure)

Comorbidities: asthma (including asthma exacerbations), other respiratory conditions (COPD, bronchiectasis, pulmonary fibrosis, lung cancer, upper and lower respiratory tract infection), cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidities, cancer, anaphylaxis, tuberculosis (TBC), human immunodeficiency virus (HIV), acute liver disease and hepatitis B or hepatitis C and conditions frequently associated with asthma (atopic dermatitis, nasal polyposis, chronic rhinosinusitis, chronic idiopathic urticaria, rhinitis)

Lifestyle factors alcohol, smoking or drug abuse.

Measurements aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP) bilirubin, blood eosinophils, and body mass index (BMI).

Drug exposure inhaled corticosteroids (ICS); systemic corticosteroids; other asthma controller medication; i.e. long acting B2 agonists (LABA), Leukotriene Receptor antagonists (LTRA), theophylline, long-acting muscarinic antagonists (LAMA), cromones; Antibiotics and antiviral therapy; Cyclosporine and Methotrexate

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. IMASIS, Parc Salut Mar Barcelona (PSMAR), Hospital del Mar (IMIM) (hospital database), Spain
5. University of Tartu - Estonian Biobank, Estonia

Sample size

No sample size has been calculated.

Data analyses

Population-level disease epidemiology: Annual incidence rate of the outcomes of interest were calculated stratified by country/database, calendar year, age and sex, within the cohort of severe asthma patients.

For the calculation of the incidence rate, the numerator was the number of patients newly diagnosed with the respective outcomes of interest and the denominator consisted of the number of person-years of the severe asthma patients fulfilling the inclusion and exclusion criteria at risk.

In addition, survival time to all-cause mortality were estimated using Kaplan Meier analysis.

Based on the application of the respective inclusion and exclusion criteria the analyses were conducted in 3 retrospective cohorts i.e. i) cohort of patients with severe asthma fulfilling inclusion criteria, ii) cohort of patients with severe asthma fulfilling inclusion and exclusion criteria and iii) a cohort of patients fulfilling inclusion criteria and with at least 1 of the exclusion criteria.

For all analyses a minimum cell count of 5 will be used when reporting results, with any smaller counts obscured.

Results

In total, more than 1.27 million of individuals with asthma across databases were identified of which CPRD GOLD (58.6%) and SIDIAP (26.0%) contributed the largest part.

Cohort 1, not applying the exclusing criteria, contained between 190 (EBB) -19,249 (CPRD GOLD) patients with severe asthma.

IMASIS did not contribute to any of the analyses due to low numbers.

In terms of baseline characteristics of patients with severe asthma, the proportion of females was higher than the proportion of males with a female to male ratio of around 2:1 (65% females and 35% males). The majority of individuals were 50 years or older at study entry. Proportion of patients with underlying comorbidity was high). In all databases, the number of patients with ACO (disease codes of asthma as well as COPD) was high and ranged from 32% in IPCI to 68% in the EBB.

When exploring incidence rates (IR) of the outcomes of interest, the IR for all-cause mortality for cohort 1 in the first year ranged between 16-30 per 1,000 PY for the primary care databases and was the highest for EBB with an IR of 58/1,000 PY. No differences in overall mortality rates could be observed between year 1 (16-30 per 1,000 PY) and year 2 (16-29/1,000 PY) following study entry. The overall mortality rates increased with age and were higher in males compared to females.

With regard to the IR of serious cardiovascular (CV) outcomes in cohort 1, in the first year following study entry, the IR of serious CV events was comparable between IPCI and CPRD GOLD namely 14 and 11/1,000 PY respectively. This IR was much higher for SIDIAP namely 41/1,000 PY and the highest for EBB namely 202 per 1,000 PY. The IR of myocardial infarction (MI) in the first year following study entry was comparable between CPRD GOLD and SIDIAP namely 4 and 3 per 1,000 PY and 8/1,000 PY for IPCI. The IR of stroke was comparable between databases with an IR of 8/1,000 PY for IPCI and SIDIAP and an IR of 7/1,000 PY for CPRD GOLD. IR of serious CV events in the second year following study entry, was slightly lower than the IR in the first year in all databases. The IR of CV outcomes increased with age, except for heart failure in the EBB.

Cohort 2 consisted of only 217 patients in IPCI, 1,036 patients in SIDIAP and 2,869 in CPRD GOLD with severe asthma.

As the number of patients with comorbidities in the year prior to study entry as well as the number of patients smoking was high in cohort 1, the number of individuals in cohort 2 was very low. As for EBB the number of individuals in cohort 2 was below 5, data from EBB could not be used for analyses.

In cohort 2, mortality rates could only be calculated in CPRD GOLD but not in the other databases because of low numbers. As cohort 2 consisted of a healthier population, the mortality rate in CPRD was 1/5th of the mortality rate in cohort 1. (both for the first and second year of follow-up). Because of the small size of cohort 2, IRs of cardiovascular outcomes could be calculated only for CPRD GOLD and for SIDIAP. In CPRD GOLD the IR of serious CV event in the first year following study entry was 4 (95% CI 2 to 8) per 1,000 PY and 5 (95% CI 3 to10) per 1,000 PY in the second year following study entry. In SIDIAP this IR was 16 (95% CI 9 to26) per 1,000 PY in the first year and 17 (95% CI 10 to28) per 1,000 PY in the second year. The IRs of these outcomes were lower for cohort 2 compared to those from cohort 1.

For cohort 3, IRs of the outcomes of interest were calculated for CPRD, SIDIAP and IPCI. In general, results were similar compared to cohort 1 with slightly higher IRs of the outcomes of interest for cohort 3 compared to cohort 1 for those outcomes which could be calculated.

Discussion

This study provides insight into the background rates of major cardiovascular events and mortality in patients with severe asthma, specifically those who share clinical profiles similar to participants in clinical trials. Notably, our findings indicate that these rates are relatively high, particularly among older individuals and males. However, it is crucial to acknowledge the inherent challenges in replicating clinical trial results in real-world settings, such as variations in patient demographics, comorbidities, and local asthma management guidelines. This underscores the importance of considering these factors when translating research findings into clinical practice.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
ACO	Asthma COPD overlap
ACS	Acute coronary syndrome
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
CV	Cardiovascular
DARWIN EU®	Data Analysis and Real World Interrogation Network
EBB	Estonian Biobank
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
HF	Heart failure
HFA	Hydrofluoroalkane
IMASIS	Institut Municipal Assistència Sanitària Information System
ICS	Inhaled Corticosteroids
IPCI	Integrated Primary Care Information Project
IR	Incidence rate
LABA	Long acting B2 agonists
LAMA	Long acting muscarinic antagonists
LOINC	Logical Observation Identifiers Names and Codes
LTRA	Leukotriene receptor antagonist
LRTI	Lower Respiratory Tract Infection
MI	Myocardial Infarction
N/A	Not applicable
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PSMAR	Parc de Salut Mar
PY	Person years
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

TBC	Tuberculosis
URTI	Upper respiratory tract infection
UTartu	University of Tartu

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment orupdate	Reason
V2.0	21/12/2022	All	Update	Response to review from EMA
V3.0	19/01/2023	All	Update	Revision following comments from EMA
V4.0	12/03/2023	Study Team	Update	Clarify role of database partners and addition of additional members in study team
V4.1	03/09/2023	All	Updated	• Study period 2015-2022 • clarification on stratified analysis • update on timelines • update on disease codes for cardiovascular, infection and musculoskeletal diseases as comorbidity

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Protocol	19th December 2022	19th December 2022
Final Study Protocol	January 2023	January 2023
Creation of Analytical code	January 2023	August 2023
Execution of Analytical Code on the data	February 2023	August 2023
Interim Study Report (if applicable)	Not applicable	Not applicable

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Report	15th June 2023	18h September 2023
Final Study Report	27th October 2023	27th October 2023
Update for archieving	17th November 2023	17th November 2023
Draft Manuscript (if agreed on)	To be discussed	
Final Manuscript (if agreed on)	To be discussed	

7. RATIONALE AND BACKGROUND

Asthma is a highly prevalent condition with an overall prevalence of 9.8%, according to a recent systematic review. (1) Although asthma cannot yet be cured, symptoms can be controlled by the use of asthma controller therapy such as Inhaled Corticosteroids. (2) The majority of patients have mild to moderate asthma but a small proportion of patients (3-10%) have severe uncontrolled asthma and are in need of new medicines. (3)

During the evaluation of the safety results of a clinical trial of an investigational product in patients with severe asthma, differences in rates of serious adverse events were observed in the experimental treatment arm compared to the control arm. In order to contextualise these differences, a non-interventional study was required to generate background rates of selected health outcomes in patients with severe asthma. The disease definition used in the present study follows from recently conducted clinical trials in severe asthma. The results of this study may inform future drug-related safety assessments in the same population.

This present study is designed to produce background information on the occurrence of the health outcomes listed below (see Study Objectives) in adolescent and adult patients with severe asthma using recent data.

8. RESEARCH QUESTION AND OBJECTIVES

The objectives of this study were

(i) To estimate the rate of mortality due to any cause stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022.

(ii) To estimate the rate of mortality due to fatal infections stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022.

(iii) To estimate the rate of mortality due to cardiovascular events stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022.

(iv) To estimate the incidence rate of serious cardiovascular events (but not necessarily leading to death) stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022

9. RESEARCH METHODS

9.1. STUDY TYPE AND STUDY DESIGN

Retrospective cohort studies were conducted using routinely collected health data from 5 databases.
Based on the application of the respective inclusion and exclusion criteria, 3 retrospective cohorts were defined (see 9.5 for a description of inclusion and exclusion criteria).
The incidence rate of mortality and the outcomes of interest were assessed using Population Level Disease Epidemiology analytical pipelines. (from the DARWIN EU Complete Catalogue of Standard Data Analyses).

9.2. STUDY SETTING AND DATA SOURCES

This study was be conducted using routinely collected data from 5 databases in 4 countries (3 EU countries and United Kingdom). All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. IMASIS, Parc Salut Mar Barcelona (PSMAR), Hospital del Mar (IMIM) (hospital database), Spain
5. University of Tartu - Estonian Biobank, Estonia

Detailed information on data source is described in Table 3.

Table 3: Description of Data sources

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g., primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Total number of subjects	Data lock for the last update
NL	IPCI	Covers primary care setting and this database has been used for previous research in patients with asthma.	Primary care	EHR	2.8 million	31st December 2022
ES	SIDIAP	Covers primary care setting and this database has been used for previous research in patients with asthma.	Primary care	EHR	8.3 million	30th June 2022
UK	CPRD GOLD	Covers primary care setting and this database has been used for previous research in patients with asthma.	Primary care	EHR	17.0 million	1st July 2022
ES	IMASIS	Covers secondary care setting, database has information on treatment of patients with asthma in the in- and outpatient setting and information on mortality and other outcomes for in-house patients	Secondary care (in and outpatients)	EHR	1.0 million	31st December 2022
Estonia	Estonian Biobank – University of Tartu	This database has been used for other studies in patients with asthma	Biobank	Claims data	0.2 million	31st December 2021

Integrated Primary Care Information Project (IPCI), The Netherlands (Erasmus)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands. The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996.(4) The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board.(4)

Information System for Research in Primary Care (SIDIAP), Spain (IDIAP Jordi Gol)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff(5). The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry. (6)

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD(7) comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases.

Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process.

Estonian Biobank – University of Tartu (Estonia)

The Estonian Biobank (EBB) is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT). Its cohort size is currently close to 200,000 participants ("gene donors" >= 18 years of age) which closely reflects the age, sex and geographical distribution of the Estonian adult population. Genomic GWAS analysis have been performed on all gene donors. The database also covers health insurance claims, digital prescriptions, discharge reports, information about incident cancer cases and causes of death from national sources for each donor. (8, 9)

9.3. STUDY PERIOD

The study period was from 1st January 2015 until 31st December 2022. The study period was categorised into a pre-pandemic period (01/01/2015-31/12/2019) and a pandemic period (01/01/2020-31/12/2022).

9.4. FOLLOW-UP

Study participants began contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2015), 2) date at which they had sufficient prior history (365 days), 3) date on which they fulfilled the respective inclusion criteria. (see Figure 1). For a description of inclusion and exclusion criteria, see 9.5.

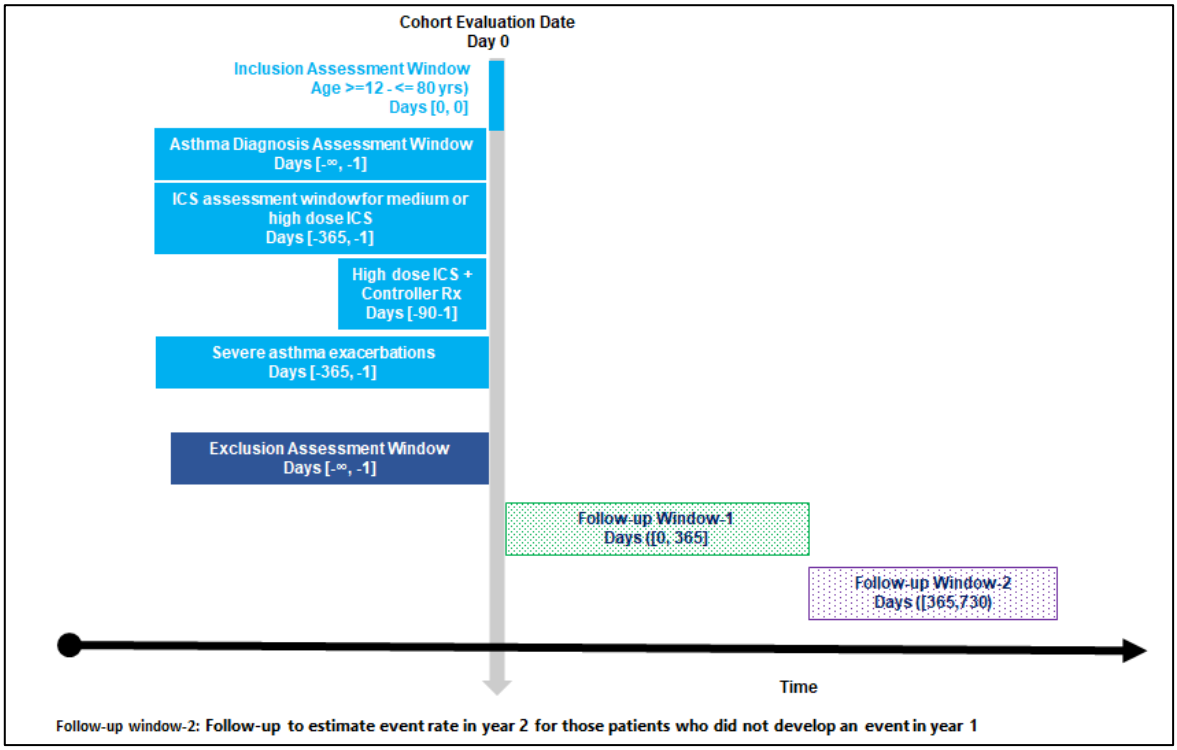


Figure 1: Included observation time for the denominator population

Participants stopped contributing person time at the earliest date of the following: 1) end date of observation period of patient in the database, 2) end of study follow-up period (365 and 730 days following cohort start), 3) date of death or 4) end of study period (31st December 2022). Follow-up for the analysis on the incidence of serious cardiovascular events ended when patients developed the outcome of interest. Only for the Kaplan-Meier estimates, follow-up did not end after 730 days.

Follow-up started either on the 1st January 2015 or following the date in which the patient fulfilled inclusion criteria during the study period for those entering the cohort after 1st January 2015 (see Figure 2)

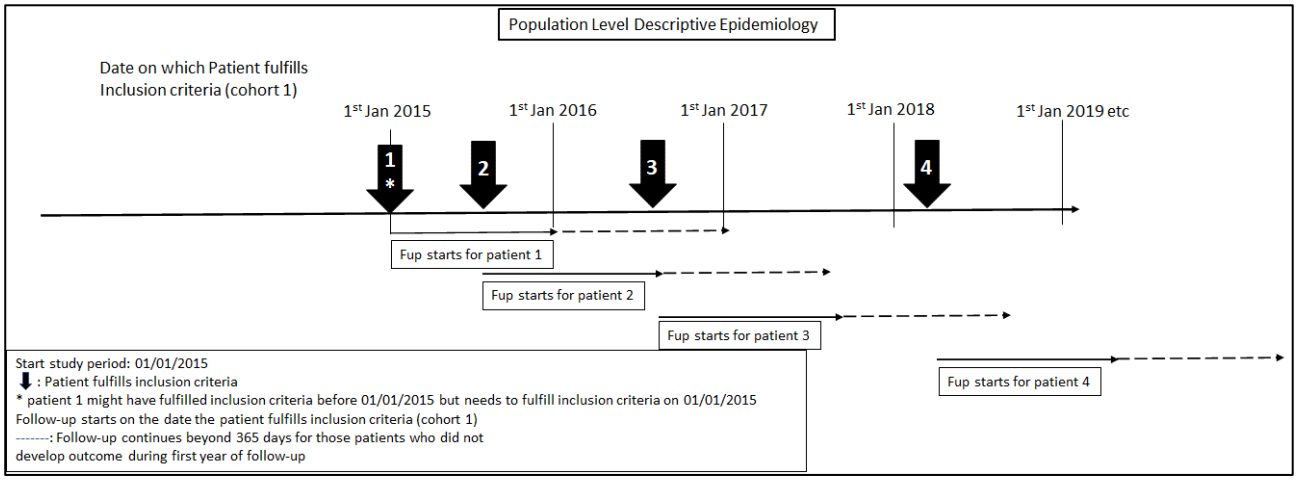


Figure 2: Start of follow-up following fulfilment of inclusion criteria

As an additional analysis, the incidence of the outcomes of interest was carried out in a long-term extension (LTE) period of 52 weeks for those in the cohort who did not experience the health outcome of interest in the first 52 weeks. (Figure 3)

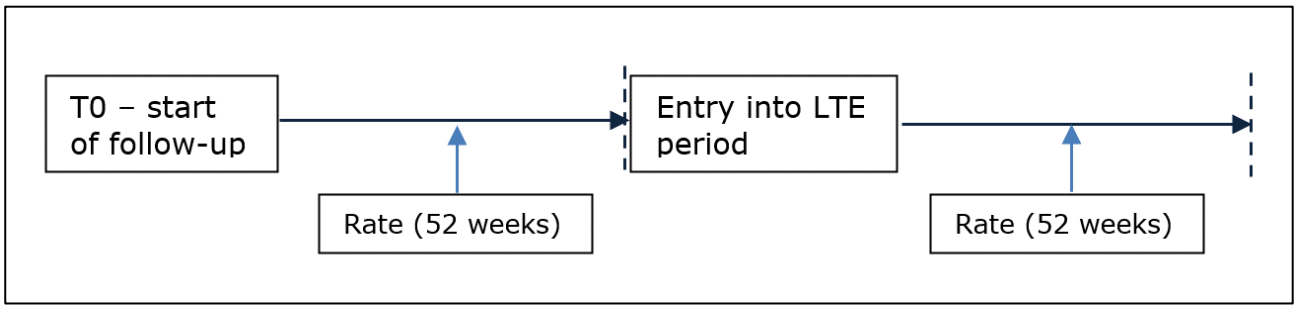


Figure 3: Start of follow-up for the long-term extension study (LTE)

9.5. STUDY POPULATION WITH IN- AND EXCLUSION CRITERIA

For this study, **all** of the following **inclusion criteria** at the time of cohort entry were applied:

- Patients with observation time during the study period and at least 1 year of prior history observed before contributing observation time.
- Patients 12 to 80 years of age at time of cohort entry
- Physician-diagnosed asthma for at least 12 months. Diagnosis of asthma will be based on SNOMED disease codes for asthma and date of diagnosis can be before 1st January 2015
- Patients treated with medium or high-dose ICS (⩾ 250 µg fluticasone propionate dry powder formulation equivalent total daily dose) as per GINA guideline – GINA 2022) for at least 12 months. (see Table 1 in appendix for GINA classification on low, medium or high dose ICS)(2)
- Patients treated with high dose ICS (⩾ 500 µg fluticasone propionate dry powder formulation equivalent total daily dose) (as per GINA guidelines – GINA 2022) for at least 12 weeks. (see Table 2 in appendix for GINA classification on low, medium or high dose ICS)(2)
- Use of at least one additional maintenance asthma controller medication, e.g., LABA, LTRA, theophylline, long-acting muscarinic antagonists (LAMA), cromones, etc for at least 12 weeks.
- Documented history of at least 2 asthma exacerbation events in the previous 12 months. Asthma exacerbations were defined as any of the following:
  a) an asthma exacerbation, requiring treatment with systemic corticosteroids for at least 3 consecutive days (a single depo-injectable dose of corticosteroids is considered equivalent to a 3-day course of systemic corticosteroids).
  b) an ER visit for reason of asthma
  c) hospitalisation due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ⩾ 24 hours).
  d) SNOMED code for “acute asthma exacerbation”

The date on which the patient fulfilled all of these inclusion criteria was called the “cohort evaluation date”. (see also Figure 2)

For this study, 3 cohorts were generated namely Figure 4

Cohort 1: Patients fulfilling inclusion criteria.

Cohort 2: Patients fulfilling inclusion criteria and not having any of the exclusion criteria. Cohort 2 is a subset of cohort 1.

Cohort 3: Patients fulfilling inclusion criteria and with at least 1 of the exclusion criteria. Patients from cohort 3 are those in cohort 1 who are not in cohort 2.

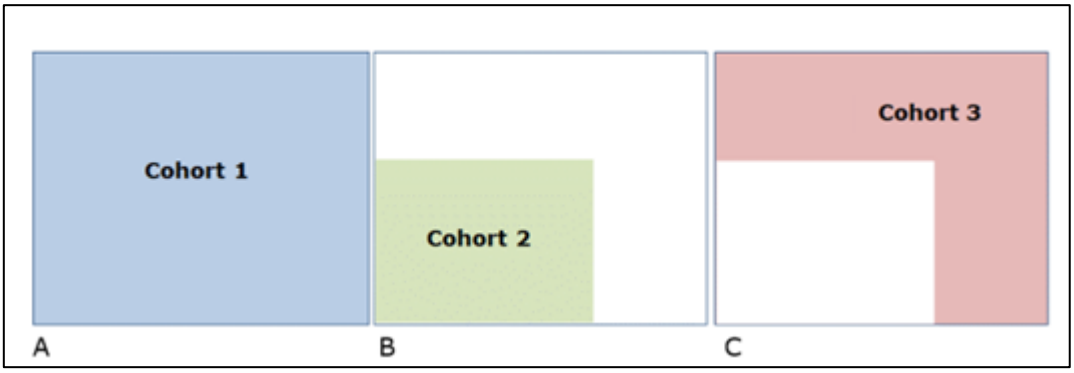


Figure 4: Describing potential cohort size of cohort 1, cohort 2 and cohort 3. A) Patients who meet the inclusion criteria (Cohort 1). B) Patients who meet the inclusion criteria and have no exclusion criteria (Cohort 2). C) Patients who meet the inclusion criteria but have no exclusion criteria (Cohort 3).

For cohort 2, the following **patients were excluded:**

- Patients with any clinically important pulmonary disease other than asthma, in particular exclusion of patients with a medical history of COPD, lung cancer, bronchiectasis or pulmonary fibrosis prior to start of follow-up
- Patients with a SNOMED disease code of cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity in the 12 months prior to start of follow-up
- Patients with cancer as comorbidity (current or history of) (except for basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix)
- Patients with a SNOMED disease code of upper or lower respiratory tract infection, requiring treatment with antibiotics or antiviral medications within 2 weeks prior to start of follow-up
- Current/past smokers
- Patients with alcohol or drug abuse in the 12 months prior to start of follow-up
- Patients with SNOMED disease code of TBC in the 12 months prior to start of follow-up
- Patients with SNOMED disease code of HIV prior to start of follow-up
- Patients who had used cyclosporine or methotrexate in the 12 weeks prior to start of follow-up
- Patients with a medical history of anaphylaxis
- Evidence of active liver disease or aspartate transaminase, alanine transaminase, alkaline phosphatase or bilirubin > 2 times the upper limit of normal (ULN) in the 12 months prior to start of follow-up
- Patient with a SNOMED disease code of Hepatitis B or Hepatitis C prior to start of follow-up.

Table 4: Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period in the database during the period 2015-2022 (or the latest available)	See under inclusion criterion	Before	N/A	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	N/A	N/A	All individuals within the selected databases	N/A	N/A
Prior database history of 1 year	Study participants will be required to have a year of prior history observed before contributing observation time	Before	1 year	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	N/A	N/A	All individuals within the selected databases	N/A	N/A
Age	Patients 12 to 80 years of age inclusive at start of follow-up	Before	N/A	Depending on the database: Primary care, Secondary care or combination	N/A	N/A	All individuals within the selected databases	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
				of primary and secondary care for Estonian Biobank					
Asthma	Physician-diagnosed asthma for at least 12 months. Date of diagnosis can be before the start of study period	Before	12 months or more	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	SNOMED	N/A	All individuals within the selected databases	N/A	N/A
ICS exposure	Patients treated with medium or high-dose ICS for at least 12 months	Before	12 months	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	RxNorm	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
ICS exposure	Patients treated with high-dose ICS	Before	12 weeks	Depending on the database:	RxNorm	N/A	All individuals within the selected	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
	for at least 12 weeks			Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank			databases and diagnosed with asthma and treated with medium or high dose ICS for at least 12 months		
Asthma controller therapy	At least one additional maintenance asthma controller medication; e.g., LABA, LTRA, theophylline, long-acting muscarinic antagonists (LAMA), cromones) for at least 12 weeks	Before	12 weeks	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	RxNorm	N/A	All individuals within the selected databases and diagnosed with asthma and treated with medium or high dose ICS for at least 12 months and treated with high dose ICS for at least 12 weeks	N/A	N/A
Asthma exacerbations	Documented history of at least 2 asthma exacerbation	Before	12 months	Depending on the database: Primary care, Secondary care or combination of primary and	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma and treated with medium or high	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
	events within 12 months.			secondary care for Estonian Biobank			dose ICS for at least 12 months and treated with high dose ICS for at least 12 weeks and on additional asthma controller therapy for at least 12 weeks		

* A patient is eligible for entry in the study cohort at the date all inclusion criteria are fulfilled

Table 5: Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Other pulmonary conditions	Patients with a medical history of COPD, lung cancer, bronchiectasis or pulmonary fibrosis prior to start of follow-up	After	∞ prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
Other Comorbidity	Evidence of cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric comorbidity; TBC; Hepatitis B or Hepatitis C	After	12 months prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
Cancer	Evidence of cancer	After	∞ prior to start of follow-up	Primary care, Secondary care and combination of	SNOMED	N/A	All individuals within the selected databases and	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
				primary and secondary care for Estonian Biobank - UTartu			diagnosed with asthma		
Upper or lower respiratory tract infection	Evidence of upper or lower respiratory tract infection requiring treatment with antiviral therapy/antibiotics within 12 weeks prior to start of follow-up	After	2 weeks prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED and RxNorm	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
Current and past Smoking	Evidence of current or past smoking	After	12 months prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED		All individuals within the selected databases and diagnosed with asthma	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Alcohol or drug abuse	Evidence of alcohol or drug abuse	After	12 months prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
HIV	Evidence of HIV	After	∞ prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
cyclosporine or methotrexate	Exposure to any of these drugs	After	2 weeks prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian	RxNorm	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
				Biobank - UTartu					
Anaphylaxis	Evidence of anaphylaxis	After	∞ prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
Acute liver disease	Evidence of active liver disease or aspartate transaminase, alanine transaminase, alkaline phosphatase or bilirubin > 2 times the upper limit of normal (ULN) in the 12 months prior to start of follow-up	After	12 months prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A

* After, as first, inclusion criteria are checked. For patients fulfilling the inclusion criteira, we next checked whether there were any exclusion criteria occurring in the prespecified windows prior to the index date. .

9.6. VARIABLES

9.6.1. EXPOSURE

For this study, drug exposure is important as part of the inclusion and exclusion criteria.

The list of drug classes (with respective ATC code) is described in Table 6. Details of drug exposure are described in Appendix I, Table 3.

Table 6: Exposure of interest to assess inclusion and exclusion criteria.

Drug Class	Ingredient	ATC code
ICS	Beclomethasone	R03BA01
	Budesonide	R03BA02
	Flunisolide	R03BA03
	Betamethasone	R03BA04
	Fluticasone	R03BA05
	Triamcinolone	R03BA06
	Mometasone	R03BA07
	Ciclesonide	R03BA08
	Fluticasone furoate	R03BA09
ICS+LABA	Salmeterol+fluticasone	R03AK06
	Formoterol+budesonide	R03AK07
	Formoterol+beclomethasone	R03AK08
	Formoterol+mometasone	R03AK09
	Vilanterol+fluticasone furoate	R03AK10
	Formoterol+fluticasone	R03AK11
	Salmeterol + budesonide	R03AK12
	Salbutamol+beclomethasone	R03AK13
	Indacaterol and mometasone	R03AK14
ICS+LABA+LAMA	Vilanterol, umeclidinium bromide, and fluticasone furoate	R03AL08
	Formoterol, glycopyrronium bromide and beclometasone	R03AL09
	Formoterol, glycopyrronium bromide, and budesonide	R03AL11
	Indacaterol, glycopyrronium bromide and mometasone	R03AL12
LABA	Salmeterol	R03AC12
	Formoterol	R03AC13
	Reproterol	R03AC15
	Procaterol	R03AC16
	Bitolterol	R03AC17
	Indacaterol	R03AC18
	Olodaterol	R03AC19
LAMA	Tiotropium bromide	R03BB04
	Aclidinium bromide	R03BB05

Drug Class	Ingredient	ATC code
	Glycopyrronium bromide	R03BB06
	Umeclidinium bromide	R03BB07
	Revefenacin	R03BB08
LABA+LAMA	Vilanterol and umeclidinium bromide	R03AL03
	Indacaterol and glycopyrronium bromide	R03AL04
	Formoterol and aclidinium bromide	R03AL05
	Olodaterol and tiotropium bromide	R03AL06
	Formoterol and glycopyrronium bromide	R03AL07
	Formoterol and tiotropium bromide	R03AL10
Leukotriene receptor antagonists (LTRA)		R03DC
Xanthines		R03DA
Cromones		A07EB
Biologics	Omalizumab	R03DX05
	Reslizumab	R03DX08
	Mepolizumab	R03DX09
	Benralizumab	R03DX10
	Dupilumab	D11AH05
Systemic steroids		H02AB
Antbiotics		J01
Antivirals		J05
Ciclosporin		L04AD01
Methotrexate		L04AX03

For drug exposures of ICS, the amount prescribed and duration are recorded in the databases. Using this information and the strength of the drug concept involved, daily dose was calculated. Based on the daily dose and the ingredient, for each exposure was determined whether it was low, medium or high dose (see Appendix I Table 6). Next, subsequent ICS exposures with the same dose category were joined if they were overlapping, or the gap between exposures was 30 days or less. From this, the total duration of use was calculated.

For drug exposures of asthma controller medication, dose was not considered. Subsequent drug exposure records were joined again, with maximum gap of 30 days between exposures.

Further details on the assessment of exposure are described in Table 7.

Table 7: Exposure details

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting	Code Type	Diagnosis position	Applied to study populations:	Incident with respect to…	Measurement characteristics / validation	Source of algorithm
ICS	Preliminary code lists provided in Table 2 of Appendix I	N/A	12 months prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	Medium or high dose ICS	N/A
ICS	Preliminary code lists provided in Table 2 of Appendix I	N/A	12 weeks prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	High dose ICS	N/A
Other asthma controller therapy	Preliminary code lists provided in Table 2 of Appendix I	N/A	12 weeks prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	N/A	N/A
Antibiotics and/or Antiviral Drugs	Preliminary code lists provided in Table 2 of Appendix I	N/A	2 weeks prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	N/A	N/A
Ciclosporine or methotrexate	Preliminary code lists provided in Table 2 of Appendix I	N/A	2 weeks prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	N/A	N/A

9.6.2. OUTCOMES

- All-cause mortality
- Fatal infections
- Fatal cardiovascular events
- Serious cardiovascular events (see details below).

As cause of death is not documented within OMOP CDM, additional cohorts were generated beside the mortality cohort. If the date of infection or cardiovascular events occurred within a window of 14 days prior to the date of mortality, cause of death was assumed to be related to these respective conditions (i.e. mortality related to infections or mortality related to cardiovascular events)

These additional cohorts consisted of an infectious cohort (covering all types of infections) and a cardiovascular event cohort (covering all types of cardiovascular events). The concept list with SNOMED codes for these conditions of interest are described in Appendix I – Table 1: List with concept definitions.

Serious cardiovascular events were defined as acute myocardial infarction, acute coronary syndrome/ischemic heart disease, stroke and hospitalisation for heart failure (HF). The incidence of the serious cardiovascular events as outcome were studied overall but also by subgroup namely i) myocardial infarction - ACS/ischemic heart disease, ii) stroke and iii) hospitalisation for HF separately.

The concept list with SNOMED codes for these conditions of interest are described in Appendix I – Table 1: List with concept definitions.

9.6.3. OTHER COVARIATES, INCLUDING CONFOUNDERS, EFFECT MODIFIERS AND OTHER VARIABLES

9.6.3.1. COVARIATES FOR STRATIFICATION IN POPULATION-LEVEL INCIDENCE STUDY

- Age: 12-17, 18-64, 65-74, 75-80.
- Calendar year (by calendar year(s) which refers to the year in which the follow-up period fell)
- Pre- and pandemic period
- Sex

9.6.3.2. COMORBIDITIES TO ASSESS INCLUSION AND EXCLUSION CRITERIA

- Asthma
- COPD
- Bronchiectasis
- Pulmonary fibrosis
- Lung cancer
- Upper and lower respiratory tract infection
- Cardiovascular comorbidity
- Gastrointestinal comorbidity

- Hepatic comorbidity
- Renal comorbidity
- Neurological comorbidity
- Musculoskeletal comorbidity
- Infectious comorbidity
- Endocrine comorbidity
- Metabolic comorbidity
- Haematological comorbidity
- Psychiatric comorbidity
- Cancer
- Anaphylaxis
- TBC (tuberculosis)
- HIV
- Acute Liver Disease
- Hepatitis B and Hepatitis C

The list with SNOMED concept codes for these conditions of interest are described in Appendix I – Table 1: List with concept definitions.

9.6.3.3. COMORBIDITIES AT THE TIME OF COHORT ENTRY

The prevalence of the following comorbidities was described at start of follow-up:

- Arterial hypertension
- Number of asthma exacerbations in previous 12 months
- Gastro-oesophageal reflux disease
- Atopic Dermatitis
- Nasal Polyposis
- Chronic Sinusitis
- Chronic spontaneous urticaria
- Rhinitis
- Diabetes mellitus
- Osteoporosis
- Comorbidities that form exclusion criteria (see above)

The list with SNOMED and LOINC (Logical Observation Identifiers Names and Codes) concept codes for these conditions of interest are described in Appendix I – Table 1: List with concept definitions.

9.6.3.4. LIFESTYLE FACTORS

- Smoking status (current/past)
- Alcohol and drug abuse

The list with SNOMED and LOINC concept codes for these conditions are described in Appendix I – Table 5: List with concept codes for Lifestyle Factors.

9.6.3.5. MEASUREMENTS

- aspartate transaminase, alanine transaminase, alkaline phosphatase and bilirubin with values and information on upper limit of normal
- blood eosinophils
- BMI

The list with SNOMED and LOINC concept codes for these conditions are described in Appendix I – Table 4: List with concept codes for measurements .

Table 8: Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
COPD, lung cancer, bronchiectasis, pulmonary fibrosis, cancer, HIV, anaphylaxis, hepatitis B or C	Check for conditions of interest at start of follow-up	Binary	All history	Primary and secondary care	SNOMED	N/A	Patients with severe asthma	N/A	N/A
Cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, TBC, liver disease	Check for conditions of interest at start of follow-up	Binary	[- 12 months, 0]	Primary and secondary care	SNOMED	N/A	Patients with severe asthma	N/A	N/A
Lifestyle factors	Check for lifestyle factors at start of follow-up	Binary	[- 12 months, 0]	Primary care and secondary care	SNOMED and LOINC	N/A	Patients with severe asthma	N/A	N/A

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Measurements	Check for measurements factors at start of follow-up	Continuous	[- 12 months, 0]	Primary and secondary care	SNOMED and LOINC	N/A	Patients with severe asthma	N/A	N/A

9.7. STUDY SIZE

No sample size had been calculated.

9.8. DATA TRANSFORMATION

All databases are mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org. This analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.9. STATISTICAL METHODS

9.9.1. MAIN SUMMARY MEASURES

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the Complete Catalogue of Data Analysis of DARWIN EU, which describes the type of analysis for common study designs.

The analysis included calculation of population-based incidence rates, as described in section 9.9.4.1 – Population-level Incidence Study,

9.9.2. MAIN STATISTICAL METHODS

This section describes the analysis approach and rationale for the choice of analysis.

R-packages

We used the R package "PatientProfiles" to extract patient characteristics and exclusion criteria, “IncidencePrevalence” for the population-level estimation of incidence rates for the outcomes of interest and "survival" for the Kaplan-Meier and Aalen-Johansen curves.

Drug exposure calculations

Drug eras were defined as follows: For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications.

Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 30 days. The time between the two joined eras was considered as exposed by the first era as shown in **Error! Reference source not found.**, first row.

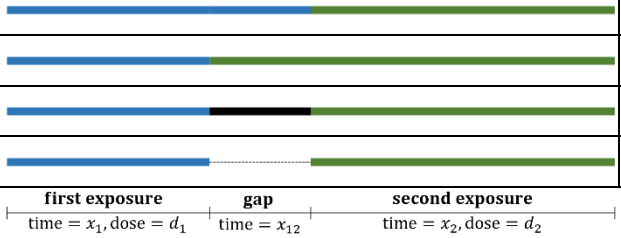
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 5: Gap era joint mode

If two eras started at the same date, the overlapping period was considered exposed by both. We did not consider repetitive exposure.

For this study, drug eras of ICS use were combined by ICS dose class and drug eras of asthma controller medication were combined within the group of controllers, as described in paragraph 9.6.1.

9.9.3. METHODS TO DERIVE PARAMETERS OF INTEREST

Calendar time

Incidence was calculated in the COVID-19 pre-pandemic and pandemic period. (**Error! Reference source not found.**) Calculation of the incidence of the outcomes by period was based on the period the follow-up period at risk of a person falls. This meant that the 1 year time at risk could fall into two different periods.

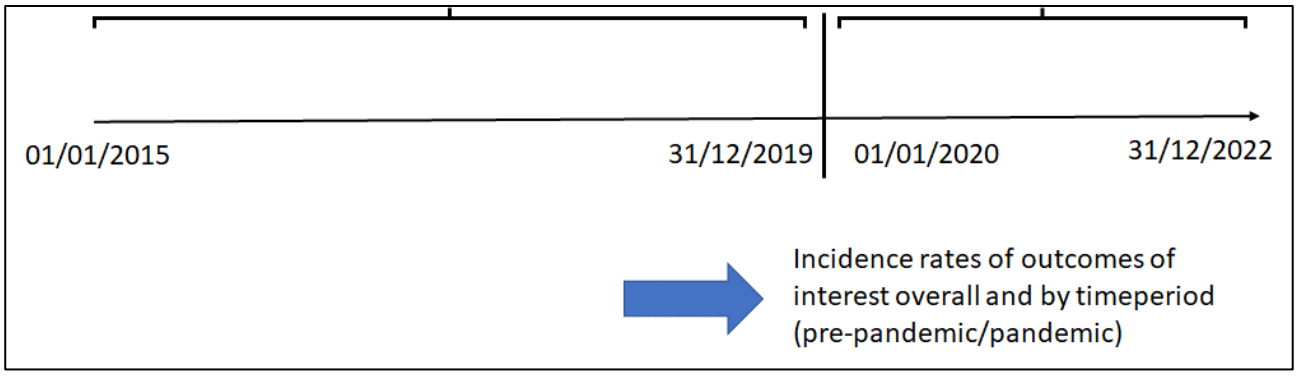


Figure 6: Incidence rate by time-period

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups were used for stratification: 12-17, 18-64, 65-74, and 75-80. Also, an overall rate for all ages combined was provided.

Sex

Results were presented stratified by sex and overall.methods planned to obtain point estimates with confidence intervals of measures of occurrence

9.9.3.1. POPULATION-LEVEL INCIDENCE STUDY

Incidence calculations were conducted separately for each outcome of interest.

Incidence calculations

Annual incidence rates of the outcome of interest were calculated as the number of patients with the outcome of interest per 100,000 person-years of the population at risk of developing the outcome during the period. Those study participants who entered the denominator population did contribute time at risk up to their first outcome during the study period. Or if they did not have an outcome, they contributed time at risk up as described above in section 9.3 and 9.4 (study period and end of study follow-up). Incidence rates were given together with 95% Poisson exact confidence intervals.

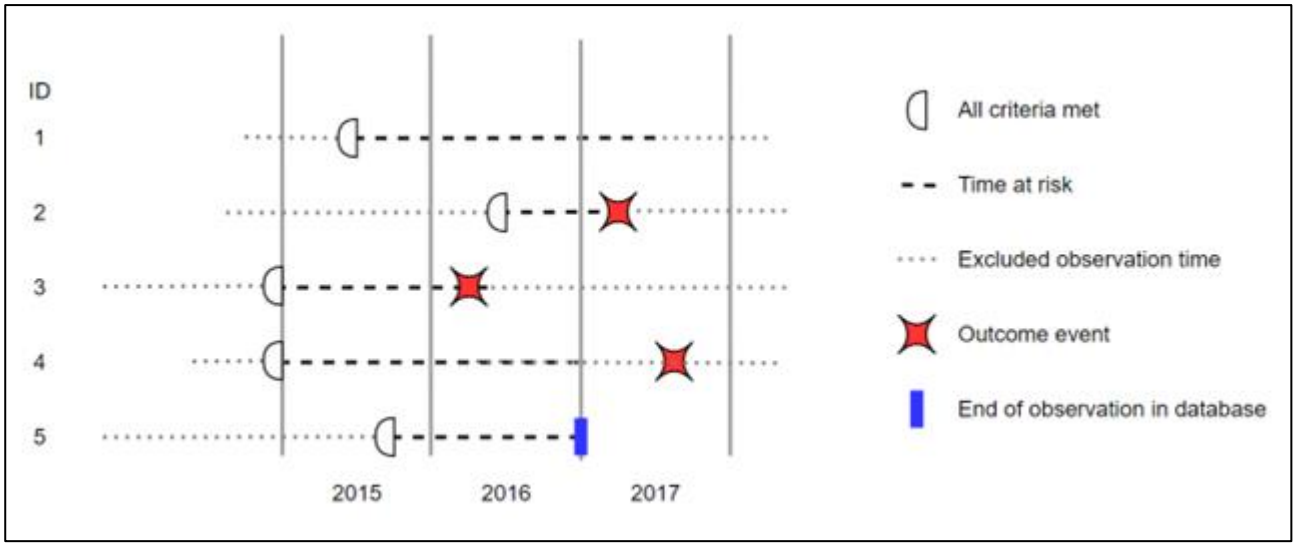


Figure 7: Incidence example for the outcome of interest

An illustration of the calculation of incidence of the outcomes is shown in **Figure 7**.

Patient ID 1 enters the study at a specific moment in time in 2015 when all inclusion and exclusion criteria are fulfilled. From that point in time he/she is at risk and as no event occurred this patient contributes time at risk during 2015, 2016 and 2017. Patient ID 2 enters the study during 2016. An outcome event occurs within a year after follow-up and in particular during 2017. This patient contributes time during 2016 and 2017. Patient ID 3 had severe asthma already before January 1, 2015. Entry in the study is on January 1, 2015. An outcome event occurs in 2016. Patient ID 4 also enters the study on January 1, 2015. An outcome event only occurs during 2017. This is beyond the 2 years follow-up time, so this event is not counted. The patient contributes time in 2015 and 2016. Patient ID 5 enters during 2015. At the end of 2016, observation time in the database ends, e.g. because the patient moves and is no longer in the GP practise. Time at risk stops at this point.

Incidence rates for the pre-pandemic and pandemic periods were provided, for the first 52 weeks after inclusion as well as for the second 52 weeks after inclusion for those who survived the first 52 weeks.

For these incidence rates, estimates over all databases were given, using meta-analysis.

9.9.3.2. KAPLAN MEIER

Kaplan Meier curves with 95% confidence intervals (Greenwood) were provided showing survival probabilities for overall mortality and for serious cardiovascular events, starting at study entry and ongoing during the available observation time of the patients within the study period. For cause-specific mortality, Aalen-Johansen estimators were used. All these curves were reported for the pre- and pandemic periods.

9.9.4. MISSING VALUES

If dosing information of ICS exposure was missing, this exposure was not used in determining the inclusion criterion of medium/high ICS dose. This means the study cohorts include only persons with recorded ICS dose exposure.

For measurements values, the most recent available measurement before study entry was used, with maximum time between measurement and study entry of 365 days. The number of persons with available measurement are reported. Measurements in observational data might be reported for selected persons or in selected situations. Missing values for measurements are likely not missing at random.

The follow-up time after study entry for a person could be shorter than one or two years. In this case, the person was censored for the Kaplan-Meier estimations and for the calculation of the IRs. This censoring is assumed to be at random, which can be considered reasonable, as caused by end of observation in the database, for example due to switching of general practitioner or the general practitioner switching information system, or by end of study period (31st December 2022) (administrative censoring).

9.9.5. SENSITIVITY ANALYSIS

The proportion of patients with prevalent severe asthma (patients who were already the necessary period on medium or high dose ICS) prior to entry in the study is likely to be different in 2015 compared to later years. During 2015, the proportion of patients with prevalent severe asthma might be considerable however during the following years this proportion will be lower as the only prevalent severe asthma cases will be those entering because their observation in the database started later. As patients with prevalent severe asthma might be more severe (as longer time since date of diagnosis of severe asthma) compared to patients with incident severe asthma, incident rates by calendar year are presented. If counts however were too low (<5), it was not possible to conduct these sensitivity analyses.

9.9.6. DEVIATIONS FROM THE PROTOCOL

When applying the inclusion and exclusion criteria according to the protocol, the number of individuals which were included in cohort 2 was low. Individuals were mainly excluded because they had a comorbidity (presence of disease codes in the 12 months prior to the index date). This first comorbidity definition included

any diagnosis recorded within the condition group within 12 months prior to the index date, irrespective of severity.

As the trial exclusion criteria involve conditions that are not stable and that could influence the safety of the subject during the study and affect their ability to complete the duration of study, additional data analyses were conducted using alternative definitions of comorbidities that represent the pre-specified exclusion criteria for cohort 2 where:

- Presence of cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity codes in the 12 months prior to the index date was *not longer considered as an exclusion criteria*. (Cohort 2A)
- Comorbidity was refined where *only severe comorbidities or comorbidities that might be uncontrolled were considered*. The list with refined comorbidity codes has been added as an appendix to the report. (Cohort 2B) (appendix – table 2)

This also served to understand the impact that exclusion of people with comorbidities would have on the trial participants.

10. DATA MANAGEMENT

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources or on a simulated set of patients and quality control checks were performed. Once all the tests were passed, the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations were performed, and additional fine tuning of the code base was needed. A service desk was available during the study execution for support.

11. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

A pharmacist/MD reviewed the codes of the drugs of interest. To obtain information on how detailed drug use was available within the database, the DrugExposureDiagnostics R package ran on the different datasources plus some specific code to check the calculation of daily dose of ICS exposures. Results of these runs indicated whether additional mapping for a specific drug (e.g. for a specific ICS of interest) was needed.

The prevalence of exclusion criteria in cohort 1 was checked. Based on these prevalences, codes for some exclusion criteria were revised.

The analyses in the study code were based on the R packages IncidencePrevalence, PatientProfiles and survival. IncidencePrevalence has been developed to estimate incidence and prevalence of conditions and drug use. This package includes numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. PatientProfiles has been developed to identify characteristics of patients. The package 'survival' is a commonly used package with solid statistical background. All three packages are available at https://cran.r-project.org/.

12. RESULTS

12.1. PARTICIPANTS

The number of patients within the different cohorts (by database) is described in Table 9.

The proportion of patients with asthma, amongst patients present within the study period and within the age range of 12-80 ranged between 3.7% to 15% across data sources.

When applying inclusion criteria to define severe asthma (cohort 1), the number of persons ranged between <5 and 19,249, the proportion of patients with severe asthma being between 0.9% and 2.6%.

When applying both inclusion and all exclusion criteria, the number of individuals dropped to 18.7% of cohort 1 in SIDIAP, 14.9% in CPRD and 13.6% in IPCI, while the number in EBB dropped below 5 (cohort 2 in Table 9). Patients were mainly excluded because of reason of underlying comorbidity (namely COPD but also other conditions) and smoking status (i.e. almost 70% of individuals within CPRD were current or past smokers). Information on comorbidity and lifestyle factors is presented in Table 10).

Because of these low numbers and that comorbidity definitions included all recorded events irrespective of severity, alternative definitions for cohort 2 were applied (see also 9.9.7 – deviations from the protocol), namely:

- Not using the presence of cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity as exclusion criteria (cohort 2A)
- Using restricted concept sets for cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity (cohort 2B) (see also appendix Table 2 for definition of stricter comorbidity)

Table 9: Description of individuals within the different databases

	CPRD GOLD (UK)	EBB (Estonia)	IMASIS (SP)	IPCI (NL)	SIDIAP (SP)
Source population	17,054,819	209,457	1,051,862	2,781,698	8,265,343
Patients aged 12-80 years active between 1st January 2015 until 31st December 2022	4,975,411	190,453	164,178	1,436,384	5,048,566
Patients with asthma code	745,233 (15.0%)	21,831 (11.5%)	6,010 (3.7%)	167,364 (11.7%)	331,303 (6.6%)
Severe asthma patients - Cohort 1 (% -= proportion of persons with asthma)	19,249 (2.6%)	190 (0.9%)	< 5	1,596 (1.0%)	5,549 (1.7%)
Severe asthma patients - Cohort 2A (% = proportion of persons from cohort 1)	4,184 (21.7%)	37 (19.5%)	< 5	547 (34.3%)	2,213 (39.9%)
Severe asthma patients - Cohort 2B (% = proportion of persons from cohort 1)	3,929 (20.4%)	20 (10.5%)	< 5	441 (27.6%)	1.951 (35.2%)
Severe asthma patients - Cohort 2 (% = proportion of persons from cohort 1) (cohort 2 is in line with original protocol)	2,869 (14.9%)	< 5	< 5	217 (13.6%)	1,036 (18.7%)
Severe asthma patients - Cohort 3 (% = proportion of persons from cohort 1)	16,380 (85.1%)	NA	NA	1,379 (86.4%)	4,513 (81.3%)

Cohort 2A – applying exclusion criteria, except for cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity

Cohort 2B – applying narrow exclusion of cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity. Narrow exclusion means that comorbidity was based on more selected comorbidity i.e. not cardiovascular overall but severe cardiovascular conditions (also see appendix table 2)

Cohort 2 – applying broad exclusion cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity. This cohort is **in line with the original protocol of this study**.

Because of low numbers (<5 patients fulfilling inclusion criteria) in cohort 1 for IMASIS, this database did not contribute to the main analyses. Low numbers that could be selected in IMASIS was mainly because inpatient data could not be used (no patients with inhouse exposure of medium or high dose ICS for 12 months). Only outpatient individuals could be used but – because of short duration of follow-up and fact that duration of ICS use was set at 30 days – less than 5 patients finally fulfilled inclusion criteria.

12.2. DESCRIPTIVE DATA

The patients' characteristics are described by cohort (and by database) within different tables.

12.2.1. CHARACTERISTICS OF COHORT 1

Patient characteristics of individuals with severe asthma, within cohort 1, by database, are described in Table 10.

There were between 190 and 19,249 patients with severe asthma in Cohort 1.

In all databases, the proportion of females is higher than the proportion of males with a female to male ratio of around 2:1. The majority of individuals were 50 years or older at time of index date and less than 50% of individuals had a history of more than 2 severe asthma exacerbations in the year prior to the index date.

Table 10 also describes the proportion of patients with comorbidities and use of concomitant medication that are part of the respective exclusion criteria to define cohort 2. Especially in the EBB, the proportion of patients with comorbidity is high. For instance, the proportion of patients for which a SNOMED code of a cardiovascular condition was reported within the 12 months prior to study entry was 73% for EBB whereas it was 23%, 17 % and 6.3% in IPCI, SIDIAP and CPRD GOLD respectively.

In all databases, the number of patients with ACO (disease codes of asthma as well as COPD) was high and ranged from 32% in IPCI to 68% in the EBB.

Table 10 also describes the proportion of comorbidity when applying the stricter criteria (i.e. more severe comorbidity)(see 9.9.7 Deviations from the protocol).

Table 10: Patients characteristics of the severe asthma cohort 1

		CPRD GOLD N = 19,249		EBB N = 190		IPCI N = 1596		SIDIAP N = 5,549	
		Freq	%	Freq	%	Freq	%	Freq	%
Sex	Female	12,374	(64.3)	125	(65.8)	1,036	(64.9)	3,759	(67.7)
	Male	6,875	(35.7)	65	(34.2)	560	(35.1)	1,790	(32.3)
Age group (years)	12-17	159	(0.8)	0	(0.0)	< 5	(NA)	30	(0.5)
	18-64	10,920	(56.7)	98	(51.6)	885	(55.5)	2,904	(52.3)
	65-74	5,583	(29)	61	(32.1)	463	(29)	1,672	(30.1)
	75-80	2,587	(13.4)	31	(16.3)	245	(15.4)	943	(17)
Number of exacerbations in previous year	2	10,174	(52.9)	111	(58.4)	895	(56.1)	3,561	(64.2)
	3	2,675	(13.9)	52	(27.4)	265	(16.6)	771	(13.9)
	4	1,655	(8.6)	8	(4.2)	156	(9.8)	428	(7.7)
	5	1,054	(5.5)	< 5	(NA)	94	(5.9)	196	(3.5)
	More than 5	3,691	(19.2)	15	(7.9)	186	(11.7)	593	(10.7)
Exclusion criteria[1]	Bronchiectasis[2]	1,334	(6.9)	13	(6.8)	15	(0.9)	515	(9.3)
	COPD[2]	7,769	(40.4)	129	(67.9)	787	(49.3)	1,788	(32.2)
	Lung cancer[2]	143	(0.7)	5	(2.6)	48	(3)	31	(0.6)
	Pulmonary fibrosis[2]	107	(0.6)	< 5	(NA)	0	(0)	38	(0.7)
	Cardiovascular	1,213	(6.3)	142	(74.7)	384	(24.1)	1,020	(18.4)
	Cardiovascular (restr)	727	(3.8)	83	(43.7)	203	(12.7)	451	(8.1)
	Gastrointestinal	1,759	(9.1)	108	(56.8)	272	(17)	899	(16.2)

	CPRD GOLD N = 19,249		EBB N = 190		IPCI N = 1596		SIDIAP N = 5,549	
	Freq	%	Freq	%	Freq	%	Freq	%
Gastrointestinal (restr)	207	(1.1)	13	(6.8)	36	(2.3)	81	(1.5)
Hepatic	122	(0.6)	8	(4.2)	7	(0.4)	164	(3)
Hepatic (restr)	128	(0.7)	8	(4.2)	7	(0.4)	172	(3.1)
Renal	313	(1.6)	25	(13.2)	61	(3.8)	336	(6.1)
Renal (restr)	214	(1.1)	12	(6.3)	12	(0.8)	116	(2.1)
Neurological	858	(4.5)	76	(40)	89	(5.6)	632	(11.4)
Neurological (restr)	62	(0.3)	< 5	(NA)	8	(0.5)	34	(0.6)
Musculoskeletal	2,166	(11.3)	88	(46.3)	256	(16)	1,059	(19.1)
Musculoskeletal (restr)	69	(0.4)	13	(6.8)	18	(1.1)	43	(0.8)
Infectious	1,743	(9.1)	74	(38.9)	358	(22.4)	1,027	(18.5)
Infectious (restr)	485	(2.5)	42	(22.1)	171	(10.7)	336	(6.1)
Endocrine	880	(4.6)	72	(37.9)	238	(14.9)	577	(10.4)
Endocrine (restr)	54	(0.3)	6	(3.2)	0	(0)	48	(0.9)
Metabolic	1,146	(6)	87	(45.8)	281	(17.6)	920	(16.6)
Metabolic (restr)	25	(0.1)	< 5	(NA)	0	(0)	0	(0)
Hematological	172	(0.9)	7	(3.7)	9	(0.6)	210	(3.8)
Hematological (restr)	8	(0)	0	(0)	0	(0)	15	(0.3)
Psychiatric	899	(4.7)	65	(34.2)	138	(8.6)	688	(12.4)
Psychiatric (restr)	68	(0.4)	< 5	(NA)	17	(1.1)	211	(3.8)
LRTI[3]	56	(0.3)	8	(4.2)	49	(3.1)	177	(3.2)
URTI[3]	106	(0.6)	< 5	(NA)	13	(0.8)	76	(1.4)
Methotrexate[4]	241	(1.3)	< 5	(NA)	21	(1.3)	68	(1.2)
Cyclosporine[4]	11	(0.1)	0	(0)	0	(0)	7	(0.1)
TBC	5	(0)	0	(0)	0	(0)	< 5	(NA)
Acute liver disease	283	(1.5)	20	(10.5)	12	(0.8)	172	(3.1)
Alcohol drug abuse	19	(0.1)	< 5	(NA)	79	(4.9)	51	(0.9)
Anaphylaxis[2]	159	(0.8)	< 5	(NA)	13	(0.8)	43	(0.8)
Cancer[2]	1,648	(8.6)	50	(26.3)	266	(16.7)	668	(12)
Hepatitis B[2]	31	(0.2)	0	(0)	5	(0.3)	80	(1.4)

		CPRD GOLD N = 19,249		EBB N = 190		IPCI N = 1596		SIDIAP N = 5,549	
		Freq	%	Freq	%	Freq	%	Freq	%
Other comorbidities	Hepatitis C[2]	50	(0.3)	5	(2.6)	< 5	(NA)	79	(1.4)
	HIV[2]	22	(0.1)	0	(0)	< 5	(NA)	15	(0.3)
	Tobacco dependency syndrome[2]	82	(0.4)	0	(0)	387	(24.2)	0	(0)
	Smoking	13,449	(69.9)	< 5	(NA)	197	(12.3)	1,477	(26.6)
	Arterial hypertension[2]	6,613	(34.4)	133	(70)	680	(42.6)	2,643	(47.6)
	Atopic dermatitis[2]	3,289	(17.1)	42	(22.1)	219	(13.7)	312	(5.6)
	Chronic idiopathic urticaria[2]	0	(0)	0	(0)	0	(0)	0	(0)
	Chronic sinusitis[2]	1,007	(5.2)	62	(32.6)	135	(8.5)	236	(4.3)
	Diabetes mellitus[2]	2,949	(15.3)	46	(24.2)	325	(20.4)	1,102	(19.9)
	Gerd[2]	2,844	(14.8)	113	(59.5)	166	(10.4)	727	(13.1)
	Nasal polyposis[2]	974	(5.1)	28	(14.7)	24	(1.5)	524	(9.4)
	Osteoporosis[2]	1,568	(8.1)	33	(17.4)	151	(9.5)	796	(14.3)
	Rhinitis[2]	4,595	(23.9)	96	(50.5)	442	(27.7)	1,455	(26.2)

LRTI= lower respiratory tract infection, URTI-upper respiratory tract infection,

[1] unless otherwise specified, presence of event during 12 months before index date

[2] presence within the complete medical history before to index date

[3] – presence during 2 weeks before index date

[4] - use of medication during 12 weeks before index date

Laboratory measurements of individuals from cohort 1 in the 12 months prior to study entry are presented in Table 11. In all databases, the median BMI was around 30, implying that half of patients with severe asthma within our study population suffered from obesity. If measured, the median values for liver functions tests were within the normal ranges. Median blood eosinophil values within all databases were 0.2 * 10^9/l which represents normal blood eosinophil counts.

Table 11: Laboratory Measurement summary and BMI for people with severe asthma (cohort 1)

	CPRD (N = 19,249)			EBB (N = 190)		
Measurement	N (%)	Median	IQR	N (%)	Median	IQR
Alanine transaminase (U/l)	10,270 (53.3)	19	[15; 27]	113 (59.5)	21	[15.3; 32]
Alkaline phosphatase (U/l)				59 (31.0)	78	[61; 99]
Aspartate transaminase (U/l)	1,167 (6.1)	20	[16; 25]	101 (53.1)	22	[18.4; 28.5]
BMI (kg/m2)	10,400 (54.0)	29.7	[25.2; 35.1]	56 (29.5)	31.55	[27.38; 35.64]
Bilirubin (direct) (mu/l)				16 (8.4)	3.2	[2.5; 5.6]
Bilirubin (total) (mu/l)				51 (26.8)	7.4	[6; 12]
Blood eosinophils (%)						
Blood eosinophils (10^9/l)	10,457 (54.3)	0.2	[0.1; 0.3]	95 (50.0)	0.2	[0.1; 0.37]
	IPCI (N = 1,596)			SIDIAP (N = 5,549)		
Measurement	N (%)	Median	IQR	N (%)	Median	IQR
Alanine transaminase (U/l)	426 (26.7)	23	[17; 30]	3,335 (60.1)	18	[14; 25]
Alkaline phosphatase (U/l)	81 (5.1)	81	[70; 98]	1,597 (28.9%	79	[64; 95]
Aspartate transaminase (U/l)	143 (9.0)	22	[19; 28]			
BMI (kg/m2)	639 (40.0)	29.06	[25.48; 33.6]	2,852 (51.4)	30.13	[26.57; 34.25]
Bilirubin (direct) (mu/l)	8 (0.5)	4	[2; 28]			
Bilirubin (total) (mg/dl)				1,864 (33.6)	0.49	[0.38; 0.63]
Bilirubin (total) (mu/l)	89 (5.6)	7	[5; 10]			
Blood eosinophils (%)				3,569 (64.3)	3.1	[1.8; 5.1]
Blood eosinophils (10^9/l)	325 (20.4)	0.2	[0.1; 0.3]			

In SIDIAP, blood eosinophils are presented as percentage of WBC.

12.2.2. CHARACTERISTICS OF COHORT 2 AND COHORT 3

There were between 217 and 2,869 patients in cohort 2 (only 3 databases contributed with data). The high prevalence of underlying comorbidities listed as exclusion factors had as result, that many patients were excluded from cohort 2, especially from the Estonian Biobank.

Other reasons for exclusion from cohort 2 were smoking status (current or past) which was 12% in IPCI, 27% in SIDIAP, 70% in CPRD GOLD, and COPD in history: 32% in SIDIAP, 40% in CPRD GOLD, 49% in IPCI and 68% in EBB.

Baseline characteristics of *cohort 2* are presented in Table 12. By definition, all persons in this cohort do not have any of the exclusion criteria, therefor these are omitted from this table. Persons in cohort 2 are younger compared to those in cohort 1, had less exacerbations in the year before index date and less comorbidity. Summary statistics of measurements in cohort 2 are presented in Table 13.

Baseline characteristics of *cohort 3* are described in Tables 1-2 of the supplementary material. As the number of individuals from the Estonian Biobank who remained in cohort 2 was very small, characteristics of cohort 3 are almost identical to those of cohort 1 for this database.

Table 12: Patients characteristics of the severe asthma cohort 2

		CPRD GOLD N = 2,869		IPCI N = 217		SIDIAP N = 1,036	
		Freq	%	Freq	%	Freq	%
Sex	Female	1,910	(66.6)	142	(65.4)	715	(69)
	Male	959	(33.4)	75	(34.6)	321	(31)
Age group (years)	12-17	119	(4.1)	< 5	(NA)	19	(1.8)
	18-64	1,976	(68.9)	169	(77.9)	618	(59.7)
	65-74	569	(19.8)	38	(17.5)	276	(26.6)
	75-80	205	(7.1)	8	(3.7)	123	(11.9)
Number of exacerbations in previous year	2	1,713	(59.7)	133	(61.3)	782	(75.5)
	3	437	(15.2)	38	(17.5)	108	(10.4)
	4	225	(7.8)	24	(11.1)	70	(6.8)
	5	153	(5.3)	10	(4.6)	26	(2.5)
	More than 5	341	(11.9)	12	(5.5)	50	(4.8)
Comorbidities in complete history before index date	Arterial hypertension	768	(26.8)	59	(27.2)	383	(37)
	Atopic dermatitis	546	(19)	35	(16.1)	72	(6.9)
	Chronic idiopathic urticaria	0	(0)	0	(0)	0	(0)
	Chronic sinusitis	178	(6.2)	20	(9.2)	48	(4.6)
	Diabetes mellitus	278	(9.7)	13	(6)	144	(13.9)
	Gerd	325	(11.3)	20	(9.2)	104	(10)
	Nasal polyposis	222	(7.7)	< 5	(NA)	133	(12.8)
	Osteoporosis	138	(4.8)	9	(4.1)	115	(11.1)
	Rhinitis	895	(31.2)	64	(29.5)	307	(29.6)

Table 13: Laboratory Measurement summary and BMI for people with severe asthma (cohort 2)

	CPRD (N = 2,869)			IPCI (N = 217)			SIDIAP (N = 1,036)		
Measurement	N	Median	IQR	N	Median	IQR	N	Median	IQR
Alanine transaminase (U/l)	1,204	21	[16; 28]	37	23	[18; 28]	502	18	[14; 25]
Alkaline phosphatase (U/l)				4	51	[47; 59]	211	79	[61; 97]
Aspartate transaminase (U/l)	124	21	[17; 23]	9	25	[21; 25]			
BMI (kg/m2)	1,152	30.8	[26.6; 36.1]	42	29	[25.48; 36.2]	437	29.57	[26.16; 34.2]
Bilirubin (total) (mg/dl)							257	0.5	[0.4; 0.64]
Bilirubin (total) (mu/l)				7	8	[7; 13]			
Blood eosinophils (%)							537	3.6	[2.1; 5.9]
Blood eosinophils (10^9/l)	1,277	0.2	[0.1; 0.37]	37	0.22	[0.13; 0.33]			

12.2.3. CHARACTERISTICS OF COHORT 2A AND COHORT 2B

Baseline characteristics of cohorts 2A (applying exclusion criteria, except for cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity) and 2B (where more severe comorbidity of cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity is considered) are described in Tables 3-6 of the supplementary material. Differences with the characteristics in cohort 2 are small.

12.3. MAIN RESULTS

In this section, we present the incidence rates of the outcomes of interest (mortality, fatal infections, fatal CV events and serious CV events (overall and stratified by MI, stroke and hospitalisation for HF). Results are presented per cohort and for the first and second year of follow-up separately.

Due to various reasons, not all databases could contribute with data to every outcome and a summary of their distribution per outcome is presented below in Table 14:

Table 14: Overview of available IRs

Outcome	Year	Missing in Cohort 1	Missing in Cohort 2	Reason
All-cause mortality	1		EBB, IPCI, SIDIAP	Low number
	2	EBB	EBB, IPCI, SIDIAP	Low number
Fatal infection	1	IPCI	CPRD GOLD, EBB, IPCI, SIDIAP	Low number

	2	EBB, IPCI, SIDIAP	CPRD GOLD, EBB, IPCI, SIDIAP	Low number
Fatal CV event	1	IPCI	CPRD GOLD, EBB, IPCI, SIDIAP	Low number
	2	EBB, IPCI, SIDIAP	CPRD GOLD, EBB, IPCI, SIDIAP	Low number
Serious CV event	1		EBB, IPCI	Low number
	2		EBB, IPCI	Low number
MI	1	EBB	EBB, IPCI, SIDIAP	Low number
	2	EBB	CPRD GOLD, EBB, IPCI, SIDIAP	Low number
Stroke	1	EBB	EBB, IPCI	Low number
	2	EBB	EBB, IPCI, SIDIAP	Low number
Hospitalization HF	1	CPRD GOLD, IPCI	CPRD GOLD, IPCI	Lack of/incomplete linkage to hospital records
			EBB	Low number
	2	CPRD GOLD, IPCI	CPRD GOLD, IPCI	Lack of/incomplete linkage to hospital records
			EBB	Low number

IMASIS is missing for all outcomes due to low number of patients in both cohorts.

12.3.1. COHORT 1

12.3.1.1. MORTALITY

The IR (95% CI) for all-cause mortality in the first year ranged between 16 (13; 19) and 30 (28; 33) per 1,000 PY for the primary care databases and was the highest for Estonia with an IR of 58 (28; 106) per 1,000 PY. (Table 15)

When exploring cause specific mortality, the incidence rate of mortality because of fatal infections was similar for SIDIAP and CPRD GOLD (2 (1; 3) per 1,000 PY) and much higher for EBB (29 (9; 67) per 1,000 PY). The IR of CV mortality was again comparable for SIDIAP and CPRD GOLD (3 (2; 5) and 4 (3; 5) per 1,000 PY respectively) and much higher for EBB (52 (24; 99) per 1,000 PY). Because of low numbers, cause-specific mortality rates could not be calculated for IPCI.

When exploring IRs for mortality in the second year following study entry, the number of events for EBB became too low to calculate overall mortality rates and too low for SIDIAP and IPCI to calculate cause-specific mortality rates. For overall mortality, rates in year 2 were similar to those in year 1, namely 16 (12; 20) to 29 (26; 32) per 1,000 PY.

The IR of overall and cause specific mortality, stratified by age category is presented in Figure 8. As expected, the IR of mortality increased by age. In age category 18-64 years the IR ranged from 6 (4; 10) to 15 (8; 26) per 1,000 PY, in age category 65-74 years 18 (12; 26) to 43 (37; 49) per 1,000 PY and in age category 75-80 years 44 (31; 61) to 76 (65; 89) per 1,000 PY. Increase of IR by age was also observed for fatal infections (CPRD

GOLD only) and fatal CV events (SIDIAP and CPRD GOLD). As the number for EBB became too low following age stratification, no mortality rates could be calculated.

Table 10 of the supplementary material describes the IR of the outcomes (including mortality) in the pre-pandemic and pandemic phase (including data up to 2022). The IR of mortality during the first year following study entry was lower in the pandemic phase compared to pre-pandemic for CPRD GOLD (18 (14; 23) vs 33 (30; 36) per 1000 PY) and IPCI (18 (8; 36) vs. 30 (20;42) per 1,000 PY) whereas it was higher for SIDIAP (19 (11:32) vs. 15 (12; 19) per 1,000 PY). Mortality rates in the second year following study entry were lower in the pandemic compared to pre pandemic phase in all databases (22 (17; 28) vs 32 (28; 35) per 1,000 PY for CPRD GOLD, 19 (8; 37) vs 33 (22; 49) per 1,000 PY for IPCI and 10 (5; 19) vs 17 (13;22) per 1,000 PY for SIDIAP). Because of the large 95% CIs these differences should be assessed carefully. Further stratification between pre-pandemic vs. pandemic for the other mortality outcomes (fatal infection and fatal CV events) was hampered because of low numbers.

Table 13 of the supplementary material describes the IR of the outcomes (including mortality) by sex. When numbers were sufficient to allow stratification (i.e., at least 5 events per strata), the IR of overall mortality as well as mortality rate following infections and mortality rate following CV events were higher in males compared to females in all databases.

The Kaplan Meier curves for mortality by database are presented in Figure 9. This shows the same differences between databases as seen in the IRs, namely lowest mortality in SIDIAP and highest mortality in year 1 in EBB. In following years, survival curves of CPRD GOLD, EBB and IPCI are very similar. Figures 1-4 and Figures 5-8 from the supplementary material provide the KM curves with 95% confidence bands of all-cause mortality and Aalen-Johansen curves for cause-specific mortality.

Table 15: Incidence rates in first and second year after study entry in people with severe asthma in cohort 1

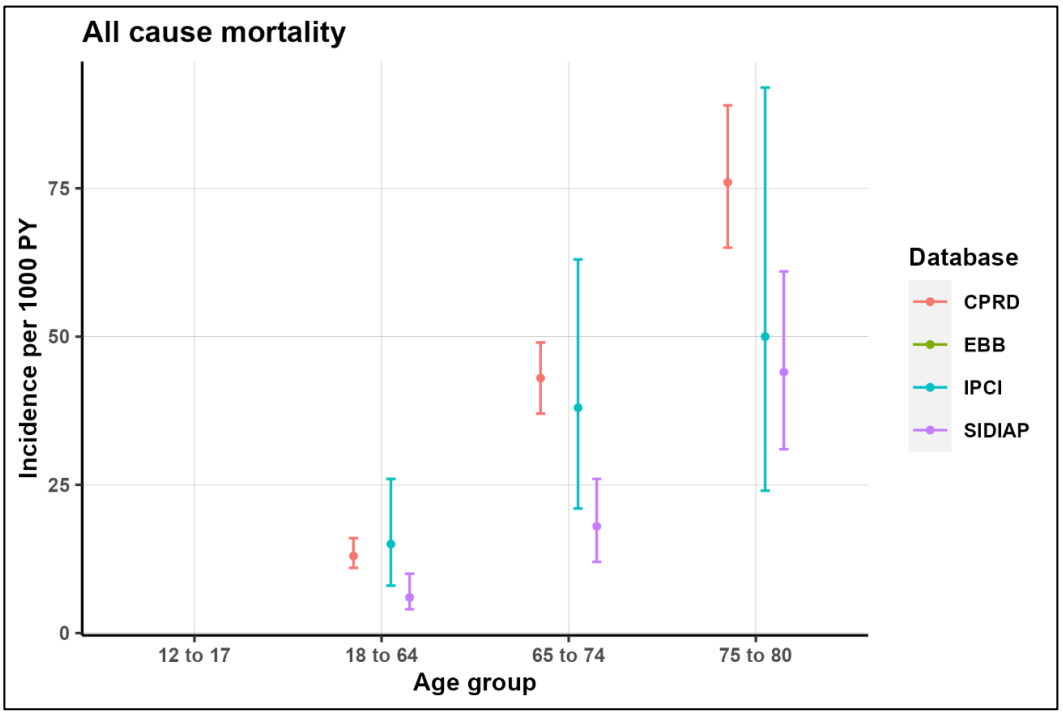
Follow-up period	Outcome	Database	N of persons	N of events	PY	IR	95% CI
First year	All-cause mortality	CPRD	19,237	517	17,114	30	(28; 33)
		EBB	190	10	173	58	(28; 106)
		IPCI	1,596	38	1,451	26	(19; 36)
		SIDIAP	5,545	84	5,339	16	(13; 19)
	Fatal infection	CPRD	19,237	31	17,114	2	(1; 3)
		EBB	190	5	174	29	(9; 67)
		IPCI	1,596	< 5	1,451	NA	
		SIDIAP	5,545	10	5,339	2	(1; 3)
	Fatal CV event	CPRD	19,237	60	17,114	4	(3; 5)
		EBB	190	9	173	52	(24; 99)
		IPCI	1,596	< 5	1,451	NA	
		SIDIAP	5,545	15	5,339	3	(2; 5)
	Serious CV event	CPRD	19,237	184	17,032	11	(9; 12)

Follow-up period	Outcome	Database	N of persons	N of events	PY	IR	95% CI
		EBB	190	33	164	202	(139; 283)
		IPCI	1,596	20	1,442	14	(8; 21)
		SIDIAP	5,545	212	5,233	41	(35; 46)
	MI	CPRD	19,237	73	17,078	4	(3; 5)
		EBB	190	< 5	173	NA	
		IPCI	1,596	11	1,446	8	(4; 14)
		SIDIAP	5,545	18	5,332	3	(2; 5)
	Stroke	CPRD	19,237	121	17,063	7	(6; 8)
		EBB	190	< 5	173	NA	
		IPCI	1,596	12	1,446	8	(4; 14)
		SIDIAP	5,545	40	5,318	8	(5; 10)
	Hospitalisation HF	CPRD	19,237	NA	NA	NA	
		EBB	190	32	164	195	(133; 275)
		IPCI	1,596	< 5	1,451	NA	
		SIDIAP	5,545	165	5,257	31	(27; 37)
Second year	All-cause mortality	CPRD	14,882	388	13,274	29	(26; 32)
		EBB	156	< 5	140	NA	
		IPCI	1,307	33	1,180	28	(19; 39)
		SIDIAP	5,093	76	4,861	16	(12; 20)
	Fatal infection	CPRD	14,882	26	13,274	2	(1; 3)
		EBB	157	< 5	140	NA	
		IPCI	1,307	< 5	1,180	NA	
		SIDIAP	5,093	< 5	4,861	NA	
	Fatal CV event	CPRD	14,882	41	13,274	3	(2; 4)
		EBB	157	< 5	140	NA	
		IPCI	1,307	< 5	1,180	NA	
		SIDIAP	5,093	< 5	4,861	NA	
	Serious CV event	CPRD	14,882	112	13,223	8	(7; 10)
		EBB	157	19	130	146	(88; 228)
		IPCI	1,307	17	1,172	15	(8; 23)

Follow-up period	Outcome	Database	N of persons	N of events	PY	IR	95% CI
		SIDIAP	5,093	167	4,782	35	(30; 41)
	MI	CPRD	14,882	53	13,248	4	(3; 5)
		EBB	157	< 5	140	NA	
		IPCI	1,307	6	1,177	5	(2; 11)
		SIDIAP	5,093	16	4,852	3	(2; 5)
	Stroke	CPRD	14,882	62	13,247	5	(4; 6)
		EBB	157	< 5	139	NA	
		IPCI	1,307	12	1,175	10	(5; 18)
		SIDIAP	5,093	28	4,848	6	(4; 8)
	Hospitalisation HF	CPRD	14,882	NA	NA	NA	
		EBB	157	18	131	137	(81; 217)
		IPCI	1,307	< 5	1,180	NA	
		SIDIAP	5,093	131	4,800	27	(23; 32)

HF -heart failure; IR= Number of events per 1,000 PY

(**Error! Reference source not found.**a – cohort 1):



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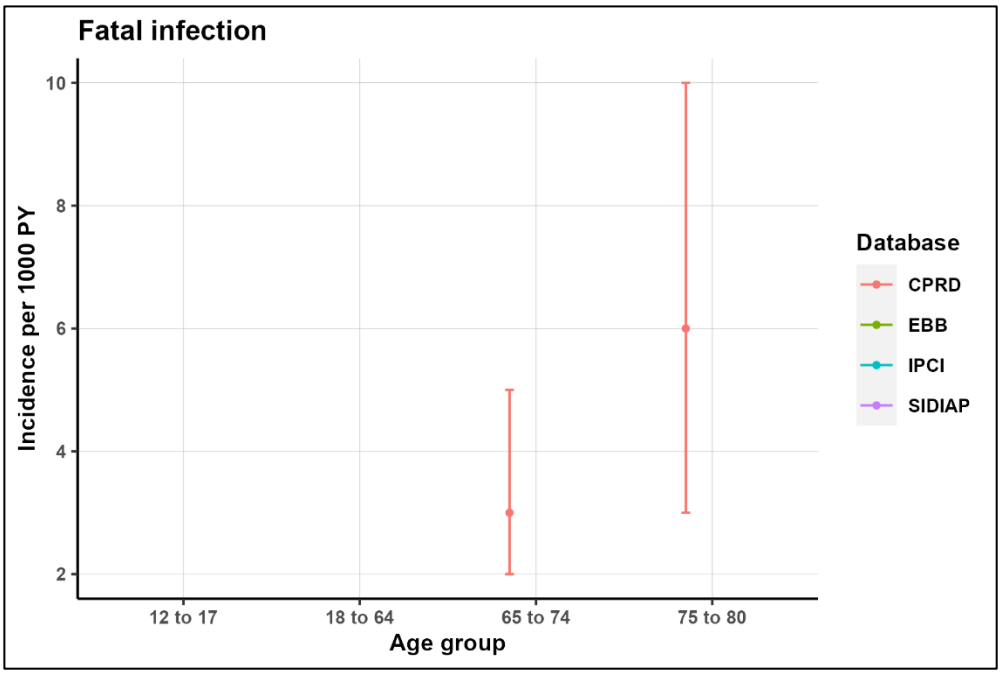

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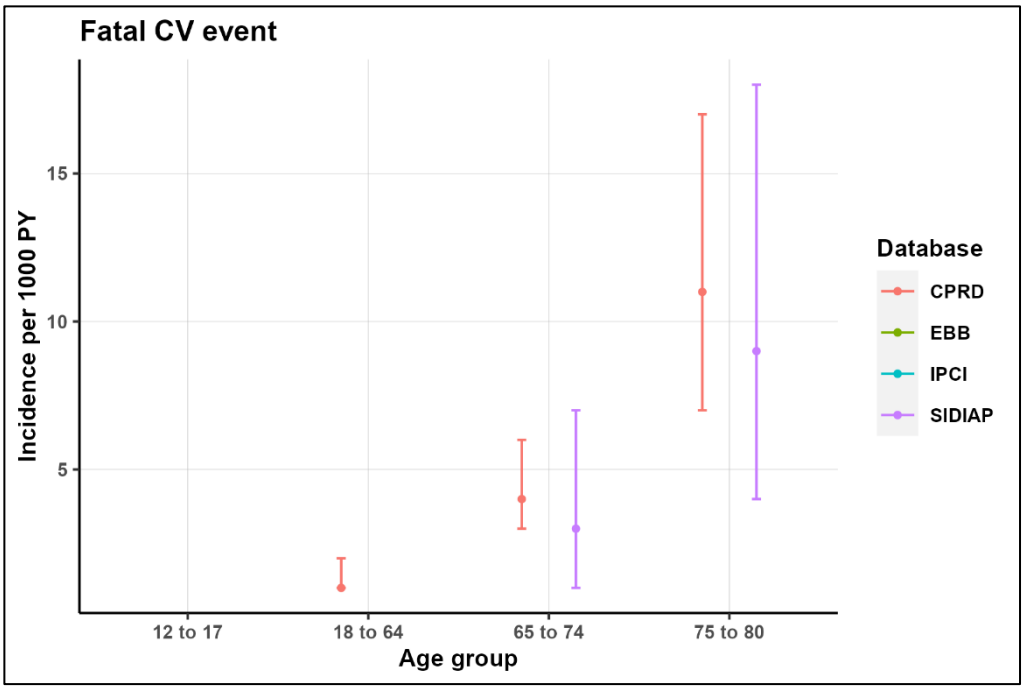


Figure 8: Incidence rates of mortality in people with severe asthma (cohort 1) by age group

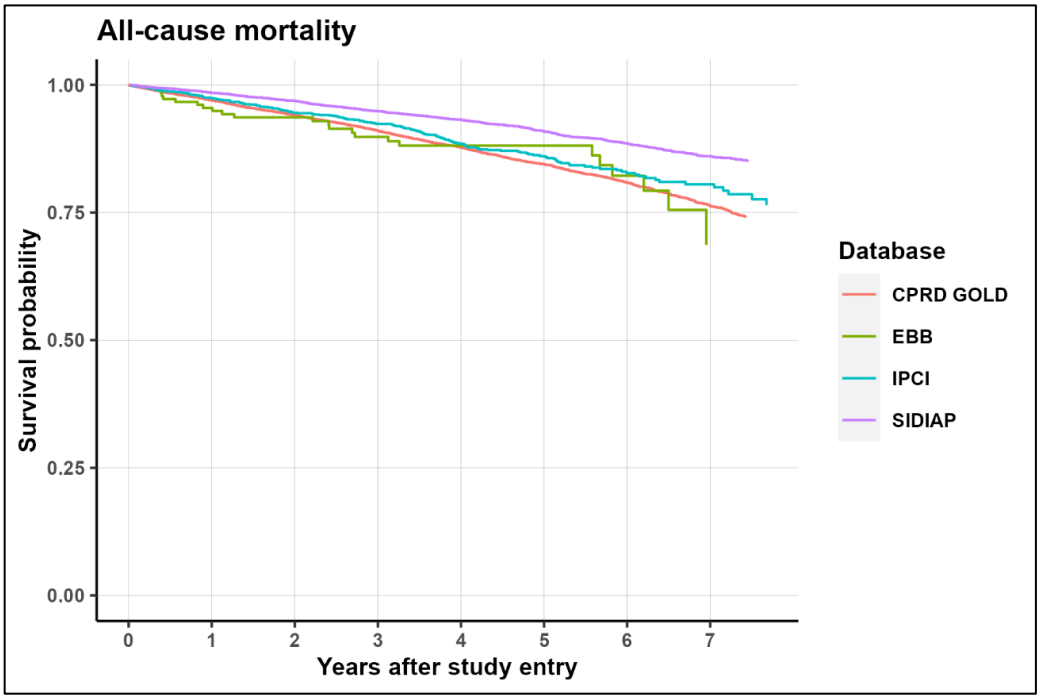


Figure 9: Kaplan-Meier curve for all-cause mortality in people with severe asthma (cohort 1)

12.3.1.2. CV EVENTS

Table 15 describes the IRs of the other outcomes of interest in particular the IR of overall CV events (as a composite endpoint) and the IR of MI, stroke and hospitalisation for heart failure separately.

In the first year following study entry, the IR of serious CV events was comparable between IPCI and CPRD GOLD namely 14 (8; 21) and 11 (9; 12) per 1,000 PY respectively. This incidence rate was much higher for SIDIAP namely 41 (35;46) per 1,000 PY and was the highest for EBB namely 202 (139; 283) per 1,000 PY. When studying individual CV events, hospitalisation for HF was low in IPCI and absent in CPRD GOLD (as expected because CPRD GOLD was not linked to HES hospital admission data). In SIDIAP the IR was 31 (27; 37) per 1,000 PY and in EBB 195 (133; 275) per 1,000 PY.

The IR of MI (in the first year following study entry) was comparable between CPRD GOLD and SIDIAP namely 4 (3; 5) and 3 (2; 5) per 1,000 PY and 8 (4; 14) per 1,000 PY for IPCI. The IR of stroke was comparable between databases with an IR of 8 (4; 14) per 1,000 PY for IPCI and 8 (5; 10) per 1,000 PY for SIDIAP and an IR of 7 (6; 8) per 1,000 PY for CPRD GOLD. The numbers of events of MI and stroke were too low in EBB (<5) to allow calculation of IRs.

When studying IR in the second year following study entry, the IR of serious CV was lower compared to the IR in the first year for CPRD GOLD (8 (7; 10) per 1,000 PY), for SIDIAP (35 (30; 41) per 1,000 PY) and for EBB (146 (88; 228) per 1,000 PY). In IPCI it was slightly higher (15 (8; 23) per 1,000 PY). Again, note that all CIs are wide. When studying individual CV events, IRs were comparable with the IR in the first year following study entry but with a somewhat larger 95% CI because of low numbers.

The IRs of serious CV events and the IRs of MI, stroke and hospitalisation for heart failure, by age category, are presented in Figure 9. Because of stratification, certain numbers of outcomes dropped below 5 and no IR

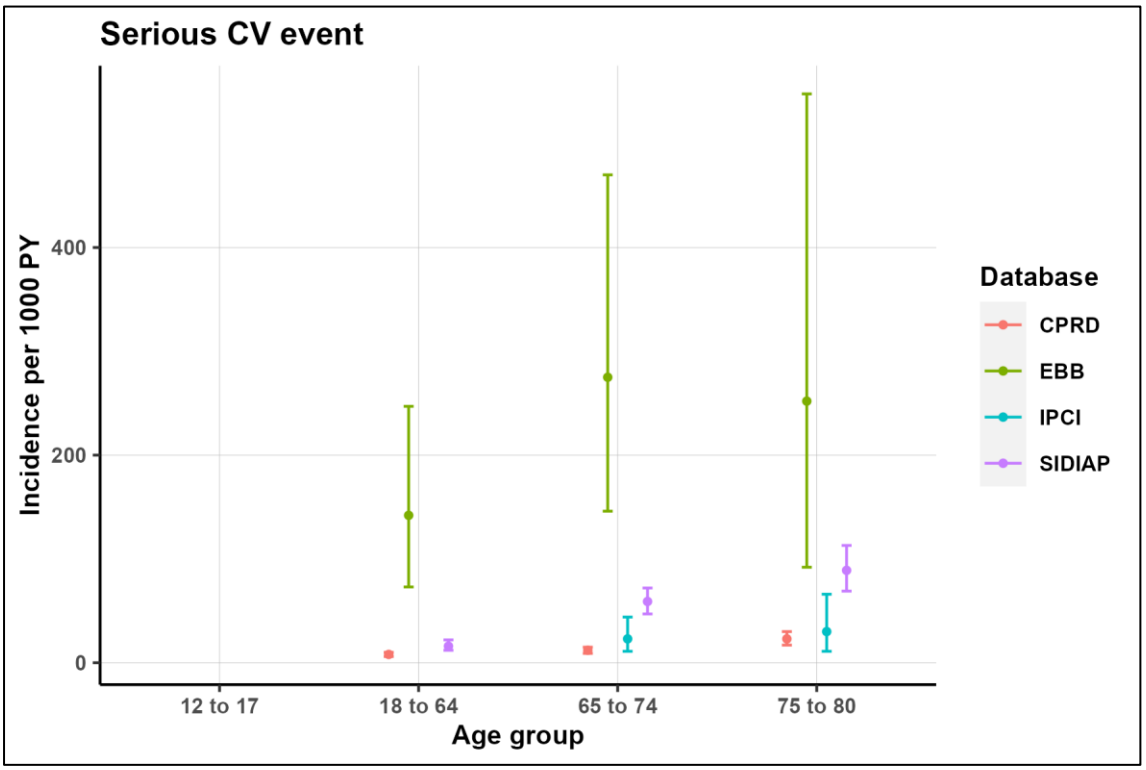
could be calculated. In case of sufficient numbers, for all of the outcomes, the IR increased with age (except for hospitalisation for HF in EBB where the IR in the eldest age category (75-80 years of age) was slightly lower than the IR in the age category 65-74 years but 95% CIs were broad).

Table 10 of the supplementary material describes the IR of the CV outcomes in the pre-pandemic and pandemic phase (including data up to 2022). In the first year following study entry, the IRs of serious CV events were similar between the pre-pandemic vs the pandemic period for CPRD GOLD (11 (10; 13) vs 9 (6; 13) per 1,000 PY), IPCI (14 (8; 23) per 1,000 PY in pre-pandemic and 14 (5; 30) per 1,000 PY in pandemic) and SIDIAP (41 (35; 48) vs 38 (26; 54) per 1,000 PY). In EBB, the IR was lower in the pandemic (185 (80; 365) per 1,000 PY) vs. the pre-pandemic period (215 (141; 316) per 1,000 PY) but 95% CIs were broad.

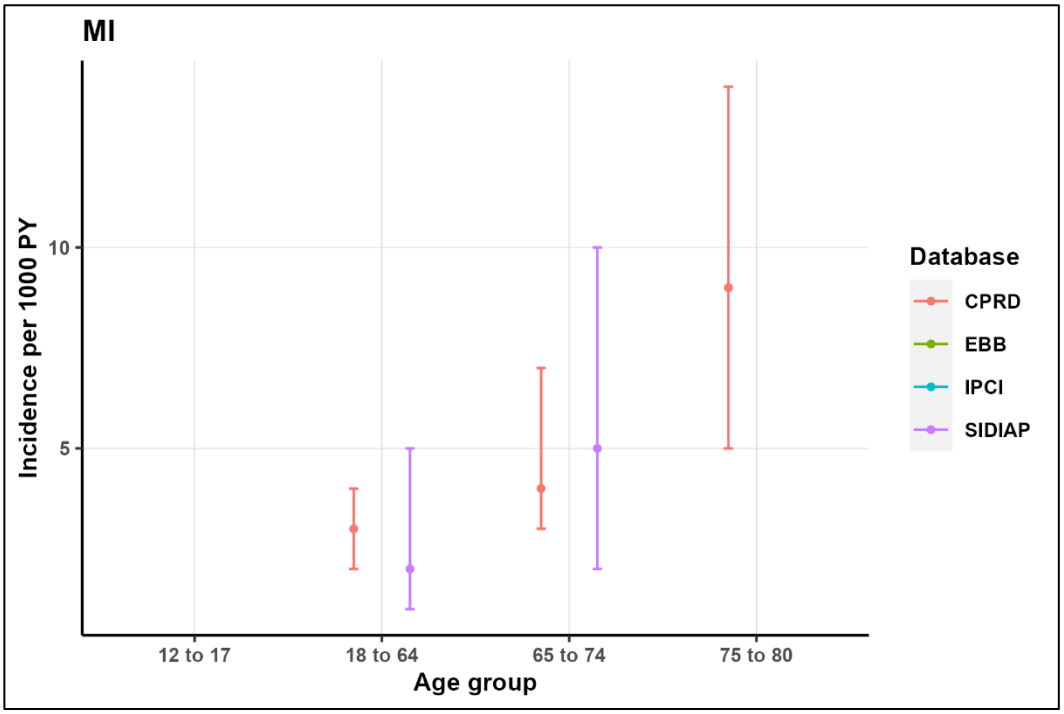
In the second year following study entry, the IR of serious CV events was slightly lower during the pandemic than in the pre-pandemic phase but 95% CIs were broad.

Table 13 of the supplementary material describes the IR of the outcomes (including CV events) by sex. In all databases, the IR of MI was higher in males than in females. In the EBB, hospitalisation for heart failure was higher in men than in females both in the first and second year following study entry. Stratification by age and sex was hampered by low numbers.

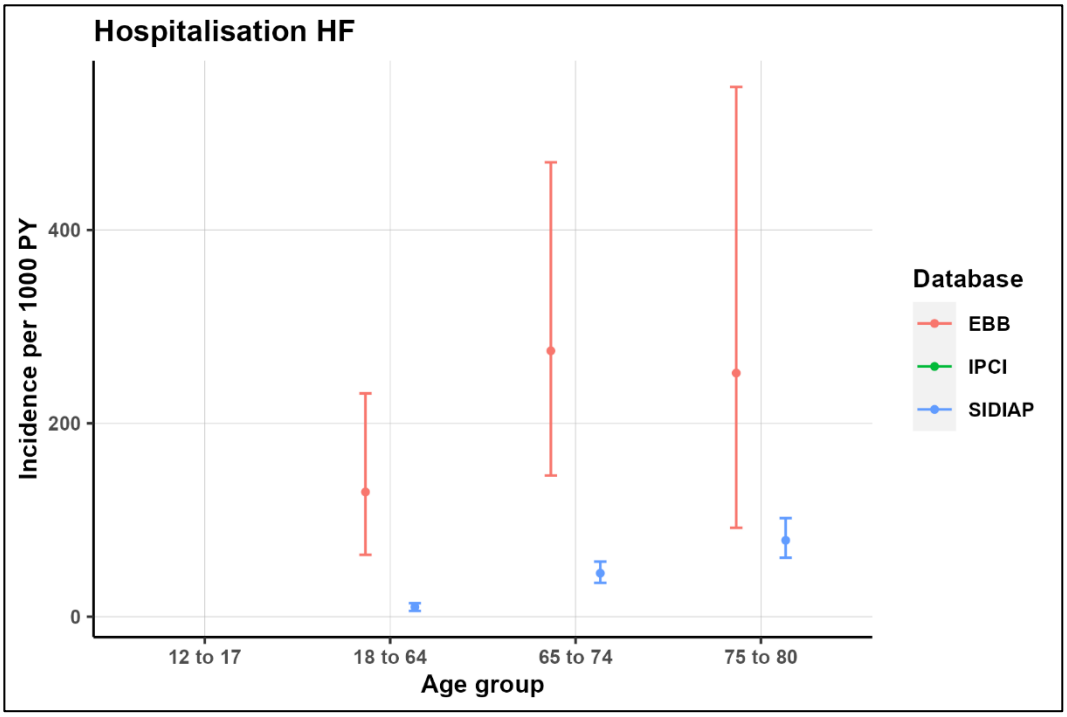
(Figure 10a – cohort 1)



(Figure 10b – cohort 1)



(Figure 10c – cohort 1)



(Figure 10d – cohort 1)

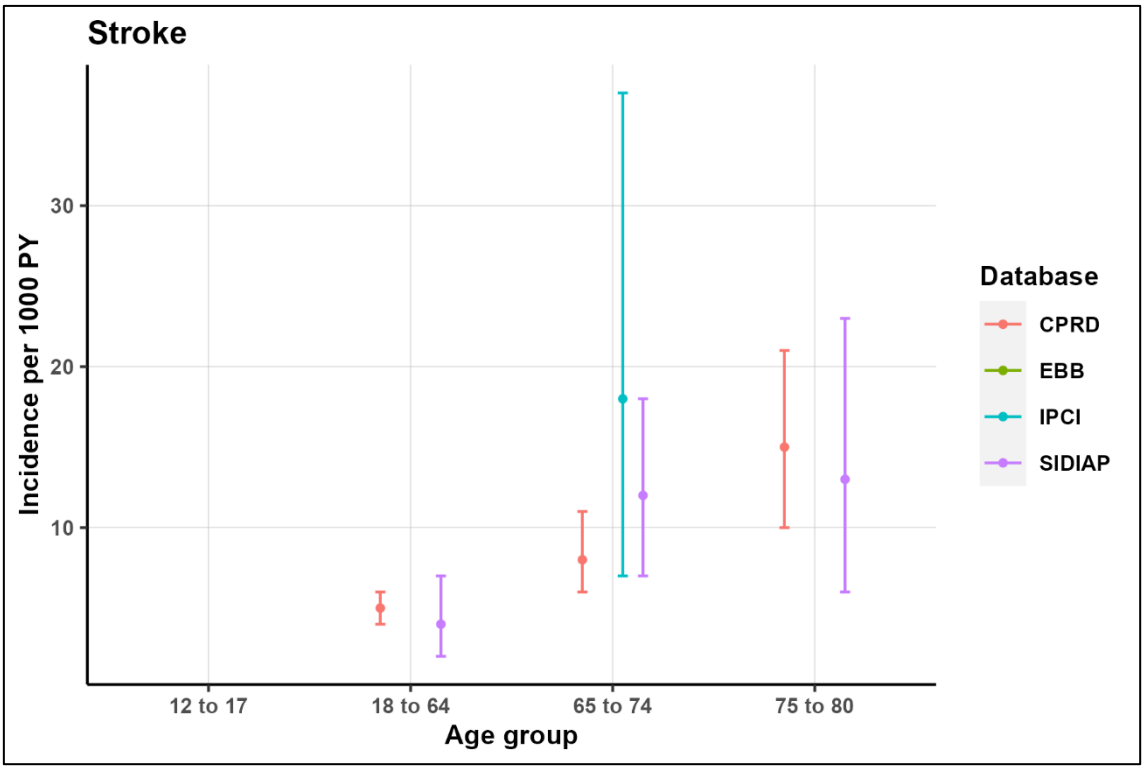
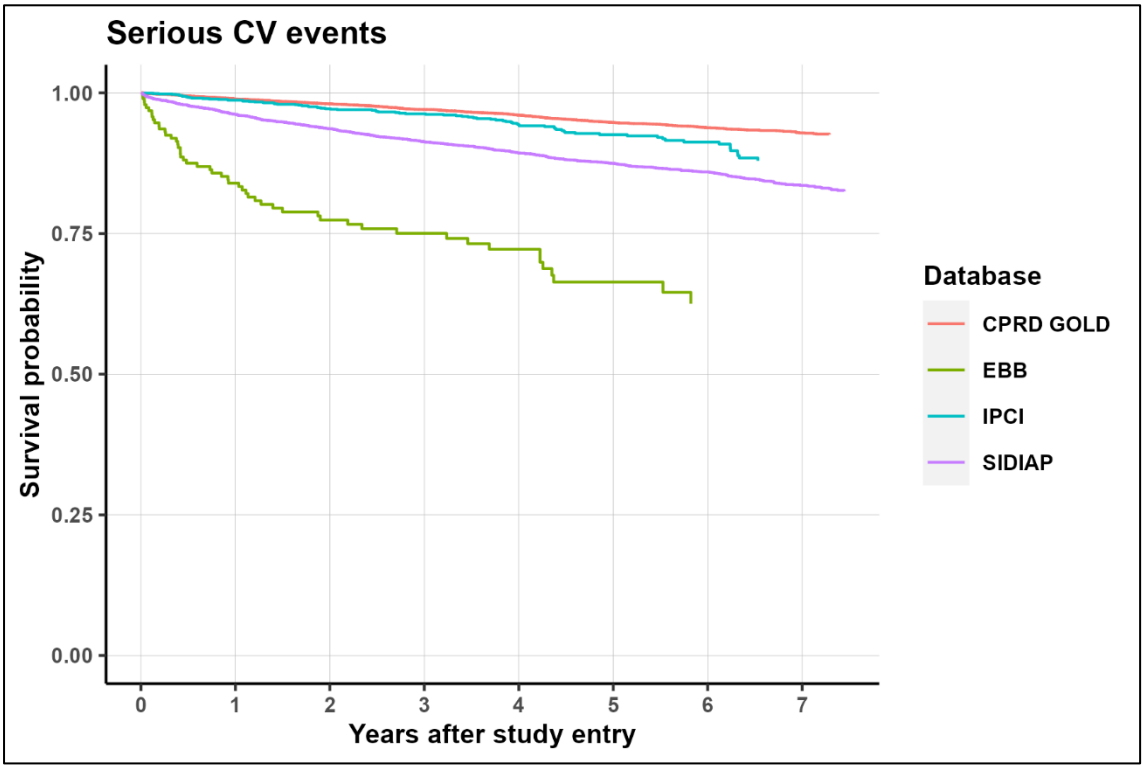
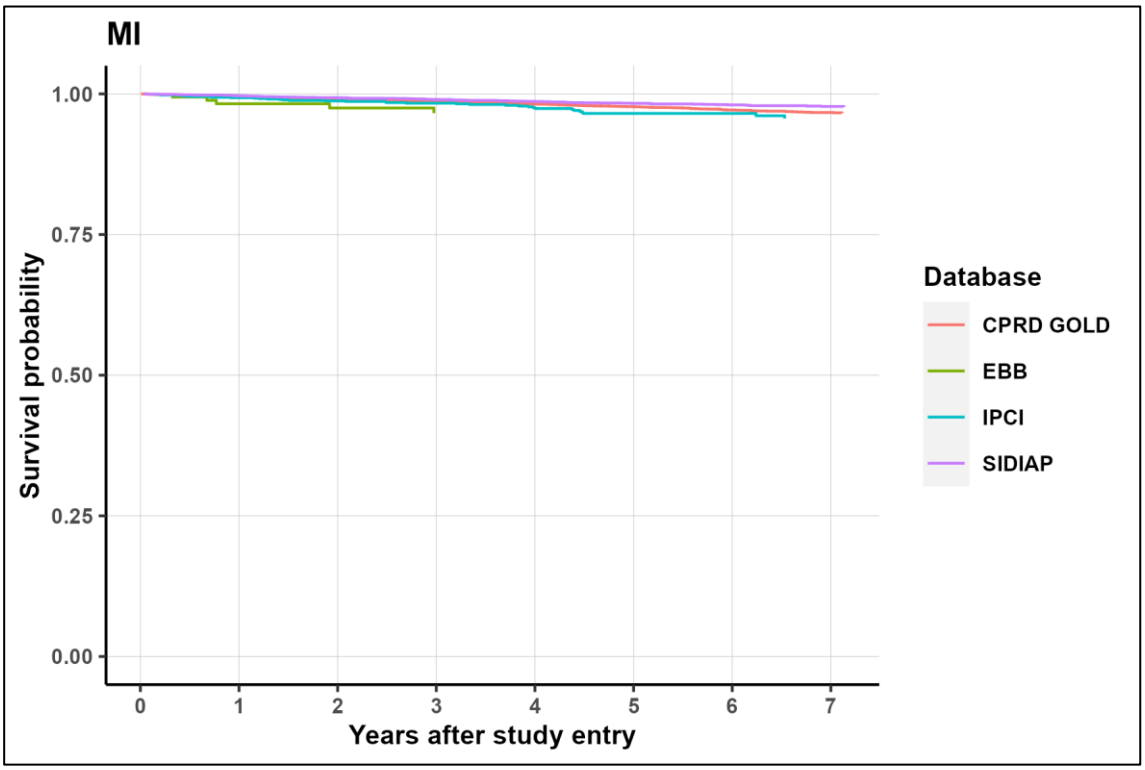


Figure 10: Incidence rates of CV events in people with severe asthma (cohort 1) by age category

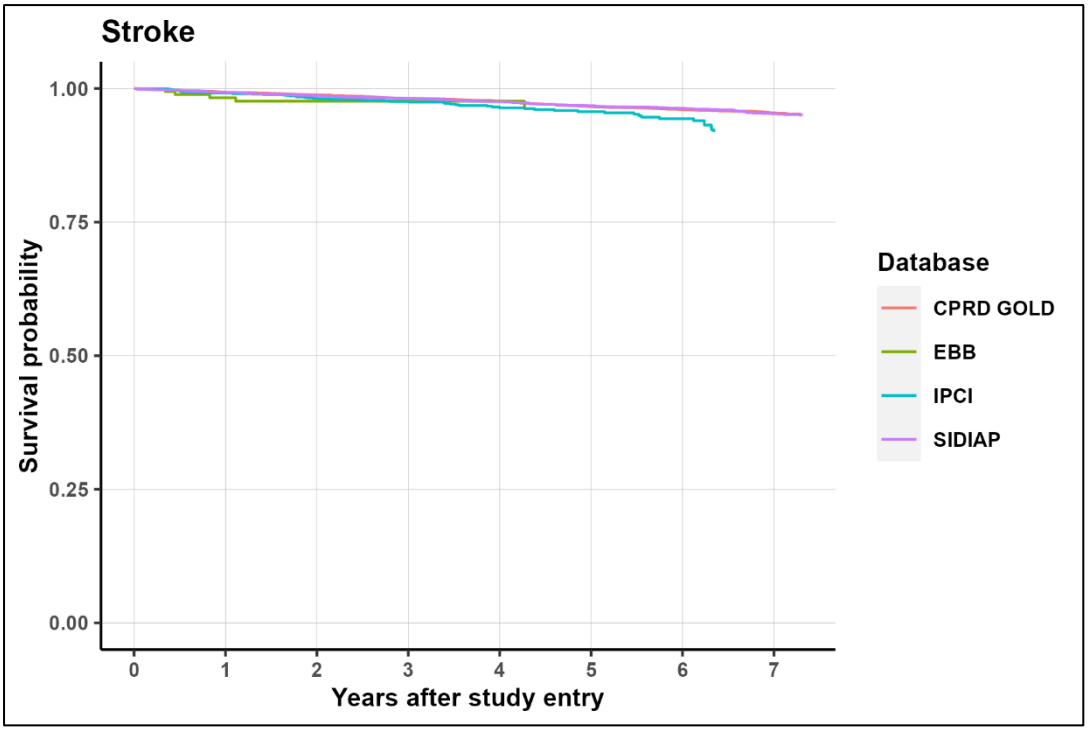
(Figure 11a – cohort 1)



(Figure 11b – cohort 1)



(Figure 11c – cohort 1)



(Figure 11d – cohort 1) (CPRD does not have information on hospitalisation in mapped data)

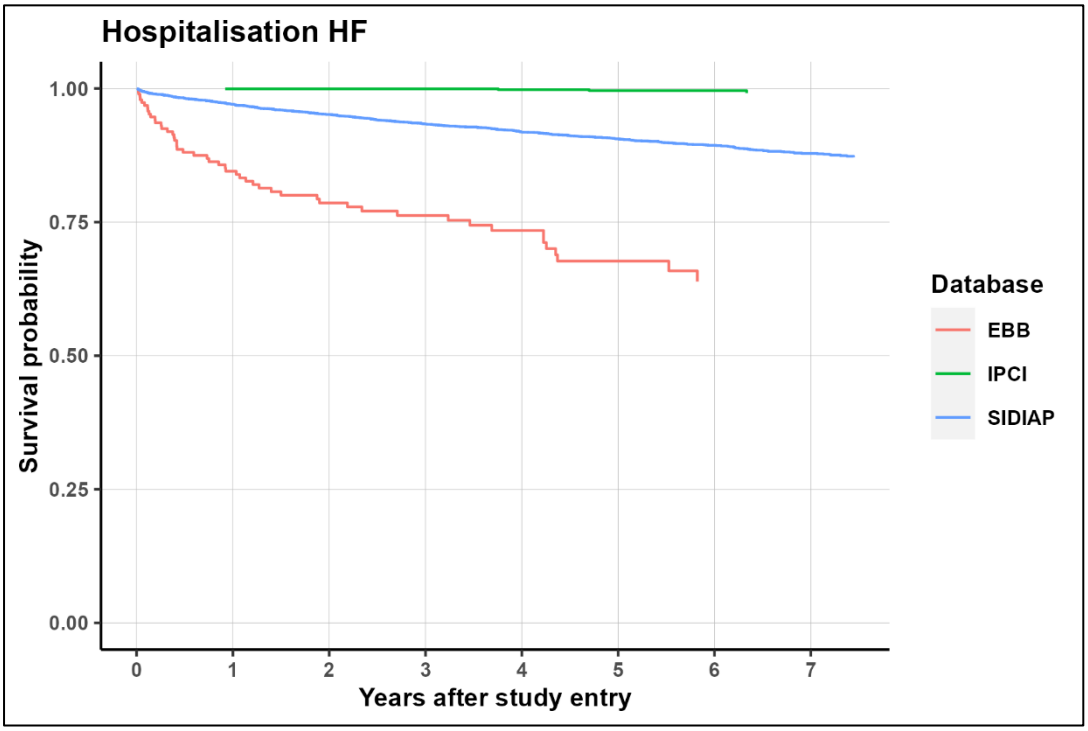


Figure 11: Kaplan-Meier curves of serious cardiovascular events in people with severe asthma (cohort 1)

12.3.2. COHORT 2

The number of individuals in cohort 2 was <5 for EBB, <5 for IMASIS, 217 (13.6% of individuals from cohort 1) for IPCI, 1,036 (18.7% of individuals from cohort 1) for SIDIAP and 2,859 (14.9% of individuals from cohort 1) for CPRD. (see also Table 9)

As for EBB the number of individuals in cohort 2 was below 5, and thus data from EBB could not be used for analyses.

12.3.2.1. MORTALITY

Calculation of IRs of mortality was hampered because of low numbers as many patients were excluded from cohort 2 because of exclusion criteria (in particular comorbidity, COPD and smoking status). This resulted in the fact that for instance no IRs of outcomes of interest could be calculated for IPCI and the Estonian Biobank. Also for SIDIAP, the number of patients who died in year 1 or year 2 following study entry was too low to calculate mortality rates (Table 16). IRs could be calculated for CPRD GOLD and were much lower compared to the IRs in cohort 1, namely 6 (3; 10) per 1,000 PY versus 30 (28; 33) per 1,000 PY in year 1 and 5 (3; 10) versus 29 (26; 32) per 1,000 PY in year 2.

Table 11 of the supplementary material describes the IR of the outcomes (including mortality) in the pre-pandemic and pandemic phase and Table 14 gives IRs by sex. However, most numbers are too low to allow reporting of IRs. Also IRs by age group are not presented for cohort 2, because of too low numbers.

The Kaplan Meier curves for mortality in cohort 2 by database are presented in Figure 12. Again, in the complete follow-up of patients, numbers for mortality are very low.

Table 16: Incidence rates in first and second year after study entry in people with severe asthma in cohort 2

Follow-up period	Outcome	Database	N of persons	N of events	PY	IR	95% CI
First year	All cause mortality	CPRD GOLD	2,859	15	2,583	6	(3; 10)
		IPCI	217	< 5	204	NA	
		SIDIAP	1,034	< 5	1,011	NA	
	Fatal infection	CPRD GOLD	2,859	< 5	2,583	NA	
		IPCI	217	< 5	204	NA	
		SIDIAP	1,034	< 5	1,011	NA	
	Fatal CV event	CPRD GOLD	2,859	< 5	2,583	NA	
		IPCI	217	< 5	204	NA	
		SIDIAP	1,034	< 5	1,011	NA	
	Serious CV event	CPRD GOLD	2,859	11	2,579	4	(2; 8)
		IPCI	217	< 5	203	NA	
		SIDIAP	1,034	16	1,006	16	(9; 26)

Follow-up period	Outcome	Database	N of persons	N of events	PY	IR	95% CI
	MI	CPRD GOLD	2,859	5	2,582	2	(1; 5)
		IPCI	217	< 5	204	NA	
		SIDIAP	1,034	< 5	1,011	NA	
	Stroke	CPRD GOLD	2,859	7	2,581	3	(1; 6)
		IPCI	217	< 5	203	NA	
		SIDIAP	1,034	7	1,008	7	(3; 14)
	Hospitalisation HF	CPRD GOLD	2,859	NA	NA	NA	
		IPCI	217	< 5	204	NA	
		SIDIAP	1,034	7	1,009	7	(3; 14)
Second year	All cause mortality	CPRD GOLD	2,280	11	2,031	5	(3; 10)
		IPCI	189	< 5	176	NA	
		SIDIAP	986	< 5	954	NA	
	Fatal infection	CPRD GOLD	2,280	< 5	2,031	NA	
		IPCI	189	< 5	176	NA	
		SIDIAP	986	< 5	954	NA	
	Fatal CV event	CPRD GOLD	2,280	< 5	2,031	NA	
		IPCI	189	< 5	176	NA	
		SIDIAP	986	< 5	954	NA	
	Serious CV event	CPRD GOLD	2,280	9	2,028	4	(2; 8)
		IPCI	189	< 5	176	NA	
		SIDIAP	986	16	944	17	(10; 28)
	MI	CPRD GOLD	2,280	< 5	2,029	NA	
		IPCI	189	< 5	176	NA	
		SIDIAP	986	< 5	951	NA	
	Stroke	CPRD GOLD	2,280	5	2,029	2	(1; 6)
		IPCI	189	< 5	176	NA	
		SIDIAP	986	< 5	952	NA	
	Hospitalisation HF	CPRD GOLD	2,280	NA	NA	NA	
		IPCI	189	< 5	176	NA	
		SIDIAP	986	8	949	8	(4; 17)

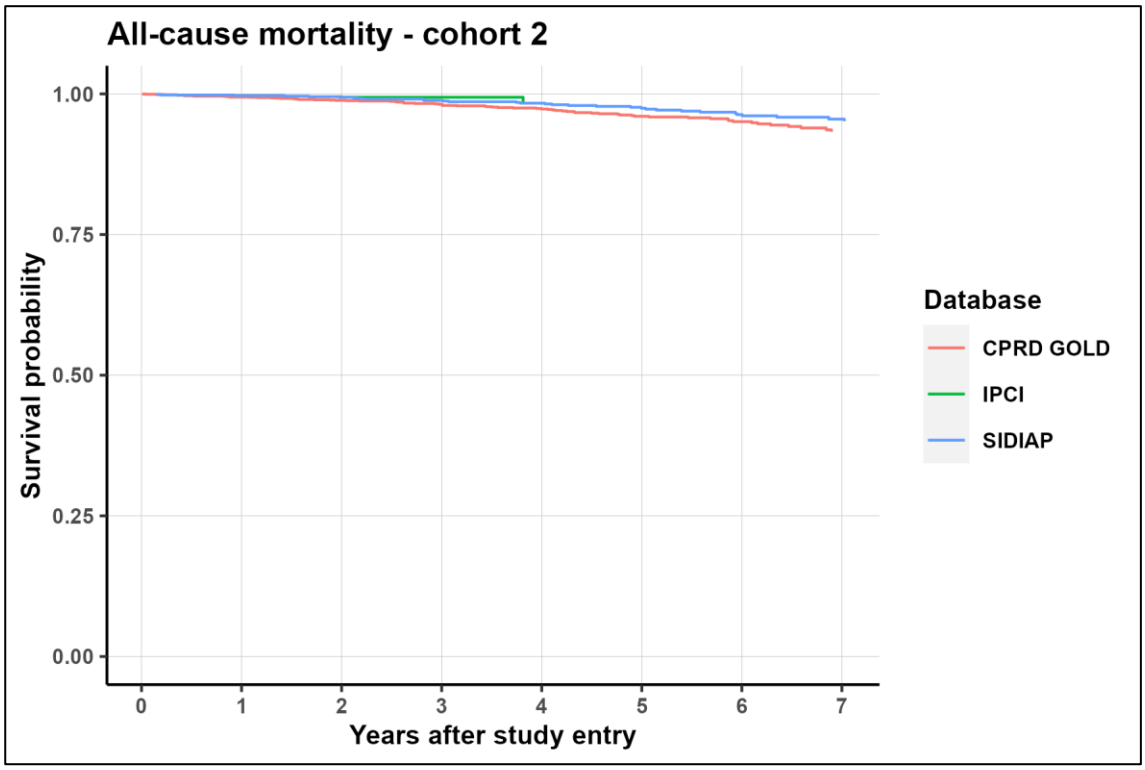


Figure 12: Kaplan-Meier curve of all-cause mortality in people with severe asthma (cohort 2)

12.3.2.2. CV EVENTS

Because of the small size of cohort 2, IRs of cardiovascular outcomes could be calculated only for CPRD GOLD and for SIDIAP (Table 16). In CPRD GOLD the IR of serious CV event in the first year following study entry was 4 (2; 8) per 1,000 PY and 5 (3; 10) per 1,000 PY in the second year following study entry. In SIDIAP this IR was 16 (9; 26) per 1,000 PY in the first year and 17 (10; 28) per 1,000 PY in the second year. An IR for MI could only be calculated for CPRD GOLD in the first year following study entry being 2 (1;5) per 1,000 PY. The IR of stroke was 3 (1; 6) per 1,000 PY for CPRD GOLD in the first year following study entry and 2 (1; 6) per 1,000 PY in the second year. For SIDIAP the IR in the first year was 7 (3; 14) per 1,000 PY and had too low counts to calculate the IR of stroke in the second year. The IR of hospitalisation of HF for SIDIAP in the first year following study entry was 7 (3; 14) per 1,000 PY and 8 (4; 17) per 1,000 PY in the second year following study entry. Hospitalisation for heart failure in SIDIAP was much lower for cohort 2 compared to cohort 1 (31/1,000 PY in the first year following study entry and 27/1,000 PY in the second year following study entry for cohort 1) (Table 16).

12.3.3. COHORT 3

Individuals within cohort 3 are those individuals from cohort 1 which were not included in cohort 2 and thus had at least one exclusion criteria. The number of individuals in cohort 3 was 1,379 (86.4% of individuals from

cohort 1) for IPCI, 4,513 (81.3% of individuals from cohort 1) for SIDIAP and 16,380 (85.1% of individuals from cohort 1) for CPRD.

12.3.3.1. MORTALITY

CPRD GOLD, IPCI and SIDIAP had sufficient numbers of patients with mortality as an outcome which allowed the calculation of the IR for mortality. (Table 7 of the supplementary material). The overall mortality in the first year following study entry was 35 (32; 38) per 1,000 PY for CPRD GOLD, 30 (22; 42) per 1,000 PY for IPCI and 19 (15; 23) per 1,000 PY for SIDIAP. Overall mortality in the second year following study entry was 34 (30; 37) per 1,000 PY for CPRD GOLD, 32 (22; 45) per 1,000 PY for IPCI and 19 (15;24) per 1,000 PY for SIDIAP. Overall mortality rates were slightly higher for cohort 3 compared to cohort 1. Because of low numbers, only IR of fatal CV events in the first year following study entry could be calculated for SIDIAP which was 3 (2; 6) per 1,000 PY and for CPRD which was 4 (3;5) per 1,000 PY

Table 12 of the supplementary material describes the IR of the outcomes (including mortality) in the pre-pandemic and pandemic phase (including data up to 2022). The IR of mortality during the first year following study entry was lower in the pandemic phase for IPCI (21 vs. 35/1,000 PY) and CPRD (38 vs. 21/1,000 PY) whereas it was higher for SIDIAP (24 vs. 18/1,000 PY). Mortality rates in the second year following study entry were lower in the pandemic phase (22 vs 37/1,000 PY for IPCI, 13 vs 21/1,000 PY for SIDIAP and 27 vs. 36/1,000 PY for CPRD). Of note, the sample size was much lower during the pandemic for all databases and thus with larger 95% CI around the incidence estimates. Further stratification between pre-pandemic vs. pandemic for the other mortality outcomes (fatal infection and fatal CV events) was hampered because of low numbers.

Similar as for cohort 1, the IR of overall mortality was higher in male compared to females (Table 15 of the supplementary material).

As cohort 3 of the EBB is almost identical to cohort 1, no IR of mortality or CV outcomes was reported for EBB as results would be similar to the results of cohort 1.

12.3.3.2. CV EVENTS

Table 7 of the supplementary material describes the IRs of the other outcomes of interest in particular the IR of overall CV events (as a composite endpoint) and the IR of MI, stroke and hospitalisation for heart failure.

For IPCI no IR of hospitalisation for heart failure could be calculated as the number of events was <5 both in the first and second year following study entry. IPCI does capture information on hospitalisation but hospitalisation is an underestimation as not linked to hospital data and based on referral and discharge letters from the specialist. In SIDIAP the IR for hospitalisation for heart failure was 37 (32;43) per 1,000 PY and 32 (27;38) per 1,000 PY in the first and second year following study entry respectively.

Because of low counts of hospitalisation for HF in IPCI and the fact that hospitalisation of HF is not present in CPRD, the IR of overall serious CV events in the first and second year following index date was higher for SIDIAP (46 (40;53) per 1,000 PY and 39 (33;46) per 1,000 PY for SIDIAP respectively vs 15 (9;24) per 1,000 PY and 17 (10;27) per 1,000 PY for IPCI and 12 (10;14) per 1,000 PY and 9 (8;11) per 1,000 PY for CPRD. The IR of stroke was comparable between IPCI, CPRD and SIDIAP whereas the IR of MI was higher for IPCI (9 (4;16) per 1,000 PY) compared to SIDIAP (4 (2;6) per 1,000 PY) and CPRD (5 (4;6) per 1,000 PY especially in the first year following study entry.

Table 12 of the supplementary material describes the IR of the CV outcomes in the pre-pandemic and pandemic phase (including data up to 2022). In the first year following study entry, the IRs of serious CV events were slightly lower in the pandemic (10 (7;15) per 1,000 PY for CPRD, 13 (4;31) per 1,000 PY for IPCI, 42 (28;61) per 1,000 PY for SIDIAP) vs the pre-pandemic (12 (10;15) per 1,000 PY for CPRD, 16 (9;27) per 1,000 PY for IPCI and 47 (40;55) per 1,000 PY for SIDIAP). A similar pattern was observed in the second year following study entry, where the IR of serious CV events was slightly lower during the pandemic than in the pre-pandemic phase but 95% CI were broad.

Table 15 of the supplementary material describes the IR of the outcomes (including CV events) by sex. Higher IR of CV events was observed in male vs females except for SIDIAP in the first year following study entry.

12.4. OTHER ANALYSIS

In Figures 9-15 in the supplementary material the IRs per calendar year for outcome events in the first year after study entry are shown for cohort 1. However, for many of these annual IRs, the number of events was too low to allow calculation. The results do not indicate higher IRs in 2015 (where also prevalent severe asthma cases will be present) compared to the following years.

12.5. POST-HOC ANALYSES

As mentioned in Section 9.9.7, when applying liberally the exclusion comorbidity criteria according to the cohort 2 definition, the number of individuals which were included in cohort 2 was low as many of the individuals did have a presence of at least one of the disease codes of the comorbidities of interest (which were exclusion criteria) in the 12 months prior to the index date. To investigate what would happen when exclusion criteria were applied less strictly that aligns more appropriately to the trial setting, alternative selection criteria for cohort 2 were applied.

- Cohort 2A consisted of individuals with severe asthma but where the presence of cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity codes in the 12 months prior to the index date was not longer considered as an exclusion criteria.
- Cohort 2B consisted of individuals with severe asthma but where exclusion criteria based on comorbidity was limited to more severe events as per trial criteria.

When applying these 2 definitions of exclusion criteria, we identified cohort 2A which consisted of 4,184 individuals in CPRD (21.7% of cohort 1), 37 (19.5%) in EBB, 547 in IPCI (34.3%) and 2,213 (39.9%) in SIDIAP. Cohort 2B was slightly smaller namely 3,929 for CPRD (20.4% of cohort 1), 20 (10.5%) in EBB, 441 (27.6%) in IPCI and 1,951 (35.2% in SIDIAP). Although restricting the definition of underlying comorbidities increased the number of individuals in cohort 2A and cohort 2B, still an important number of individuals were excluded from cohort 1 for reasons of smoking and COPD as underlying comorbidity.

Incidence rates of the outcomes of interest are reported in Table 8 from the supplementary material for cohort 2A and Table 9 from the supplementary material for cohort 2B.

Although the number of individuals in cohort 2A and 2B were higher than cohort 2 of the main protocol, calculation of IRs of mortality was still hampered because of low numbers and for instance no mortality rate for IPCI could be calculated. The mortality rates in cohort 2A in the first year following index date were 8 (5;11) per 1,000 PY for CPRD and 3 (1;7) per 1,000 PY for SIDIAP with similar mortality rates in the second year following index date. When considering serious CV events, IRs were 6 (3;9) per 1,000 PY (first year) and 4 (2;8) per 1,000 PY (second year) for CPRD; 26 (19;33) per 1,000 PY (first year) and 21 (15;29) (second year)

for SIDIAP and 17 (7;35) per 1,000 PY for IPCI in the second year (number of events <5 to calculate IR for serious CV events in IPCI in first year).

When calculation of IRs was further restricted to cohort 2B, (supplementary material – Table 9), the analysis was further hampered by low numbers. The mortality rates for CPRD GOLD were 7 (4;10) and 8 (5;12) per 1,000 PY for first and second year respectively. For SIDIAP only the first-year mortality rate could be calculated as 3 (1;7). For serious CV events, IRs were 5 (3;7) per 1,000 PY (first year) and 5 (3;8) per 1,000 PY (second year) for CPRD; 20 (14;27) per 1,000 PY (first year) and 14 (9;20) (second year) for SIDIAP; 15 (5; 36) in second year for IPCI.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the new guideline on good pharmacovigilance practice (EMA/873138/2011), there were no requirements for expedited reporting of adverse drug reactions as mainly secondary data will be used. Only in case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

14. DISCUSSION

14.1. KEY RESULTS

We conducted a retrospective study where we identified patients with severe asthma within 5 healthcare databases. Cohort 1 consisted of patients with severe asthma with at least two severe asthma exacerbations in the past year and being treated with medium/high dose ICS for at least 12 months and with high dose ICS (in combination with controller therapy) for at least 12 weeks prior to study start. From the total number of patients with asthma, the number of patients with severe asthma fulfilling inclusion criteria were 19,249 (2.6% of asthma population) for CPRD GOLD, 190 (0.9%) for the Estonian Biobank, <5 for IMASIS, 1,596 (1.0%) for IPCI and 5,549 (1.7%) for SIDIAP.

Cohort 2 consisted of patients from cohort 1 meeting at least one of the exclusion criteria. As the number of patients with comorbidities in the year prior to study entry as well as the number of patients with a smoking status and a medical history of COPD was high, the number of individuals remaining in cohort 2 was very low with only 217 (13.6% of cohort 1) individuals in IPCI, 1,036 (18.7%) individuals in SIDIAP, 2.869 (14.9%) in CPRD and <5 in the Estonian Biobank.

Cohort 3 consisted of those individuals with severe asthma that were excluded from cohort 2 because of at least 1 exclusion criteria. Patients were mainly excluded because of smoking status (current and/or past smoking) (i.e. 69.9% in CPRD, 12.3 % in IPCI and 26.6% in SIDIAP), COPD (40.4% in CPRD, 67.9% in EBB, 49.3% in IPCI and 32.2% in SIDIAP) and underlying comorbidity.

With regard to the patient characteristics of cohort 1, in all databases, the proportion of females was higher than the proportion of males with a female to male ratio of around 2:1. The majority of individuals were 50 years or older at time of index date and less than 50% of individuals had a history of more than 2 severe asthma exacerbations in the year prior to the index date. The proportion of patients with comorbidities was high especially in the EBB. In all databases, the number of patients with ACO (disease codes of asthma as well as COPD) was high and ranged from 32% in IPCI to 68% in the EBB.

The IR for all-cause mortality for cohort 1 in the first year ranged between 16-30/1,000 PY for the primary care databases and was the highest for Estonia with an IR of 58/1,000 PY. When exploring IRs for mortality in the second year following study entry, no differences in overall mortality rates could be observed between year 1 (16-30/1,000 PY) and year 2 (16-29/1,000 PY) for primary care databases. Because of low numbers, no mortality rates in the second year following study entry could be calculated for the Estonian Biobank. The overall mortality rates increased with age and were higher in males compared to females.

With regard to the IR of CV outcomes in cohort 1, in the first year following study entry, the IR of serious CV events was comparable between IPCI and CPRD GOLD namely 14 and 11/1,000 PY respectively. This IR was much higher for SIDIAP namely 41/1,000 PY and the highest for EBB namely 202/1,000 PY. Amongst the type of serious CV events, hospitalisation for HF was low in IPCI and absent in CPRD GOLD (as CPRD GOLD was not linked to HES). The IR of MI (in the first year following study entry) was comparable between CPRD GOLD and SIDIAP namely 4 and 3/1,000 PY and 8/1,000 PY for IPCI. The IR of stroke was comparable between databases with an IR of 8/1,000 PY for IPCI and SIDIAP and an IR of 7/1,000 PY for CPRD GOLD. IR of serious CV events in the second year following study entry was slightly lower than the IR in the first year in all databases. The IR of CV outcomes increased with age, except for heart failure in the EBB. There was no consistent association between sex and CV outcomes except for the IR of MI which was higher in males compared to females in all databases.

In cohort 2, IRs for mortality could only be calculated for CPRD GOLD and were much lower compared to the IRs in cohort 1, namely 6 (3; 10) per 1,000 PY versus 30 (28; 33) per 1,000 PY for cohort 1 in year 1 and 5 (3; 10) versus 29 (26; 32) per 1,000 PY for cohort 1 in year 2. Because of the small size of cohort 2, IRs of cardiovascular outcomes could be calculated only for CPRD GOLD and for SIDIAP. In CPRD GOLD the IR of serious CV event in the first year following study entry was 4 (2; 8) per 1,000 PY and 5 (3; 10) per 1,000 PY in the second year following study entry. In SIDIAP this IR was 16 (9; 26) per 1,000 PY in the first year and 17 (10; 28) per 1,000 PY in the second year.

As an additional analysis, alternatives for cohort 2 were defined which consisted of individuals without exclusion of underlying comorbidity (cohort 2A) or those where exclusion of underlying comorbidity was restricted to severe and more acute events (cohort 2B) (see appendix table 2 for list of disease codes) Although the number of individuals in cohort 2A and 2B were higher than cohort 2 of the main protocol, calculation of IRs of mortality was still hampered because of low numbers. For cohort 2A, the mortality rates in the first year following index date were 8 (5;11) per 1,000 PY for CPRD and 3 (1;7) per 1,000 PY for SIDIAP with similar mortality rates in the second year following index date. When considering serious CV events, IRs were 6 (3;9) per 1,000 PY (first year) and 4 (2;8) per 1,000 PY (second year) for CPRD; 26 (19;33) per 1,000 PY (first year) and 21 (15;29) (second year) for SIDIAP and 17 (7;35) per 1,000 PY for IPCI in the second year (number of events <5 to calculate IR for serious CV events in IPCI in the first year).

When calculation of IRs was further restricted to cohort 2B, (supplementary material – Table 9), the analysis was further hampered by low numbers but mortality rates and rates of serious CV events (for those databases where this could be calculated (SIDIAP and CPRD) were in line with IRs as reported for cohort 2A.

For cohort 3, IRs of the outcomes of interest were calculated for CPRD, SIDIAP and IPCI. In general, results were similar compared to cohort 1 with slightly higher IRs of the outcomes of interest for cohort 3 compared to cohort 1 for those outcomes which could be calculated.

14.2. LIMITATIONS OF THE RESEARCH METHODS

For this study, severe asthma is based on the daily use of medium- or high-dose ICS as described in recent GINA guidelines. (2) To categorise ICS use, information on type of device, strength, and dosing was needed, and these details were not always completely available within all data sources. Also, duration was not always documented or was set at 30 days, implying that duration of use had to be derived from the treatment pattern (e.g., for the Estonian biobank). Initially, we also considered the use of IMASIS as hospital database capture outcomes such as hospitalisation for CV outcomes (MI, stroke, heart failure, etc.) better than primary care databases. However, the inclusion criteria for this study required that patients needed to be treated for a whole year with medium- or high-dose ICS. This implied that only outpatients could be considered as duration of stay for an inpatients will never be as long as one year. When considering outpatients, only a few patients within IMASIS fulfilled these inclusion criteria, also because ICS prescriptions are often repeated by primary care physicians and thus no continuous ICS exposure could be documented in the secondary care patient records. Although the number of patients with asthma in IMASIS based on feasibility assessment was considerable, (more than 18,000 individual of asthma of which 7,400 during the study period), few of this individuals fulfilled inclusion criteria.

For this study, we applied inclusion and exclusion criteria in line with recent published RCTs on the treatment of severe asthma and defined severe asthma based on internationally agreed definitions, in particular GINA guidelines. To apply these inclusion and exclusion criteria, however, we required detailed clinical information, which is not always routinely collected as part of medical care.(10) For instance, information on smoking status, lab values, and whether or not a specific medical condition is “under control” is not constantly reported within a patient’s medical file. Inclusion and exclusion criteria were translated into criteria that can be applied to electronic health care records, but this resulted in the fact that many of the patients included in cohort 1 were excluded from participating in cohort 2. Exclusions were mainly because of a history of smoking status, disease codes for COPD and/or ACO, and in particular, the presence of a disease code for one of the comorbidities of interest in the previous year. Patients, for instance, with a disease code of gastrointestinal, musculoskeletal, psychiatric conditions, etc. in the previous year prior to study entry were excluded, although these patients might have had stable disease at time of study start and would not have been excluded from the RCT. It is worth noticing that the exclusion criterion around comorbidities in RCTs typically refers to diseases that are not stable in the opinion of the physician, whereas in this study this has been implemented by removing subjects with a disease code in the list of those comorbidities. To explore what would happen with the size of cohort 2 (and IRs within these cohort), we conducted an additional analysis where underlying comorbidity was not longer an exclusion criteria or comorbidity as exclusion criteria was limited to acute and more severe conditions. When applying these new criteria, the number of individuals in cohort 2 increased but still many patients were still excluded for reason of smoking status and underlying COPD.

For this study, CPRD GOLD was used, but linkage to HES was not available (for mapped data). This implied that one of the outcomes of interest (i.e., hospitalisation for heart failure) was missing for CPRD Gold. For IPCI, which is a primary care database, information on hospitalisation was available; however, as IPCI is not linked to hospital data, information on hospitalisation is not complete. This explains why IR for hospitalisation for heart failure was, lower in IPCI compared to SIDIAP.

The proportion of smoking (current/past) for CPRD was higher compared to the other databases, and this had an effect on selection of patients in cohort 2. High proportion of smoking within CPRD has also been reported in other research papers. (11) The exact reason why the proportion of smoking in CPRD is higher compared to the other databases is unknown.

Also, selection bias could be a concern. For instance, the population included in the Estonia Biobank, was less healthy compared to the cohorts as selected in the other databases. Potential explanations for the higher prevalence of comorbidities are the following: i) the Estonian Biobank data covers primary care, secondary care (specialist care), and hospitalizations (including emergency care), ii) the Estonian Biobank might capture preliminary diagnoses not yet confirmed by the specialist, iii) the sample is not random, but people have to express a wish to join the Biobank, implying that people with a higher disease burden or who are more health conscious (visit more doctors and get more diagnoses) might be more likely to contribute to the Biobank and iv) finally, diagnosis assignment practices are different in different countries.

In addition, no manual validation of asthma recording was done and the recording of events (comorbidity, measurements, and lifestyle factors (e.g., smoking status)) may vary across databases and may be incomplete. However, the methods we applied to identify patients with asthma are in line with previous published methods on the identification of patients with asthma using electronic health care databases. This is supported by the fact that the prevalence of asthma and underlying comorbidities are in line with published data (11). The prevalence of severe asthma in our study ranged between 1-2.6%. Our definition was strict as we required at least one year of continuous exposure of medium or high dose ICS in combination with a history of at least 2 severe asthma exacerbations. Prevalence of severe asthma as reported in other studies ranges between 0.4% to prevalences up to 10% depending on the definition being used. (12-14)

14.3. INTERPRETATION

For this study, we reported an overall mortality rate between 16-30/1,000 PY for the primary care databases and an IR of 58/1,000 PY for the Estonian Biobank. The overall mortality rates are somewhat higher than the mortality rates as published by Engelkes et al who also conducted a multinational study using EHR to explore the IR of mortality and risk factors of mortality in patients with (severe) asthma. Engelkes et al reported an age- and sex- stratified mortality rate between 7.3/1,000 PY and 25/1,000 PY. These mortality rates were slightly lower compared to the results of our study, but Engelkes et al excluded patients with COPD in all analyses. (11) Cohort 2 of our study consisted of individuals without COPD. Because of low numbers, mortality rates in cohort 2 could only be calculated for CPRD but these are in line with the study by Engelkes et al namely 6 (3; 10) per 1,000 PY for year 1 and 5 (3; 10) per 1,000 PY for year 2. A prospective cohort study of 865 adults with severe asthma from the Northern California Kaiser Permanente database in the United States found an all-cause mortality rate of 67 (95% CI 56 - 78)/1,000 PY, which is comparable to the mortality rate in the Estonian Biobank but remarkably higher than the overall mortality rate in the other databases.(15) The Global Burden of Disease recently reported on asthma-related mortality in the period from 1990 to 2019 and reported a decline in asthma-related mortality from 8.6/100,000 to 6.0/100,000 with a larger decline in males compared to females. However, the GBD investigated asthma-related mortality and not overall mortality in patients with asthma. (16)

In our study, we observed an incidence rate of serious cardiovascular events in primary care databases, which ranged between 11-41/1000 PY. This rate was slightly higher than the rates reported by Dayal et al. in their study involving 32,439 patients with severe asthma in the US claims database, where the rate was 8.0 (95% CI 7.2–8.9) per 1000 PY.(17) Moreover, there are some differences between our study and Dayal et al.'s

retrospective cohort study. Specifically, Dayal et al. encompassed a broader range of cardiovascular events, including unstable angina, transient ischemic attack, coronary revascularization, MI, stroke, and hospitalization for heart failure (HF), while our study focused on MI, stroke, and HF hospitalization as the primary cardiovascular events of interest. Importantly, one potential factor contributing to the observed differences in event rates between the two studies is the age of the study population, the population in the current study being older.

The aim of this study was to generate background rates of selected health outcomes in patients with severe asthma. For regulators, having access to these background rates is important when interpreting results from RCT on the efficacy and safety of drugs for the treatment of asthma. Background rates were calculated in a cohort of patients with severe asthma where in- and exclusion criteria similar to those from RCTs were applied. Applying these exclusion criteria however was challenging as many patients were excluded in particular for reasons of underlying comorbidity, ACO or smoking status. Especially underlying comorbidity was an issue as patients were excluded because of the presence of a disease code in the previous 12 months prior to study start whereas this does not mean that the patient has active disease. A recent systematic review examined the percentage of clinical populations with a physical health condition who would be excluded by RCTs of treatments for that condition. Median exclusion rates for trials in common chronic conditions were high and ranged up to 96.0% in patients with asthma. The authors of this article reported that the most commonly applied exclusion criteria related to age, co-morbidity and co-prescribing, (18) This difference in patient population between individuals from an RCT and observational data was further described in the position paper by Sheffield et al describing the challenges to emulate RCTs for reasons of differences in healthcare settings and patient populations, differences in effect measures and data analysis. (10)

14.4. GENERALISABILITY

This study included data from four different European countries and healthcare systems (primary care in IPCI, SIDIAP, and CPRD GOLD; secondary care in IMASIS and the Estonian Biobank). Patients with severe asthma were identified based on internationally accepted criteria (in particular GINA). Still, national guidelines on the treatment of asthma might have been adhered to with regard to the choice, dose and duration of drugs used for asthma treatment.

However, although some of the analyses were hampered by low numbers, our findings are in line with the data as published before, which is reassuring as to the level of external validity (15). The characteristics of patients with severe asthma in terms of age, sex, and comorbidities are in line with what has been published before (11).

15. CONCLUSION

We conducted a retrospective cohort study using data from 5 databases to identify IRs of outcomes of interest (mortality and serious CV events) in patients with severe asthma. The prevalence of severe asthma ranged between 1-2.6% across databases. Because of low numbers for IMASIS, only data from CPRD Gold (19, 249 for cohort 1 (i.e. cohort of severe asthma), 2,869 (14.9%) for cohort 2), EBB (190 for cohort 1, <5 for cohort 2), IPCI (1,596 for cohort 1, 217 (13.6%) for cohort 2) and SIDIAP (5,549 for cohort 1, 1,036 (18.7% for cohort 2) could be used for the analysis.

The IR for all-cause mortality for cohort 1 (i.e. only applying inclusion criteria) in the first year ranged between 16-30/1,000 PY for the primary care databases and was the highest for Estonia with an IR of 58/1,000 PY.

When exploring IRs for mortality in the second year following study entry, no differences in overall mortality rates could be observed between year 1 (16-30/1,000 PY) and year 2 (16-29/1,000 PY). The overall mortality rates increased with age and were higher in males compared to females. The IR of serious CV events was comparable between IPCI and CPRD GOLD namely 14 and 11/1,000 PY respectively. This IR was much higher for SIDIAP namely 41/1,000 PY and the highest for EBB namely 202/1,000 PY. The IR of CV outcomes increased with age, except for heart failure in the EBB.

When applying exclusion criteria, the number of individuals within cohort 2 dropped and mortality rates could only be calculated for CPRD with mortality rates which were 1/5th of the mortality rates of cohort 1. Because of the small size of cohort 2, IRs of cardiovascular outcomes could only be calculated for CPRD and for SIDIAP. In CPRD the IR of serious CV event in the first year following study entry was 4 (2; 8) per 1,000 PY and 5 (3; 10) per 1,000 PY in the second year following study entry. In SIDIAP this IR was 16 (9; 26) per 1,000 PY in the first year and 17 (10; 28) per 1,000 PY in the second year.

Strict application of in and exclusion criteria from RCTs obviously had a large impact on patient counts and translation of RCT criteria to criteria that are feasible and identifiable in the real-world setting is recommendable.

16. REFERENCES

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17. ANNEXES

APPENDIX I

APPENDIX I – TABLE 1: LIST WITH CONCEPT DEFINITIONS

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Infections	132736, 256451, 432250, 42597240, 4280729, 37395594, 255848, 132797, 4270490	437474
Asthma	317009, 4293734, 4308356, 46287068, 4279553	4029337, 4312524
COLD	255573, 256448, 36685451, 36685452, 36685453, 36685454, 36685455, 36685456, 36685457, 36685458, 44782563, 44788819	
Bronchiectasis	256449	
Pulmonary fibrosis	4197819	
Lung cancer	443388, 35610239, 4201621	
Upper respiratory tract infection	4110027, 4181583	
Lower respiratory tract infection	255848, 256451, 4270490	
Cardiovascular comorbidity (hypertension, ischemic heart diseases, heart failure, cardiac valve disorders, cardiac arrhythmia, pulmonary embolism, atherosclerosis, deep venous	381316, 373503, 321318, 312327, 319844, 316866, 316139, 44784217, 314054, 319843, 316993, 319845, 4133004, 440417, 40479625	

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
thrombosis, stroke, TIA)		
Gastrointestinal comorbidity	4000610	443568, 4244495, 36715498
Hepatic comorbidity	4093333	4115573, 4243887, , 4246127, 4130519
Renal comorbidity	4091056	4217308, 196653, 4243885
Neurological comorbidity	376337	4157331
Musculoskeletal comorbidity	80180, 80809, 4046660, 372409, 440674, 80502	
Infectious comorbidity (LRTI and URTI excluded)	4099350, 132797, 378143, 435785, 3739614, 440448, 192956, 195856, 4291005, 196152, 314383, 4138837, 441589, 140480, 435613, 439840, 4291025, 434557, 4267414	
Endocrine comorbidity	31821	
Metabolic comorbidity	436670	
Haematological comorbidity	317248	
Psychiatric comorbidity	432586	4244690
Cancer	443392	4112752, 4111921, 4116082

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Anaphylaxis	441202	
Tuberculosis	434557	
HIV-infection	439727, 4013106, 4083350, 4186235, 4221489, 4298853, 40484507, 44783623	
Acute liver disease	201343, 4049298, 37396531, 4184847, 4243475, 36715006, 36676901, 4058676, 4250743, 4331678, 196455	
Hepatitis B	200031, 439673, 4013553, 4014007, 4244873, 4247369, 4281232, 42537336, 44792587, 45772057, 46286608	
Hepatitis C	197494, 439672, 4132902, 4153375, 4196134, 4227247, 4340380, 43531723, 44789328, 44792611, 44806379, 44813294, 45757360, 45757396, 46273598, 46286609	
Arterial hypertension	316866	4071202
Severe asthma exacerbations	4152913	
Gastro-oesophageal reflux disease	36717641, 36713494, 4175650, 318800, 30437	
Atopic dermatitis	133834	
Nasal polyposis	42537251	
Chronic sinusitis	257012	
Chronic idiopathic urticaria	4199697	
Rhinitis	257007	

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Diabetes mellitus	201820, 442793, 604741, 760977, 760978, 760979, 760980, 760989, 761050, 761063, 765375, 4019513, 4034961, 4055679, 4060085, 4065354, 4129379, 4130165, 4144221, 4146514, 4175440, 4182243, 4219466, 4220981, 4242853, 4305491, 4307799, 37018224, 40482801, 40484648, 40484649, 40485020, 42536400, 42689695, 43020791, 45766963, 45768456	
Osteoporosis	80502, 36716194, 4109181, 44783850, 37204244	
Smoking (current or past)	619068, 437264	
Alcohol abuse	436607, 4322643, 4030588, 195300, 4106575, 378421, 4214950, 4302744, 4176651, 4202330, 46269816, 46269817, 37016176, 45757494, 318773, 36714559, 619608, 45757783, 35610532, 46269818, 3655834, 44782445	
Drug abuse	606210, 436954, 4127868, 4022666, 40480941, 40482269, 4295481	
Drug abuse	42529475, 4168205, 4239438, 4206984, 4219142, 3022196, 36031658, 36031249, 4017177, 4229859, 42529480, 4036792, 4038240, 4037138, 42539778, 1616455	
Alcohol abuse	4116983, 4053784, 45766930, 4080065, 36674487, 45772695, 44793164, 37206970, 4207141, 44792459, 3036878, 762596, 4145860, 4042872, 4027638, 44786671, 432456, 44786700, 40481082, 4038704, 3027199, 608490, 44812667	

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Smoking (current or past)	44788975, 44788976, 762499, 3012697, 4052948, 600776, 44786669, 762498, 4131520, 37395605, 1616974, 42528924, 44804450, 4206526, 4203874, 4046886, 4141787, 44809281	

Concept IDs include descendants unless highlighted as being excluded. By OMOP standards descendants automatically include the ancestor.

APPENDIX I – TABLE 2: LIST WITH CONCEPT DEFINITIONS – STRICTER CRITERIA FOR COMORBIDITY AS EXCLUSION CRITERIA

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Cardiovascular conditions		
Ischemic heart disease	4185932	
Heart valve disorder	4281749	Exclusion of congenital valvopathy
Arrhythmia: atrial fibrillation, ventricular tachycardia/ventrillation, AV block	4103295, 437894, 4226399, 316135	
Heart failure	316139	
Severe Hypertension	44809027, 45768449	
Aneurysma dissecans	320739	
Lung embolism	440417	
Deep venous thrombosis	4133004	
Cerebrovascular accident	40557547	
Gastrointestinal conditions		
Crohn's disease	201606	
GI hemorrhage	192671	
GI ulcer	4247120	

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Ulcerative colitis	81893	
Hepatic condition		
Viral hepatitis	4291005	
Disease of liver	194984	
Cirrhosis of liver	4064161	
Renal conditions		
Nephrotic syndrome	195314	
Nephritis	193253	
Chronic Renal Failure	198185	
CKD stage 5	443611	
CKD stage 4	443612	
CKD stage 3	443597	
Acute Nephropathy	4242411	
Neurological		
Parkinsonism	4140090	
Myasthenia Gravis	76685	
Multiple Sclerosis	374919	
Motor Neuron Disease	374631	
Dementia	4182210	
Musculoskeletal		
Spondyloarthritis	37205058	
Rheumatoid arthritis	80809	
Infections		

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Sepsis	132797	
Pyelonephritis	198199	
Pneumonia	255848	
Peritonitis	196152	
Meningitis	435785	
Lymphangitis	439840	
Infectious mediastinitis	4193989	
Female PID	199067	
Encephalitis	378143	
Cholangitis	195856	
Carditis	4164489	
Bacterial arthritis	4167984	
Endocrine disorders		
Thyrotoxicosis	138387	
Severe Hypothyroidism	4223217	
Disorder of Pituitary Gland	23986	
Adrenal corticol hypofunction	435508	
Metabolic condition		
Ketoacidosis	4209145	
Diabetic – poor control	443238	
Coma due to diabetes mellitus	443735	
Hematological condition		
Sickle Cell Disease	22281	

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Sickle cell trait	25518	
Polycythemia Vera	135214	
Myelodysplasia	40492268	
Leukopenia	435224	
Hemophilia	4236898	
Beta thalassemia	4278669	
Aplastic anemia	137829	
Psychiatric condition		
Suicidal thoughts	4273391	
Severe Depression	4149321	
Severe Anxiety	4214746	
Psychotic disorder	436073	
Major Depressive Disorder	4152280	
Bipolar disorder	436665	

Concept IDs include descendants unless highlighted as being excluded. By OMOP standards descendants automatically include the ancestor

APPENDIX I – TABLE 3: LIST WITH CONCEPT CODES FOR EXPOSURE

Prescriptions will be identified based on the relevant ingredient. Non-systemic products will be excluded from the code list except for respiratory drugs given via inhalation.

Drug Classes	Include plus descendants	Exclude plus descendants
ICS	21085349, 40152662, 40734060, 40830728, 40143708, 35885804, 35887474, 36035528, 36036727, 36894464, 40143326, 40223712, 40892816, 44817882, 2910652, 42615152, 783228, 1356140, 1356143, 1830424, 1970732, 2069097, 35133500, 35135829, 35831802, 35898300, 36787269, 37002305, 40142910, 40142920, 42479684, 43291282, 44120753, 44120754, 21090035, 21158944, 35130061, 36421291, 36787954, 36812530, 36883710, 36894458, 40142784, 40745353, 42480194, 42483138, 792484, 2070676, 2070686, 2070702, 2071140, 21089505, 35147990, 35149212, 36882733, 37592046, 40144020, 40144024, 40144035, 40144037, 40754973, 40755794, 41048760, 41267401, 42482744, 42925104, 43291091, 43532281, 40156382, 41174011	
Systemic corticosteroids	36894465, 36894466, 40001300, 40085175, 40085179, 40085513, 40085516, 40085517, 40141448, 40830330, 40830543, 40861538, 40861617, 40861848, 40861854, 40892891, 40986496, 41017247, 41048603, 41080565, 41174426, 41236863, 41298307, 42629017, 43618522, 43733331, 43764799, 2069519, 35151839, 35161377, 35831814, 36277138, 36891530, 40018136, 40018148, 40018149, 40018160, 40018161, 40018167, 40018168, 40018860, 40018864, 40018865, 40019090, 40019099, 40019100, 40145461, 40862057, 40986723, 41080439, 41298715, 41298716, 42479030, 43133389, 43271284, 43697442, 44120815, 21104723, 21110192, 21149460, 35152433, 35604729, 36810746, 37003051, 40036255, 40049686, 40049691, 40049693, 40049698, 40049700, 40049728, 40052988, 40053001, 40097635, 40115558, 40831001, 40861708, 40862260, 40892978, 40893427, 40924493, 40924574, 40955710, 40986444, 41111782, 41112007, 41142946, 41143298, 41205490, 41205491, 41236653, 41236930, 41236997, 41267929, 42481321, 42482500, 42483100, 43213290, 43715288, 44042956, 44081562, 44094631, 44107536, 44187021,	

Drug Classes	Include plus descendants	Exclude plus descendants
	41079961, 41079962, 21158588, 35606532, 40012593, 40060701, 40060705, 40060728, 40923904, 41111375, 42479078, 42480795, 42901434, 43697439, 44068805, 21089621, 21099519, 21099520, 40026665, 40026666, 40026668, 40831106, 44179592, 1719010, 1719021, 2055931, 35147323, 40010223, 40010224, 40022479, 40022480, 40027148, 40027149, 40027150, 40027151, 40027452, 40027453, 40027454, 40027455, 40027461, 40028260, 40028569, 40028598, 40028599, 40028601, 40028607, 40028865, 40028866, 40030154, 40160933, 40823867, 40830638, 40830658, 40830659, 40830660, 40861836, 40861855, 40861856, 40861857, 40861858, 40893020, 40893023, 40893042, 40893426, 40924090, 40924091, 40924102, 40924103, 40924182, 40955308, 40955309, 40955310, 40955331, 40955332, 40955398, 40986509, 41017529, 41017530, 41017544, 41017696, 41017899, 41048833, 41049172, 41049240, 41080245, 41080249, 41080264, 41080265, 41111559, 41111560, 41111561, 41111897, 41143081, 41143082, 41143086, 41143105, 41174078, 41174080, 41174083, 41174102, 41205893, 41236558, 41236559, 41236579, 41236783, 41267495, 41267497, 41267514, 41298498, 41298520, 41298595, 42479771, 42479772, 43157462, 43180508, 43180854, 43202833, 43690608, 43781012, 43853864, 44025603, 44030023, 44042956, 44042957, 44120595, 44120597, 44158898, 35149489, 40013687, 40036261, 40066473, 40072752, 40073185, 40073190, 40073191, 40073197, 40073454, 40073458, 40073467, 40149642, 40171266, 40823867, 40823871, 40825736, 40830847, 40831053, 40861608, 40861791, 40861841, 40861857, 40861923, 40892759, 40892776, 40893002, 40893035, 40893385, 40893498, 40893499, 40923843, 40924167, 40924178, 40924286, 40955209, 40955250, 40955563, 40955667, 40955675, 40986252, 40986383, 40986507, 40986733, 40986947, 41017481, 41017529, 41017544, 41017801, 41018007, 41048618, 41048739, 41049165, 41049240, 41080242, 41080245, 41080264, 41080455, 41080456, 41080489, 41111346, 41111549, 41111718, 41111738, 41174314, 41174498, 41205402, 41205735, 41206037, 41236314, 41236784, 41236873, 41236907, 41267314, 41267407, 41267498, 41267512,	

Drug Classes	Include plus descendants	Exclude plus descendants
	41267632, 41267870, 41298184, 41298208, 41298265, 41298519, 41298573, 41298965, 42482154, 42970587, 43168161, 43661632, 43805225, 44120678, 40073529, 40073531, 40073813, 40077886, 40077887, 40077888, 40143531, 40830453, 40892984, 40924346, 40924453, 40955250, 41049173, 41173847, 42482157, 42873418, 44029985, 40055571, 40055572, 40102083, 40955045, 40070931, 40070932, 40955071, 41267259, 40095885, 21031784, 40041462, 40041493, 41143003, 41236629, 41267406, 41267579, 40059478, 43148942, 1592256, 40054909	
Inhalant long acting B2 agonists (LABA)	1137529, 1196677, 19043191, 19097824, 40240664, 43532539, 45775116	2069155, 35132439, 35142595, 35155079, 35853184, 35853185, 35855413, 35870190, 40008351, 40008352, 40030511, 40030512, 40100370, 40100371, 42926217, 42927690, 42931195, 42931201, 42931239, 42931241, 42935429, 42935522, 42943288, 42956253, 42958521, 42963137, 42963186, 42966617, 42967026, 44042713
Oral leukotriene Receptor antagonists (LTRA)	43009091, 1154161, 43009065, 1111706	35161116
Systemic theophylline	1237049	41048814, 41080205, 41205733
Inhalant long-acting muscarinic antagonists (LAMA)	42873639, 45775571, 1106776, 44785907	42963186, 42935429, 42935434, 42967026, 42967030, 1758690, 35200237, 35201370, 35605660, 36274577, 40046883, 40046884, 40047197, 40047199, 40224968, 40745498, 40745499, 40745500, 40745501, 40745502, 40745505, 42963137, 42963144
Systemic cromones	1114620, 19008867	35151945, 40071499, 40071501, 40924115, 40955339, 41205665, 41298258, 41298531, 43257911, 43279669, 43821122, 44164517

Drug Classes	Include plus descendants	Exclude plus descendants
Systemic antibiotics	792531, 901845, 902722, 904356, 915175, 915981, 920293, 923081, 925952, 948582, 956653, 986864, 990069, 997496, 997881, 1036425, 1036475, 1036487, 1361385, 1560047, 1592954, 1701651, 1702364, 1702559, 1702911, 1705674, 1707164, 1707687, 1707800, 1708100, 1708880, 1709170, 1712549, 1713332, 1713905, 1713930, 1714527, 1715117, 1716721, 1716903, 1717327, 1717963, 1721543, 1724666, 1724703, 1728416, 1729720, 1733765, 1734104, 1734205, 1736887, 1738366, 1738521, 1740546, 1741122, 1742253, 1742432, 1743222, 1746114, 1746940, 1747005, 1747032, 1748975, 1749008, 1749083, 1750500, 1759842, 1768849, 1769535, 1771162, 1773402, 1774470, 1774932, 1775741, 1776684, 1777254, 1777806, 1778162, 1778262, 1784749, 1786617, 1786621, 1786842, 1789276, 1789515, 1790024, 1790692, 1790868, 1796435, 1796458, 1797513, 1800835, 1836191, 1836241, 1836391, 1836430, 1836503, 1836948, 19000817, 19000818, 19000820, 19000821, 19001904, 19002077, 19003644, 19006043, 19007701, 19008870, 19009138, 19010400, 19010564, 19015123, 19015464, 19017585, 19018516, 19018742, 19023254, 19023508, 19024197, 19027679, 19028241, 19028286, 19028288, 19036545, 19040624, 19041153, 19047071, 19047240, 19047265, 19050750, 19051271, 19051345, 19052683, 19054936, 19063874, 19064329, 19069006, 19070174, 19070251, 19070680, 19072054, 19072122, 19072255, 19072857, 19078399, 19086759, 19086790, 19088223, 19088795, 19092353, 19095043, 19096054, 19100438, 19101402, 19102105, 19123240, 19123877, 19125201, 19126622, 19129642, 19136024, 19136044, 19136210, 19136423, 19136426, 19136429, 19136481, 19136493, 19137362, 35197853, 35197897, 35197938, 35197975, 35197989, 35198003, 35198093, 35198107, 35198137, 35198144, 35198145, 35198165, 35198192, 35200469, 35200881, 35200953, 35834909, 35884386, 36878831, 37496518, 37498010, 40166675, 40798700, 40798704, 40798709, 40798981, 40799027, 40799118, 40799120, 40799121, 40799124, 43008993, 43008994, 43009009, 43009011, 43009022, 43009030, 43009044,	702514, 782669, 1127224, 1127226, 1355743, 1356134, 1356252, 1356265, 1356342, 1356348, 1356350, 1356387, 1356388, 1356390, 1361355, 1592220, 1592227, 1594364, 1594376, 1594381, 1594394, 1594403, 1594495, 1594502, 1594661, 1594690, 1594693, 1831782, 1970313, 1971418, 2035392, 2047724, 2052920, 2052922, 2052955, 2059681, 2068131, 2074040, 2918158, 2934751, 21032191, 21032837, 21034617, 21062030, 21069852, 21070276, 21071756, 21072254, 21081480, 21081483, 21084208, 21091714, 21096152, 21099998, 21105903, 21111150, 21130349, 21132307, 21139721, 21140439, 21140538, 21145117, 21155060, 21159759, 21160318, 21160640, 21164972, 21168381, 35129269, 35129793, 35130946, 35133340, 35134453, 35136033, 35138368, 35141028, 35141912, 35142897, 35143240, 35144130, 35144660, 35146037, 35146548, 35147967, 35153174, 35154779, 35156452, 35156547, 35157195, 35158419, 35158846, 35158972, 35159437, 35159764, 35160132, 35201849, 35605255, 35770401, 35830217, 35830590, 35832008, 35851018, 35851383, 35851392, 35851400, 35851598, 35851732, 35852004, 35852136, 35852549, 35852869, 35852870, 35853726, 35853889, 35856292, 35856522, 35856524, 35857086, 35857832, 35857838, 35857844, 35857993, 35858117, 35858133, 35858134, 35858521, 35858522, 35858524, 35858630, 35858631, 35858962, 35859790, 35860600, 35860696, 35860698, 35860990, 35861002, 35861018, 35861664, 35861723, 35861725, 35861925, 35862078, 35862084, 35862169, 35862341, 35862351, 35862353, 35862688, 35862748, 35863069, 35872071, 35873672, 35873678, 35874205, 36118706, 36259244, 36261799, 36264349, 36266909, 36269500, 36274602, 36406497,

Drug Classes	Include plus descendants	Exclude plus descendants
	43009045, 43009067, 43009082, 43009083, 43009087, 43012398, 44012563, 45774861, 45775686, 45776147, 45892419, 45892599, 46221507, 46274210	36408024, 36408036, 36408764, 36408767, 36408768, 36409570, 36421232, 36888521, 37497505, 37499288, 40000267, 40001157, 40001285, 40001286, 40001295, 40001926, 40007220, 40007222, 40007237, 40008577, 40009804, 40009805, 40010078, 40013471, 40013952, 40013956, 40013957, 40013958, 40013960, 40013961, 40013962, 40013966, 40013972, 40013973, 40013982, 40013984, 40013990, 40013994, 40013996, 40014634, 40014637, 40014639, 40015664, 40015668, 40018152, 40018153, 40018154, 40018155, 40018156, 40020954, 40022926, 40022927, 40022928, 40022930, 40022931, 40022932, 40022933, 40022934, 40022935, 40022936, 40022937, 40022938, 40022939, 40022940, 40022941, 40022942, 40022943, 40022944, 40022945, 40023482, 40023487, 40023500, 40023504, 40023505, 40023878, 40025388, 40027153, 40027161, 40027162, 40027168, 40027170, 40027174, 40027175, 40027448, 40027449, 40027450, 40027456, 40027458, 40027636, 40028359, 40028361, 40028718, 40028720, 40030803, 40030804, 40030826, 40030831, 40030833, 40030884, 40030885, 40030886, 40030890, 40030894, 40030899, 40031315, 40036245, 40037356, 40037357, 40040110, 40040112, 40040113, 40040114, 40040115, 40041049, 40041050, 40041238, 40041241, 40041269, 40041274, 40041276, 40041279, 40041418, 40041911, 40041912, 40046035, 40046787, 40046788, 40046789, 40046790, 40046791, 40047938, 40052932, 40052947, 40052961, 40052963, 40052964, 40052965, 40052966, 40052967, 40052968, 40052969, 40052971, 40052972, 40052974, 40052975, 40052977, 40053580, 40053581, 40054813, 40057263, 40057265, 40057467, 40059318,

Drug Classes	Include plus descendants	Exclude plus descendants
		40059607, 40062637, 40062641, 40062646, 40062648, 40062649, 40063382, 40063556, 40064154, 40064525, 40064526, 40066583, 40066585, 40066772, 40066892, 40066893, 40067028, 40067031, 40067033, 40067405, 40069651, 40069655, 40069978, 40071896, 40071898, 40071899, 40071901, 40071902, 40071903, 40071904, 40071905, 40071906, 40071907, 40071908, 40071909, 40071910, 40072290, 40072291, 40072292, 40072301, 40072303, 40072305, 40072307, 40072308, 40072626, 40073113, 40073114, 40073115, 40081806, 40082165, 40082190, 40082191, 40087787, 40087790, 40088148, 40088149, 40088151, 40088728, 40088730, 40088738, 40093197, 40093198, 40095894, 40095895, 40101806, 40101854, 40101856, 40101857, 40105920, 40105923, 40105936, 40119085, 40123985, 40131262, 40131263, 40131789, 40131790, 40131791, 40131820, 40131827, 40131829, 40131831, 40133137, 40135906, 40136212, 40136419, 40139853, 40140235, 40144501, 40150582, 40151082, 40160496, 40170022, 40180925, 40224235, 40225755, 40235501, 40235511, 40237657, 40241740, 40721707, 40737589, 40752961, 40753319, 40754848, 40754915, 40755236, 40823553, 40824184, 40830335, 40830342, 40830430, 40830471, 40830574, 40830870, 40830871, 40830895, 40830896, 40831103, 40861595, 40861596, 40861622, 40861623, 40861624, 40861733, 40861837, 40861838, 40861880, 40861896, 40861940, 40861941, 40861942, 40861943, 40861944, 40862000, 40862094, 40862190, 40862308, 40892732, 40892823, 40893009, 40893086, 40893136, 40893137, 40893138, 40893141, 40893232, 40893250, 40893273, 40893274, 40893384, 40893386, 40923891,

Drug Classes	Include plus descendants	Exclude plus descendants
		40923892, 40923905, 40923946, 40923968, 40923969, 40924017, 40924059, 40924077, 40924174, 40924183, 40924225, 40924452, 40955003, 40955004, 40955083, 40955147, 40955185, 40955186, 40955411, 40955414, 40955415, 40955792, 40986220, 40986223, 40986283, 40986284, 40986285, 40986300, 40986301, 40986390, 40986405, 40986491, 40986578, 40986586, 40986587, 40986588, 40986752, 40986889, 40986923, 40986998, 41017237, 41017296, 41017318, 41017319, 41017414, 41017417, 41017489, 41017579, 41017627, 41017631, 41017632, 41017640, 41017720, 41017766, 41017789, 41017904, 41048539, 41048551, 41048552, 41048553, 41048701, 41048729, 41048730, 41048831, 41048883, 41048884, 41048918, 41048926, 41048927, 41048946, 41049021, 41049022, 41049034, 41049065, 41049155, 41049166, 41049167, 41079933, 41079934, 41079935, 41080028, 41080029, 41080047, 41080100, 41080123, 41080141, 41080154, 41080161, 41080164, 41080198, 41080200, 41080229, 41080247, 41080248, 41080303, 41080328, 41080334, 41080342, 41080343, 41080473, 41080587, 41080616, 41111338, 41111435, 41111460, 41111587, 41111752, 41111768, 41111889, 41142765, 41142774, 41142874, 41142987, 41143036, 41143065, 41143083, 41143088, 41143146, 41143171, 41143173, 41143179, 41143180, 41143181, 41143182, 41143350, 41143481, 41173786, 41173824, 41173853, 41173877, 41173888, 41173962, 41173980, 41173995, 41174008, 41174010, 41174081, 41174135, 41174177, 41174178, 41174272, 41174277, 41174329, 41174455, 41205371, 41205492, 41205632, 41205884, 41205895, 41205896, 41236280, 41236318, 41236340,

Drug Classes	Include plus descendants	Exclude plus descendants
		41236344, 41236359, 41236438, 41236463, 41236476, 41236492, 41236634, 41236640, 41236641, 41236666, 41236771, 41236880, 41267185, 41267266, 41267344, 41267345, 41267381, 41267385, 41267438, 41267494, 41267536, 41267591, 41267603, 41267731, 41267746, 41267869, 41267996, 41298215, 41298216, 41298226, 41298257, 41298373, 41298399, 41298404, 41298596, 41298736, 41298737, 41298857, 42479089, 42479696, 42479725, 42479727, 42480133, 42480780, 42481931, 42482512, 42483110, 42483137, 42613529, 42614500, 42620715, 42629035, 42873748, 42948109, 42961482, 42963090, 42963093, 42965658, 42970795, 43013733, 43023710, 43030076, 43135095, 43135467, 43146339, 43146353, 43157270, 43158691, 43173476, 43177386, 43177613, 43179753, 43180605, 43199938, 43200492, 43201503, 43201691, 43210737, 43214695, 43258666, 43266736, 43278414, 43283021, 43600599, 43603372, 43605428, 43606620, 43617892, 43622866, 43674454, 43678347, 43678432, 43695029, 43709206, 43709550, 43726548, 43727748, 43743995, 43744478, 43745005, 43761831, 43815878, 43816976, 43836922, 43853162, 43858131, 44029805, 44029898, 44030232, 44030233, 44030339, 44042662, 44042765, 44042892, 44042898, 44042948, 44043303, 44043415, 44043416, 44055876, 44055989, 44056269, 44056275, 44056388, 44056444, 44068862, 44068863, 44081628, 44094488, 44094575, 44094887, 44094935, 44094969, 44094970, 44095070, 44107434, 44107456, 44107535, 44107858, 44120279, 44120402, 44120448, 44120477, 44120495, 44120651, 44120903, 44121002, 44160698, 44160702, 44175740, 44175753, 44183238, 44183242,

Drug Classes	Include plus descendants	Exclude plus descendants
		44187011, 45774469, 45774589, 45892421, 45892681, 46221668
Systemic antivirals	32764, 32765, 739588, 792929, 793843, 908126, 981654, 1146410, 1703063, 1703069, 1703603, 1703687, 1704183, 1708748, 1710281, 1710612, 1711246, 1711523, 1712889, 1715472, 1717002, 1717704, 1724700, 1724827, 1724869, 1727223, 1729323, 1736829, 1736971, 1736999, 1738135, 1738170, 1745072, 1746244, 1747157, 1748921, 1756831, 1757803, 1758392, 1758536, 1762711, 1763339, 1769389, 1781406, 1787101, 1789428, 1799139, 19010924, 19078156, 19083285, 19101679, 19122130, 35198023, 35198210, 35200354, 35200446, 35201105, 35605546, 35606465, 35606467, 36042920, 37499271, 40167569, 40238770, 40238930, 40239330, 42544019, 42874212, 43009047, 43532424, 43560385, 44785086, 44785094, 45892552, 45892558, 46221696, 46233931	1356184, 2042290, 2935753, 21022861, 21102304, 35131215, 35153292, 35156005, 35157549, 35161740, 35829278, 35857252, 35858570, 35859531, 35859532, 35859533, 35859534, 35859544, 35859800, 35860190, 35862028, 35862196, 35862840, 36404954, 36881801, 36882754, 36891506, 40006507, 40006509, 40006520, 40006526, 40012442, 40012443, 40021923, 40022935, 40047166, 40048619, 40048641, 40048643, 40048645, 40048646, 40048647, 40079438, 40088497, 40088499, 40098632, 40100094, 40100095, 40147465, 40223217, 40830620, 40830621, 40861701, 40893266, 40923795, 40955222, 41017406, 41017631, 41205307, 42480751, 42482730, 42613396, 42706878, 42966785, 43147470, 43290988, 43714284
Systemic cyclosporine	19010482	35200336, 40028532, 40236657
Systemic methotrexate	1305058	
Biologics	1110942, 35606631, 35603983, 792993, 1593467	

APPENDIX I – TABLE 4: LIST WITH CONCEPT CODES FOR MEASUREMENTS

Measurements	Include plus descendants	Exclude plus descendants
Aspartate transaminase	3013721, 3042781, 3052577, 37392189, 37398463, 4197974, 37394375, 37208565, 37208512, 4263457, 44810795	
Alanine transaminase	3017537, 3006923, 3052018, 46236949, 37393142, 4190899, 44810789, 37208490, 44788835, 4146380, 37393531, 37208513	
Alkaline phosphatase	3005090, 3001110, 37208509, 37208510, 37393131, 3035995, 37398460, 4156813, 44810790, 4193028	
Blood eosinophils	3013115, 3006504, 3004123, 3015956, 3028615, 3009932, 3010457, 43055367, 43055372, 37393857, 37399255, 44805924, 4216098, 40484040, 37208633, 37208634	
BMI, weight, height	3038553, 4245997, 44783982, 1616652, 36304833, 44807883, 3036277, 607590, 3035463, 4177340, 3023540, 3015514, 3019171, 3030674, 3044852, 4030731, 4093975, 4268280, 3025315, 4099154, 46234683, 3026600, 4178502, 3013762, 3009617, 3015644, 3019336, 3005422, 3023166, 21492642, 4310154, 4175354, 37205098, 37206608, 40759189	
Bilirubin (total)	3006140, 3024128, 3024733, 3028833, 40757494, 46235782, 1175191, 1175183, 1616780, 37394117, 37208618, 37208619, 4041529, 4195338, 4118986, 4210860, 4230543, 37398233, 37399653, 37398424	
Bilirubin (direct)	3028638, 3019676, 3005772, 3027597, 3035521, 3044599, 3043347, 37394191, 37392379, 37208552, 37208553, 4195339, 4198887, 4216632, 44805650, 37398232, 37398235, 37398377	

APPENDIX I – TABLE 5: LIST WITH CONCEPT CODES FOR LIFESTYLE FACTORS

Conditions	Include plus descendants	Exclude plus descendants
Drug abuse	42529475, 4168205, 4239438, 4206984, 4219142, 3022196, 36031658, 36031249, 4017177, 4229859, 42529480, 4036792, 4038240, 4037138, 42539778, 1616455	
Alcohol abuse	4116983, 4053784, 45766930, 4080065, 36674487, 45772695, 44793164, 37206970, 4207141, 44792459, 3036878, 762596, 4145860, 4042872, 4027638, 44786671, 432456, 44786700, 40481082, 4038704, 3027199, 608490, 44812667	
Smoking (current or past)	44788975, 44788976, 762499, 3012697, 4052948, 600776, 44786669, 762498, 4131520, 37395605, 1616974, 42528924, 44804450, 4206526, 4203874, 4046886, 4141787, 44809281	

APPENDIX I – TABLE 6: CATEGORISATION INTO MODERATE AND SEVERE ASTHMA BASED ON ICS DOSING (BASED ON GINA GUIDELINES) (2)

Asthma Therapy	**Total Daily Dose (ug)**	
ICS	Medium	High
Beclomethasone dipropionate (non HFA)	>=500-1000	>1000
Beclomethasone dipropionate (HFA)	>=200 <=400	>400
Ciclesonide	>=160-320	>320
Triamcinolone acetonide	>=1000-2000	>2000
Flunisolide	>=1000-2000	>2000
Fluticasone furoate	>= 92 - <= 199	>199
Fluticasone propionate	>=250 - <=500	>500
Fluticasone propionate HFA	>=250 - <=500	>500
Budesonide	>=320 - <=800	>800
Mometasone furoate	>=200 - <=440	>440

Use of these daily dose cut-off points will be reviewed following the execution of the "DrugExposureDiagnostics" R package developed for DARWIN EU.