RESEARCH PROTOCOL:

Characterizing Inflammatory Bowel Disease: Protocol for an OHDSI Network Study

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# 1. List of Abbreviations

|  |  |
| --- | --- |
| CDM | Common Data Model |
| CD | Crohn’s disease |
| IBD | Inflammatory bowel disease |
| OMOP | Observational Medical Outcomes Partnership |
| OHDSI | Observational Health Data Science and Informatics |
| RxNorm | US-specific terminology that contains all medications available on the US market |
| SNOMED | Systematized Nomenclature of Medicine |
| UC | Ulcerative colitis |

# 2. Responsible Parties

## 2.1. Investigators and Authors

|  |  |
| --- | --- |
| **Investigator/Author** | **Institution/Affiliation** |
| Chen Yanover | KI Research Institute |

\* Co-Principal investigator

Authorship may vary from paper to paper. The Responsible Parties involved in this protocol take accountability for the overarching protocol, package development, helping sites running the analysis and ensuring site-specific governance is adhered to in all publications generated from this protocol.

## 2.2 Sponsor

This study was undertaken by Observational Health Data Science and Informatics (OHDSI), an open collaboration.

# 3. Abstract

In this study we will describe the baseline demographic and clinical characteristics, as well as the occurrence of treatments and outcomes of individuals diagnosed with inflammatory bowel disease (IBD), and specifically with Crohn’s disease (CD) and ulcerative colitis (UC).

# 4. Amendments and Updates

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Number** | **Date** | **Section of study protocol** | **Amendment or update** | **Reason** |
|  |  |  |  |  |

# 5. Rationale and Background

Crohn's disease and ulcerative colitis are chronic inflammatory bowel conditions with consistently increasing incidence rates in both newly industrialized and developed countries (Benchimol et al., 2014; Windsor and Kaplan, 2019). The highest incidence is between the age of 18-35 years (Windsor and Kaplan, 2019), but both pediatric onset IBD (age 10-18 years) and early onset IBD (under the age of 10 years) are steadily increasing (Benchimol et al., 2014; Sýkora et al., 2018; Carroll et al., 2019). The fastest growth in cases is observed in the elderly (65 years and older) (Windsor and Kaplan, 2019), as patient age and new cases diagnosed.

These diseases considerably affect the quality of life of patients and family members, contributing to a negative psychological effect, which has been demonstrated to exacerbate disease progression (Sajadinejad et al., 2012; Yeh et al., 2017). The increase in its prevalence has a significant impact on healthcare financial burden due to chronically administered medications, especially biologic drugs, which are used more frequently in recent years, hospitalizations and surgical procedures (Windsor and Kaplan, 2019).

IBD pathogenesis is not well understood. It is considered to be multifactorial with genetic susceptibility and environmental influence, potentially mediated through the microbiome. Presumed contributing factors are urban versus rural residency in early life (Benchimol et al., 2017), nutrition (specifically, high animal protein and low fiber intake) as well as smoking and stressors (Ananthakrishnan, 2013; Yeh et al., 2017; Windsor and Kaplan, 2019), antibiotic treatment and high dose or long duration and high frequency of treatment with NSAIDS (Ananthakrishnan, 2013).

Due to the high and increasing incidence of IBD and its negative impact on patients, it is of great importance to study its risk factors, treatments pathways, and long-term complications, in order to establish better therapies and slow down or prevent the steady increase in its incidence.

# 6. Objective

The primary objective of the study is to describe the baseline demographic and clinical characteristics, as well as treatments and occurrence of outcomes of interest among individuals diagnosed with inflammatory bowel disease, Crohn’s disease, and ulcerative colitis, overall and in various strata (e.g., by sex and age).

# 7. Methods

This study is a multinational cohort study describing the baseline characteristics, treatments, and outcomes of four cohorts, namely:

1. Persons with IBD
2. Persons with Crohn’s disease
3. Persons with ulcerative colitis
4. Persons with undetermined IBD

## 7.1 Data Sources

The study will be conducted using data from real world data sources that have been mapped to the OMOP Common Data Model in collaboration with the Observational Health Data Sciences and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) initiatives. The OMOP Common Data Model (<https://github.com/OHDSI/CommonDataModel/wiki>) includes a standard representation of health care trajectories (such as information related to drug utilization and condition occurrence), as well as common vocabularies for coding clinical concepts, and enables consistent application of analyses across multiple disparate data sources (Voss et al., 2015).

**Table 1**. Data sources formatted to the OMOP CDM participating in the IBD characterization study.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Data source** | **Source population** | **Sample size** | **Data type** | **Longitudinal history** |
| **IQVIA Medical Research Data (IMRD) UK** | General population in the UK | 12.7 million | Primary care EHRs including diagnoses, treatments, prescriptions, and procedures. | From mid 1990s to 3/2019 |

## 7.2 Study design

The study is an observational cohort study based on routinely-collected health care data which has been mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). Cohorts of individuals with IBD, Crohn’s disease or ulcerative colitis will be identified. Characteristics of these individuals will be assessed in the periods preceding and at the index date and analysis of their treatments and outcomes following it.

## 7.3 Target cohorts

IBD cohorts

**Target Cohort #1:** Persons with IBD have either:

* ≥2 records of IBD diagnosis OR ≥1 records of IBD diagnosis and ≥1 prescription for IBD medications

**Target Cohort #2:** Persons with undetermined IBD will have either:

* ≥2 records of IBD diagnosis OR ≥1 records of IBD diagnosis and ≥1 prescription for IBD medications

AND

* No records of type-specific (Crohn’s disease or ulcerative colitis) diagnosis OR records of both Crohn’s disease and ulcerative colitis diagnoses

Crohn’s disease cohort

**Target Cohort #3:** Persons with a Crohn’s disease diagnosis will:

* ≥2 records of IBD diagnosis OR ≥1 records of IBD diagnosis and ≥1 prescription for IBD medications

AND

* ≥1 Crohn’s disease diagnosis

AND

* no ulcerative colitis diagnosis

Ulcerative colitis cohort

**Target Cohort #4:** Persons with ulcerative colitis diagnoses will:

* ≥2 records of IBD diagnosis OR ≥1 records of IBD diagnosis and ≥1 prescription for IBD medications

AND

* have ≥1 ulcerative colitis diagnosis

AND

* have no Crohn’s disease diagnosis

These cohorts will all be identified without any requirement for prior observation time and with the added restriction of having a minimum of 365 days of prior observation time available to characterize disease onset cohorts.

## 7.4 Characteristic Time Windows

We will extract baseline characteristics during patients’ entire history, the year and month before the index date (date of cohort entry event) , and the index date itself. Outcomes and treatments will be identified during the 1, 3, 5, and 10 years following the index date as well as each patient’s full follow-up time windows.

## 7.5 Stratifications

Each target cohort will be analyzed in full and stratified on factors based on the following pre-index characteristics:

* Follow-up time: overall, and with full 1-, 3-, 5-, and 10-year follow-up
* Sex (Male vs. Female)
* Specific age groups:
  + Very early onset IBD (Age 2-5)
  + Early onset IBD (Age 6-10)
  + Pediatrics (Age 11-17)
  + Adults (Age 18-65)
  + Elderly (Age >= 65)
* Race: white, black or African American, Asian
* Index date year (in 5y windows)
* Obesity, overweight, normal weight, underweight
* Pregnant women

All strata are pending meeting minimum reportable cell counts (as specified by data owners).

## 7.6 Features of interest

The following list of features spans across the full set of target cohorts and research questions of interest in subgroups (incl. pediatrics, pregnant women, etc.); some features will only be relevant in a subset of target cohorts or subgroups.

Pre-index characteristics

These features will be described as assessed in three different time windows: the last 30 days (-1 to -30 days), the year (-1 to -365 days), and each patient’s full history pre-index:

**Demographics**:

* Age: calculated as (year of cohort start date – year of birth) and with 5 year groupings
* Sex
* Race

**Concept-based:**

* Condition groups (SNOMED + descendants), >=1 occurrence during the interval
* Drug era groups (ATC/RxNorm + descendants), >=1 day during the interval which overlaps with at least 1 drug era

Post-index characteristics

These features will be described in six different time windows: at index date (day 0), in the 1-, 3-, 5-, and 10-year period (0 to 365, 1095, 1825, and 3650 days, respectively) and each patient’s full follow-up post index date. The characteristics will include:

**Concept-based:**

* Condition groups (SNOMED + descendants), >=1 occurrence during the interval
* Drug era start groups (ATC/RxNorm + descendants), >=1 drug era start during the interval

**Cohort-based**

* Risk factors
  + Family history of IBD
  + Smoker
  + Appendectomy procedure
* Related comorbidities
  + Prevalent Autoimmune condition (exl. IBD)
  + Prevalent type 2 diabetes mellitus
  + Prevalent type 1 diabetes mellitus
  + Prevalent rheumatoid arthritis
  + Prevalent celiac disease
  + Hypothyroidism
  + Grave's disease
  + Vitiligo
  + Hashimoto thyroiditis
  + Irritable bowel syndrome
  + Alcohol misuse or dependence
* Symptoms
  + Gastrointestinal bleeding events
  + Diarrhea
  + Abdominal pain
  + Rectal bleeding
  + Bloody diarrhea
  + Aphthae
  + Bloating
* Laboratory result
  + Anemia
  + Iron deficiency anemia
  + Low serum albumin level
  + Low platelet count
  + Low hemoglobin level
* Extra-intestinal manifestation
  + EIM: Peripheral arthritis
  + EIM: Axial arthritis
  + EIM: skin
  + EIM: eyes
  + EIM: liver
  + EIM: Perianal disease
  + Arthritis
  + Uveitis
  + Erythema nodosuma
  + Pyoderma gangrenosum
  + Arthralgia
* IBD complications
  + Death
  + Hospitalization episodes
  + Colostomy procedure
  + Colostomy present
  + Colectomy procedure
  + Colectomy present
  + Ileostomy procedure
  + Ileostomy present
  + Gastrointestinal stenosis
  + Intestinal obstruction
  + Penetrating IBD
  + Small intestinal resection
  + Strictureplasty
  + Balloon dilation
  + Drainage of perianal abscess
  + Drainage of intra-abdominal abscess
  + Anorectal fistula
  + Abnormal weight loss
  + Low bone density
  + Growth failure
* Malignancy
  + Prevalent malignant neoplasm excluding non-melanoma skin cancer
  + Non-melanoma skin cancer
  + Lymphoma
  + Cervical cancer benign
  + Cervical cancer malignant
  + Lung cancer malignant
  + Colon cancer benign
  + Colon cancer malignant
  + Small bowel carcinoma
  + Anal carcinoma
  + Urinary tract neoplasm benign
  + Urinary tract neoplasm malignant
  + Cholangiocarcinoma
  + Melanoma
* Psychiatric
  + Hospitalization for psychosis
  + Suicide and suicidal ideation
  + Depression
  + Anxiety
  + Stress
* IBD medications
  + Immunomodulator exposure
  + 5-ASA exposure
  + IBD biologics exposure
  + IBD steroid exposure
  + Modulen exposure
  + IBD steroid (broad) exposure
  + IBD-specific antibiotic exposure
  + TNF-alpha inhibitors
  + Anti-migration immunosuppressant
  + Interleukin 12, 23 inhibitors
  + JAK inhibitors
* Antibiotic exposure
  + Tetracyclines (antibiotic) exposure
  + Amphenicols (antibiotic) exposure
  + Penicillin (antibiotic) exposure
  + Non-penicillins beta-lactam(antibiotic) exposure
  + Sulfonamides and trimethoprim (antibiotic) exposure
  + Macrolides, lincosamides and streptogramins(antibiotic) exposure
  + Aminoglycoside antibacterials (antibiotic) exposure
  + Quinolone antibacterials (antibiotic) exposure
  + Combinations of antibacterials (antibiotic) exposure
  + Other antibacterials (antibiotic) exposure
* Other medications
  + Loperamide, codeine exposure
  + SSRI exposure
  + Proton-pump inhibitor exposure
  + Mebeverine exposure
  + Alverine exposure
  + Butylscopolamine exposure
  + Peppermint oil exposure
  + Psyllium exposure
  + NSAID exposure
* Vaccines
  + Pneumococcal vaccines
  + Pneumovax 23
  + Prevnar 13
  + Hepatitis B vaccine
  + Influenza vaccine
  + Diphtheria and Pertussis vaccine
  + HPV vaccine
  + MMR vaccine
  + Shingles vaccine

## 7.7 Analysis: Characterizing cohorts

All analyses will be performed using code developed for the OHDSI Methods library. The code for this study can be found at <https://github.com/ohdsi-studies/IbdCharacterization>. A diagnostic package, built off the OHDSI Cohort Diagnostics (<https://ohdsi.github.io/CohortDiagnostics/>) library, is included in the base package as a preliminary step to assess the fitness of use of phenotypes on your database. If a database passes cohort diagnostics, the full study package will be executed. Baseline covariates will be extracted using an optimized SQL extraction script based on principles of the Feature Extraction package (<http://ohdsi.github.io/FeatureExtraction/>) to quantify Demographics (Gender, Prior Observation Time, Age Group), Condition Group Eras and Drug Group Eras (at the above-listed time windows). Additional cohort-specific covariates will be constructed using OMOP standard vocabulary concepts.

Number and proportion of persons with feature variables during time-at-risk windows will be reported by target cohort and specific stratifications. Standardized mean differences (SMD) will be calculated when comparing characteristics of study cohorts, with plots comparing the mean values of characteristics for each of the features (with the color indicating the absolute value of the standardized difference of the mean).

## 7.8 Logistics of Executing a Federated Analysis

Sites will run the study analysis package locally on their data coded according to OMOP CDM. Only aggregate results will be shared with the study coordinator. Result files will be automatically staged into a ZIP file that can be transmitted using the OhdsiSharing R Library (<http://ohdsi.github.io/OhdsiSharing/>) or through a site’s preferred SFTP client using a site-specific key provisioned by the OHDSI Study Coordinator. Local data stewards are encouraged to review study parameters to ensure minCellCount function follows local governance. At a minimum, it is encouraged to keep this value to >5 to avoid any potential issues with re-identification of patients. Note: covariates are constructed using controlled ontologies from the OMOP standard vocabularies though some labels may be replaced with publication-friendly labels due to space restrictions of the submitting journal.

# 8. Sample Size and Study Power

Placeholder, need to update:

The study package is designed to suppress any analyses which have less than 140 unique persons. This cut point was informed by a power calculation performed by the OHDSI COVID Consortia to assess the computational cut point of when a cell count would be too small to merit additional subdivision within the target-stratum-feature combination. This means that each data owner will only generate results for target-stratum-feature pairs that meet this minimum threshold.

# 9. Strengths and Limitations

## 9.1 Strengths

We hope to generate the world’s largest observational sets of analyses of secondary health data for IBD. We are running a multi-country, multi-center characterization study to understand baseline covariates, treatments and outcomes observed in IBD. The use of a common data model and standard vocabularies ensures interoperability and portability of phenotypes utilized in this analysis. The use of a federated study model will ensure no movement of patient-level data from institutions participating in this analysis. This is critically important to ensure the protection of patient privacy in the secondary use of routinely collected patient data. Data custodians will remain in control of the analysis run on these data and will conduct their own site-based validation processes to evaluate case reports against public health reporting.

## 9.2 Limitations

Condition phenotyping may be inaccurate as it is based on the presence of condition and medication codes, with the absence of such records taken to indicate the absence of a disease. Furthermore, medication records indicate that an individual was prescribed or dispensed a particular drug, but this does not necessarily mean that an individual took the drug as originally prescribed or dispensed. Our study could be subject to exposure misclassification with false positives if a patient had a dispensing but did not ingest the drug but may also be subject to false negatives for non-adherent patients who continued their medication beyond the days supply due to stockpiling. Medication use estimates on the date of hospitalization is particularly sensitive to misclassification and may conflate baseline concomitant drug history with immediate treatment upon admission. Finally, patient data in different healthcare systems, settings or geographies may follow distinct subpopulations along (parts of) their disease-related trajectory; combining such data calls for careful diagnostics to avoid biases.

# 10. Protection of Human Subjects

The study uses only de-identified data. Confidentiality of patient records will be maintained at all times. Data custodians will remain in full control of executing the analysis and packaging results. There will be no transmission of patient-level data at any time during these analyses. Only aggregate statistics will be captured. Study packages will contain minimum cell count parameters to obscure any cells which fall below allowable reportable limits. All study reports will only contain aggregated data and will not identify individual patients or physicians.

# 11. Management and Reporting of Adverse Events and Adverse Reactions

This study will provide a descriptive summary of individuals with IBD; drug effects are currently outside the scope of the study.

# 12. Plans for Disseminating and Communicating Study Results

The results will be shared and discussed among study participants during the time of research. Study results will be posted on the OHDSI website (<https://data.ohdsi.org/>) after completion of the study. The results will also be presented at the OHDSI in-person or virtual events. Finally, we plan to publish this research as a scientific manuscript in a top-tier journal.

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# Appendix 1: Cohort Definitions

IBD target definitions –

|  |  |  |
| --- | --- | --- |
| Name | Atlas Link | JSON Link |
| Persons with IBD with at least 365d prior observation | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776609> |  |
| Persons with IBD with no required prior observation | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776610> |  |
| Persons with undetermined IBD (no type-specific codes) with at least 365d prior observation | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777393 |  |
| Persons with undetermined IBD (no type-specific codes) with no required prior observation | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777394 |  |
| Persons with undetermined IBD (both type-specific codes) with at least 365d prior observation | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777395 |  |
| Persons with undetermined IBD (both type-specific codes) with no required prior observation | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777396 |  |

Crohn’s disease target definitions –

|  |  |  |
| --- | --- | --- |
| Name | Atlas Link | JSON Link |
| Persons with Crohn's disease with at least 365d prior observation | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776617> |  |
| Persons with Crohn's disease with no required prior observation | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776618> |  |

Ulcerative colitis target definitions –

|  |  |  |
| --- | --- | --- |
| Name | Atlas Link | JSON Link |
| Persons with ulcerative colitis with at least 365d prior observation | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776625> |  |
| Persons with ulcerative colitis with no required prior observation | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776626> |  |

Stratum Definitions –

|  |  |  |
| --- | --- | --- |
| Name | Atlas Link | JSON Link |
| Pregnant women | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776627> |  |
| Prevalent obesity | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776628> |  |
| Overweight | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776629> |  |
| Normal weight | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776630> |  |
| Underweight | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776631> |  |

Feature Definitions –

|  |  |  |
| --- | --- | --- |
| Name | Atlas Link | JSON Link |
| Risk factors | | |
| Family history of IBD | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776674> |  |
| Smoker | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776669> |  |
| Appendectomy procedure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776656> |  |
| Related comorbidities | | |
| Prevalent Autoimmune condition (exl. IBD) | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777398> |  |
| Prevalent type 2 diabetes mellitus | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777397> |  |
| Prevalent type 1 diabetes mellitus | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776671> |  |
| Prevalent rheumatoid arthritis | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776672> |  |
| Prevalent celiac disease | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776673> |  |
| Hypothyroidism | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776688> |  |
| Grave's disease | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776675> |  |
| Vitiligo | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776676> |  |
| Hashimoto thyroiditis | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776677> |  |
| Irritable bowel syndrome | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777399 |  |
| Alcohol misuse or dependence | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776670> |  |
| Symptoms | | |
| Gastrointestinal bleeding events | <https://atlas.ohdsi.org/#/cohortdefinition/245> | <https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis/blob/master/inst/cohorts/187.json> |
| Diarrhea | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777437> |  |
| Abdominal pain | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777438> |  |
| Rectal bleeding | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777439> |  |
| Bloody diarrhea | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777440> |  |
| Aphthae | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777441> |  |
| Bloating | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777442> |  |
| Lab results | | |
| Anemia | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776686> |  |
| Iron deficiency anemia | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777413> |  |
| Low serum albumin level | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777414> |  |
| Low platelet count | [http://atlas-demo.ohdsi.org/#/cohortdefinition/1777415](http://atlas-demo.ohdsi.org/#/cohortdefinition/1777415/definition) |  |
| Low hemoglobin level | [http://atlas-demo.ohdsi.org/#/cohortdefinition/1777416](http://atlas-demo.ohdsi.org/#/cohortdefinition/1777416/definition) |  |
| Extra-intestinal manifestation | | |
| EIM: Peripheral arthritis | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776678> |  |
| EIM: Axial arthritis | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776679> |  |
| EIM: skin | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776680> |  |
| EIM: eyes | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776681> |  |
| EIM: liver | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776682> |  |
| EIM: Perianal disease | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776683> |  |
| Arthritis | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777400 |  |
| Uveitis | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777401 |  |
| Erythema nodosuma | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777402 |  |
| Pyoderma gangrenosum | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777403> |  |
| Arthralgia | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777404 |  |
| IBD complications | | |
| Death | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777405> |  |
| Hospitalization episodes | <https://atlas.ohdsi.org/#/cohortdefinition/280> | <https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis/blob/master/inst/cohorts/151.json> |
| Colostomy procedure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776648> |  |
| Colostomy present | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776649> |  |
| Colectomy procedure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776650> |  |
| Colectomy present | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776651> |  |
| Ileostomy procedure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776652> |  |
| Ileostomy present | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776653> |  |
| Gastrointestinal stenosis | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776654> |  |
| Intestinal obstruction | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776655> |  |
| Penetrating IBD | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777408 |  |
| Small intestinal resection | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776657> |  |
| Strictureplasty | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776658> |  |
| Balloon dilation | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776659> |  |
| Drainage of perianal abscess | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776660> |  |
| Drainage of intra-abdominal abscess | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776661> |  |
| Anorectal fistula | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777406 |  |
| Abnormal weight loss | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776687> |  |
| Low bone density | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776689> |  |
| Growth failure | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777407 |  |
| Malignancy | | |
| Prevalent malignant neoplasm excluding non-melanoma skin cancer | <https://atlas.ohdsi.org/#/cohortdefinition/222> | <https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis/blob/master/inst/cohorts/105.json> |
| Non-melanoma skin cancer | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776684> |  |
| Lymphoma | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776685> |  |
| Cervical cancer benign | [http://atlas-demo.ohdsi.org/#/cohortdefinition/1777417](http://atlas-demo.ohdsi.org/#/cohortdefinition/1777417/definition) |  |
| Cervical cancer malignant | [http://atlas-demo.ohdsi.org/#/cohortdefinition/1777418](http://atlas-demo.ohdsi.org/#/cohortdefinition/1777418/definition) |  |
| Lung cancer malignant | [http://atlas-demo.ohdsi.org/#/cohortdefinition/1777419](http://atlas-demo.ohdsi.org/#/cohortdefinition/1777419/definition) |  |
| Colon cancer benign | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777420> |  |
| Colon cancer malignant | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777421> |  |
| Small bowel carcinoma | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777422> |  |
| Anal carcinoma | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777423> |  |
| Urinary tract neoplasm benign | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777424> |  |
| Urinary tract neoplasm malignant | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777425> |  |
| Cholangiocarcinoma | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777426> |  |
| Melanoma | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777427> |  |
| Psychiatric | | |
| Hospitalization for psychosis | <https://atlas.ohdsi.org/#/cohortdefinition/236> | <https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis/blob/master/inst/cohorts/196.json> |
| Suicide and suicidal ideation | <https://atlas.ohdsi.org/#/cohortdefinition/235> | <https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis/blob/master/inst/cohorts/197.json> |
| Depression | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776666> |  |
| Anxiety | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776667> |  |
| Stress | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776668> |  |
| IBD medications | | |
| Immunomodulator exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776632> |  |
| 5-ASA exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776633> |  |
| IBD biologics exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776634> |  |
| IBD steroid exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776635> |  |
| Modulen exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776636> |  |
| IBD steroid (broad) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776637> |  |
| IBD-specific antibiotic exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776638> |  |
| TNF-alpha inhibitors | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777409 |  |
| Anti-migration immunosuppressant | http://atlas-demo.ohdsi.org/#/cohortdefinition/1777410 |  |
| Interleukin 12, 23 inhibitors | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777411> |  |
| JAK inhibitors | [http://atlas-demo.ohdsi.org/#/cohortdefinition/1777412](http://atlas-demo.ohdsi.org/#/cohortdefinition/1777412/definition) |  |
| Antibiotic exposure | | |
| Tetracyclines (antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776639> |  |
| Amphenicols (antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776640> |  |
| Penicillin (antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776641> |  |
| Non-penicillins beta-lactam(antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776642> |  |
| Sulfonamides and trimethoprim (antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776643> |  |
| Macrolides, lincosamides and streptogramins(antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776644> |  |
| Aminoglycoside antibacterials (antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776645> |  |
| Quinolone antibacterials (antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776646> |  |
| Combinations of antibacterials (antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776647> |  |
| Other antibacterials (antibiotic) exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1776662> |  |
| Other medications | | |
| Loperamide, codeine exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777428> |  |
| SSRI exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777429> |  |
| Proton-pump inhibitor exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777430> |  |
| Mebeverine exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777431> |  |
| Alverine exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777432> |  |
| Butylscopolamine exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777433> |  |
| Peppermint oil exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777434> |  |
| Psyllium exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777435> |  |
| NSAID exposure | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777436> |  |
| Vaccines | | |
| Pneumococcal vaccines | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777443> |  |
| Pneumovax 23 | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777444> |  |
| Prevnar 13 | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777445> |  |
| Hepatitis B vaccine | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777446> |  |
| Influenza vaccine | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777447> |  |
| Diphtheria and Pertussis vaccine | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777448> |  |
| HPV vaccine | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777449> |  |
| MMR vaccine | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777450> |  |
| Shingles vaccine | <http://atlas-demo.ohdsi.org/#/cohortdefinition/1777451> |  |