Risk of serious infections with bDMARDs in psoriasis/psoriatic arthritis patients: a large-scale cohort study using the Italian VALORE Project distributed database

Summary

Introduction

Psoriasis (PsO) is a common chronic, multisystem, immuno-mediated dermatologic disease.

PsO has different clinical phenotypes, but the most frequent and most easily recognized is chronic plaque or psoriasis vulgaris [Griffiths et al., 2021]. PsO is associated with many diseases, most notably with psoriatic arthritis (PsA), a seronegative inflammatory arthritis observed in 10–40% of patients with PsO, which can further deteriorate quality of life by affecting physical function [Vena et al., 2010; FitzGerald et al., 2021]. Estimated prevalence of PsO ranges from 0.1% in east Asia to 1.5-2.7% in western Europe and Italy. [Griffiths et al., 2021; Pezzolo et al., 2019; Ingrasciotta et al., 2021].

Several therapeutic options for PsO/PsA are available. Choice of treatment depends on disease severity, location, and multimorbidity. First-line PsO treatment involves topical therapies including emollients, corticosteroids, vitamin D3 analogues, calcineurin inhibitors, keratolytics, and

combination topical agents, as cream, ointment, foam, or gel formulations, as well as targeted phototherapy. Moderate to severe diseases require oral systemic therapies, with heterogeneous mechanisms of action, documented efficacy and safety profiles [Ogdie et al., 2020]. For the PsA treatment, nonsteroidal anti-inflammatory agents (NSAIDs) can be used as a symptomatic treatment, while glucocorticoids should be used only as a relief treatment at the lowest dose and for the shortest time duration [Ogdie et al., 2020; FitzGerald et al., 2021]. Other commonly used oral drugs for PsO/PsA treatment include acitretin, fumarates, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), e.g., methotrexate, sulfasalazine, leflunomide, cyclosporine, and, more recently, biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (PDE4 inhibitors – apremilast) and JAK inhibitors (tofacitinib, upadacitinib, baricitinib) [Griffiths et al., 2021; Bakshi et al., 2020]. As for bDMARDs, in Europe a large number of molecules for moderate to severe PsO/PsA treatment have been authorized (see **Table A1**) [Griffiths et al., 2021; Bakshi et al., 2020]: Tumour Necrosis Factor-α (TNF-α) antagonists (adalimumab, certolizumab pegol, golimumab, etanercept, infliximab), Interleukin-17 Receptor Antagonist (IL-17RA) (brodalumab), IL-17 antagonists (ixekizumab, secukinumab, bimekizumab), IL-23 antagonists (guselkumab, risankizumab, tildrakizumab), IL-12/IL-23 antagonists (ustekinumab), T cell modulator (abatacept).

PsO/PsA patients have an increased baseline risk for infections per se, due to the loss of the integrity of skin barrier and intrinsic cellular immunity alterations [Schön, 2019; Lowes et al., 2014; Haddad et al., 2016]. Based on record linkage analyses of claims and clinical databases (CPRD GOLD) in United Kingdom, Yiu et al. [Yiu et al., 2021] found around 30% increased risk of severe infections in patients with PsO, as compared to matched patients PsO-free, after adjustment for potential confounders such as systemic therapies and other comorbidities. Several RCTs and observational studies of patients with moderate-to-severe PsO/PsA reported a differential increase in the infection risk across various systemic drugs (see **Table A2**). While bDMARDs have shown dramatic improvement in terms of benefit, safety issues have been largely documented, including the risk of serious infection [Ingrasciotta et al., 2018; Cutroneo et al., 2014]. Results from a recent systematic review and meta-analysis [Yiu et al., 2016; Manounah et al., 2021] of RCTs of patients with PsO/PsA on bDMARDs therapies show that the total number of serious infections reported across all RCTs was low (n = 54) and eight studies did not report any serious infections in either study arm. However, most RCTs included past serious infection as an exclusion criteria. Indeed, many observational studies identified infection as one of the primary reasons for therapy discontinuation; however, these studies did not include more recently commercialized bDMARDs [Yiu et al., 2019; Yiu et al., 2017; Li et al., 2019; Penso et al., 2021; Grijalva et al., 2011; Jin et al., 2022; Kalb et al., 2015; Dávila-Seijo

et al., 2017; Wang et al., 2022]. Some cohort studies found that adalimumab and infliximab are associated to a higher risk of serious infections compared with other bDMARDs or non-biologic therapies, while ustekinumab is associated to a lower risk [Penso et al., 2021; Kalb et al., 2015; Jin et al., 2022; Penso et al., 2021; Quartuccio et al., 2018; Siegel et al., 2019]. In the aforementioned cohort studies, gastrointestinal, skin and subcutaneous tissue, pulmonary, and urinary tract infections were the most commonly reported severe infections.

To the best of our knowledge, no prior studies compared the risk of severe infections among bDMARDs in a large Italian cohort of patients affected by PsO/PsA, nor the risk related to more recently approved bDMARDs.

Objective

Primary objective: To evaluate the association between the use of individual bDMARDs approved for PsO/PsA treatment and the occurrence of severe infection risk in an Italian real-world setting in the years 2010-2021 among different drug class (TNF-alpha inhibitors, IL inhibitors, T cell modulator), using the large-scale "VALORE" project distributed database network.

Secondary objective: To assess the incidence of severe infection between bDMARDs in monotherapy and in combination therapy with csDMARDs and/or systemic corticosteroids.

Methods

Data source

Fully anonymized data will be extracted from the VALORE project multi-regional claims databases, covering a total underlying population of around 2/3 (around 40 millions) of the total Italian population from 2010 to 2022. In particular, the following regional claims databases will be considered: (1) inhabitant registry, including demographic information about the date of birth, sex, and date of registration in the regional healthcare system; (2) drug dispensing from hospital and territorial pharmacy claims database; (3) Hospital Discharge Records (HDR), including information on the date of hospital admission and discharge, diagnosis-related group (DRG), principal diagnosis and up to five secondary diagnoses, and principal procedure and up to five secondary procedures; (4) Exemptions (EXE) from healthcare service co-payment database, collecting coded information about chronic diseases or socioeconomic factors and outpatient diagnostic tests and specialist's visits database. Health coverage, and thus capture of the Italian population in the multi-regional claims databases, is very high since Italy has National Health Service offering universal care for all residents in each region. Drugs were coded using the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose (DDD) was used as the unit to estimate drug exposure for

Commentato [PE1]: Maybe quantify in million of people for international readers

Commentato [MC2R1]: We have added "around 40 millions", and we'll have the exact count when we will have data

Commentato [PE3]: Can we also see the medications used during the hospitalization?

Commentato [MC4R3]: No, unfortunately we can not.

Commentato [PE5]: Only orders and no results, right?

Commentato [MC6R5]: Right, only orders

bDMARDs, while indication of use and causes of hospitalization were coded using the International Classification of Disease, 9th revision, Clinical Modification (ICD 9-CM).

In Italy, bDMARDs with subcutaneous formulations are dispensed to patients by hospital pharmacists for outpatient use, whereas intravenous bDMARDs (e.g., infliximab) are administered in dedicated hospital ambulatory care centers. In each region, information on dispensing of bDMARDs, irrespective of the formulations, are collected in claims data. The VALORE project distributed database network has been previously described elsewhere [Trifirò et al., 2021].

An R-based open-source tool "TheShinISS," developed by the Italian National Institute of Health for conduction of distributed analyses and described elsewhere [Trifirò et al., 2021], was customized for the purposes of the study, in compliance with EU General Data Protection Regulation regulations.

Study design

A propensity score-matched, cohort study.

Cohort selection

All users of bDMARDs approved for PsO/PsA with at least one year of look-back period will be considered. Subjects will be included in the cohort only if all the following inclusion criteria will be met:

a) Incident users, defined as all bDMARDs users without any dispensing of bDMARD in the year prior to the index date (ID) (i.e., first date of bDMARD dispensing). The first dispensing of bDMARDs will be considered as the index drug.
b) A diagnosis of PsO/PsA registered anytime prior to ID, identified using a validated coding algorithm (**Table A3**) [Pezzolo et al., 2021]. As for those drugs approved exclusively for PsO/PsA (brodalumab, guselkumab, tildrakizumab, risankizumab) this criterion will not be considered.
c) At least one dispensing of bDMARDs during the study period.

Patients will be followed from the ID until one of the following events, whichever comes first: a) hospitalization for severe infection (see **Table A4** for the list of severe infections); b) switch/swap to different bDMARD or bDMARD discontinuation, c) death; d) end of follow-up (31 December 2021), or e) emigration from the region.

Commentato [PE7]: Is this derived based on the presence of specific comorbidities at a specific time or is the specific indication of use available in the databases?

Commentato [AS8R7]: Dear Elisabetta, unfortunately we don't have this information in our claims data. We developed a META-algorithm to find indication of use of biological drugs which was found to have good validity estimates. The article will be submitted in September

Commentato [PE9]: Will the follow-up start at the second dispensing? Alternatively, to avoid conditioning cohort entry on a future event, is it not possible to only rely on 1 dispensing (i.e., use the secondary analysis as the primary)?

Commentato [MC10R9]: We agree and we modified as suggested: we will rely on 1 dispensing. We deleted the part about sensitivity analysis

Commentato [PE11]: Does discontinuation count as a censoring reason?

Commentato [MC12R11]: Yes, we agree and we added "or bDMARD discontinuation" in the text

Drug exposure

The list of biological drugs approved in Italy for the treatment of PsO/PsA up to 31st December 2022 to be included in the study is reported in **Table A1** : a) Tumor Necrosis Factor (TNF)-alpha inhibitors: infliximab (L04AB02), etanercept (L04AB01), adalimumab (L04AB04), golimumab (L04AB06) and certolizumab pegol (L04AB05); b) Interleukin-17 Receptor Antagonists: brodalumab (L04AC12); c) Interleukin-17 antagonists: ixekinumab (L04AC13), secukinumab (L04AC10), bimekizumab (L04AC21); d) IL-23 antagonists: guselkumab (L04AC16), risankizumab (L04AC18), tildrakizumab (L04AC17); e) IL-12/IL-23 antagonists: ustekinumab (L04AC05); f) T cell modulator: abatacept (L04AA24).

Outcome

The occurrence of a serious infection during follow up will be considered the outcome. Infections reported either in the literature as potentially associated to the bDMARDs under study, or in section 4.4 "Special Warnings and Appropriate Precautions for Use" of summary of product characteristics or in the "Important identified or potential risks" section of the risk management plan of individual bDMARDs approved for PsO/PsA treatment were considered. In particular the following severe infections requiring hospitalization will be included in the outcome definition: herpes simplex, herpes zoster, primary tuberculosis, pulmonary tuberculosis, extra-pulmonary tuberculosis, non-invasive candidiasis, invasive candidiasis, sepsis, endocarditis, viral hepatitis, pneumonia, non-invasive fungal infections, invasive fungal infections, infections of conjunctiva and other infections of the eye, COVID-19, osteomyelitis/infection of joints, cystitis, infections of kidney, infections of skin and subcutaneous tissue, intestinal infectious diseases (See **Table A4** of the Appendix**)**.

Time to onset will also be estimated as number of days between the ID and the severe infection disease occurrence.

Other variables

Demographic characteristics: Sex (0: male; 1: female) and age (years) at index date.

Year of cohort entry.

Region.

Previous use of immunosoppressants (y/n): At least one drug dispensing in the year before index date for the following drugs: csDMARDs (methotrexate: L04AX03, sulfasalazine: A07EC01, leflunomide: L04AA13, cyclosporine: L04AD01), systemic corticosteroids (ATC: H02*).

Previous use of other drugs (y/n): antibiotics, proton pump inhibitors, and NSAIDs. Please refer to **Table 5**, **Table 6**, and **Table 7**, for the complete list of considered medications and their ATC codes, respectively.

Concomitant drugs (y/n): At least one dispensing of csDMARDs (1,0), systemic corticosteroids (1,0) in the 3 months pre and 3 months after index date.

Charlson's Comorbidity Index: see table **Table A8** for definition.

Comorbidities (y/n): Previous record in the year before index date from exemptions and hospital discharge records of one of the following disease: obesity, diabetes mellitus, chronic obstructive pulmonary disease, infections, including HIV, concomitant autoimmune diseases other than PsO/PsA [i.e. rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, celiac disease, multiple sclerosis, autoimmune hepatitis; IBD (Crohn's disease and ulcerative colitis), hidradenitis suppurativa]. (Please see **Table A9** for those variables' codes and descriptions).

Statistical analysis plan

Descriptive analysis: characteristics of incident users of bDMARDs at the index date (baseline), stratified by drug classes, will be reported as means and standard deviations (SDs) and as absolute and relative frequencies (percentages) for continuous and categorical variables, respectively.

The difference between the two cohorts of bDMARDs users' characteristics will be assessed by the standardized difference (d) [Austin et al., 2009]. This measure quantifies the magnitude of the overall difference in terms of "effect size" (i.e. denoting the clinical relevance): for d< 20% there is a small difference between groups (for d< 10% this difference is negligible) [Sawilowsky, 2009].

Moreover, in the unmatched (i.e. original) sample, such comparisons will be statistically assessed using the two-sample t-test and the Chi-Square (or Fisher as appropriate) test for continuous and categorical variables, respectively.

Incidence of severe infections:

- Primary objective: Estimation of the incidence of severe infection between different drug classes (TNF alpha vs IL-inhibitors/Selective Immunosuppressive agents).

Propensity score (PS) matching procedure: A 5 to 1 greedy 1:1 PS matching algorithm [Parsons et al., 2004] will be used to create two cohorts of bDMARDs users with the same baseline characteristics: TNF-alpha vs other bDMARDs (IL-inhibitors/selective immunosuppressive agents). This was done since selective immunosuppressive agents account only for abatacept which is reported to have a similar infection safety profile to IL-inhibitors [Chen et al., 2020]. To compute PS, a binary logistic regression will be built to predict the individual probability of having other bDMARDs vs

Commentato [PE13]: See comment above

Commentato [PE14]: In addition to history of any infections, would it be of interest to capture the occurrence of serious infections (leading to an hospitalization) during the 1-year baseline?

Commentato [MC15R14]: Yes, we agree. As we search on HDRs, we'll find only infections leading to hospitalization

Commentato [PE16]: In addition to comorbidities, are there other medication classes that may be interesting to capture during the 1-year baseline? For example, use of NSAIDs, antibiotics, etc.?

Commentato [AS17R16]: Thank you for your comment. We added other classes of drugs to the protocol

Commentato [PE18]: Will you consider any formal quantification of the differences in patient characteristics between groups, e.g., standardized differences or similar?

Commentato [AS19R18]: Yes, as specified below, we will calculate standardized mean difference before and after matching

Commentato [AF20R18]: Yes, the magnitude of the difference between the two cohorts' characteristics will be quantified in terms of an effect size measure, i.e. the standardized difference (Cohen's d). This is calculated as the difference between the two sample means or proportions, in case of continuous and categorical variables respectively, divided by the estimate of a "pooled" standard deviation, as detailed by Austin PC (DOI: 10.1002/sim.3697). Furthermore, the assessment of a statistical difference will be also performed.

Commentato [AF21]: As the continuous variables will be the age at index date and the Charlson comorbidity index only, it would be more appropriate to simplify this sentence by simply reporting their means and SD only. Furthermore, because the effect size measure is a standardized mean difference, it makes even more sense to consider the mean and SD instead of their medians.

Commentato [AF22]: It would probably be better to state that it is a "standardized difference" rather than a "standardized mean difference" because of the presence of mixed-type variables (continuous and dichotomous) and then replace the acronym "SMD" with "d"

Commentato [AF23]: Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009 Nov 10;28(25):3083-107. DOI: 10.1002/sim.3697

Commentato [PE24]: Fixed or variable 1:5 ratio?

Commentato [AF25R24]: This is not a "ratio" but the number of PS digits, used by the Parsons' greedy algorithm, to set a matched pair. The "5 to 1 matching" means that the first cohort of bDMARDs (e.g., TNF-alpha) users will first be matched to the other cohort based on 5 digits of the propensity score. For those that did not match, TNF-alpha users will then be matched to the other cohort on 4 digits of ...

Commentato [PE26]: Would you have the numbers to check this hypothesis in your own data, maybe as a secondary comparison?

Commentato [MC27R26]: Yes, we will compare single molecules in the secondary analysis

TNF-alpha dispensed based on the following covariates: age at ID (categorical variable with the following groups: ≤18, 19-44, 45-64, 65-79, ≥80 years), sex, calendar year, region, previous use of drugs (immunosuppressant as well as other classes), and comorbidities (see previous section)..

To assess the adequacy of covariates balance, both the standardized difference and the paired t-test and McNemar's tests will be performed in the matched sample for continuous and categorical variables, respectively.

The incidence of serious infections requiring hospitalization will be estimated as the number of occurred events out of the total number of person-years and will be reported per 100 person-years for ease of interpretation.

Cox Proportional-Hazards regression model: The effect of bDMARDs classes (using TNF-α antagonists as the reference drug class) on the incidence of serious infections requiring hospitalizations, among incident users of bDMARDs in PsO/PsA patients, will be estimated using the Cox Proportional-Hazards regression model. Risks will be reported as Hazard ratios (HR) along with their 95% confidence interval (CI) and will be estimated both in the unmatched cohort (crude and adjusted for other covariates) as well as in the PS matched cohort. In the latter case, the sandwich (robust) variance estimator will be used to adjust the covariance estimates of the model parameters to account for the correlations within paired individuals. The assumption of proportionality of the hazards over time will be checked for each covariate included in the model by the Kolmogorov-Type Supremum test [Lin et al., 1993]. In case of violation of this assumption, different strategies for dealing with the problem will be considered, such as time stratification or the inclusion of a time-by-covariate interaction in the model as appropriate.

Moreover, both crude and fully-adjusted Cox models will be estimated to assess the effect of each active ingredient (using infliximab as the reference active ingredient, as it is generally considered the drug with higher risk of serious infection [Yiu et al., 2019; Kalb et al., 2015]) on the incidence of serious infections requiring hospitalizations in the unmatched cohort. The same covariates used for the propensity score matching procedure will be included in the fully-adjusted Cox model.

- Second objective: Risk of serious infections using bDMARDs alone vs bDMARDs + corticosteroids or csDMARDs

Cox Proportional-Hazards regression model: also in this case, the effect of using bDMARDs alone vs bDMARDs + concomitant corticosteroids or csDMARDs on the incidence of serious infections requiring hospitalizations, among incident users of bDMARDs in PsO/PsA patients, will be estimated

Commentato [PE28]: Will you not consider any other potential confounders for estimating PS? I see above in "Other variables" there is a long list of patient characteristics that may be of interest, e.g., history of serious infections, other comorbidities?

Commentato [MC29R28]: We agree and we modified as suggested

Commentato [AF30R28]: Please pay close attention to the selection of covariates to be considered for PS computation, prioritizing those that really can play a confounding role and excluding those with very low prevalence, unless a very large sample size for each group is assumed (thus achieving sufficient statistical power). Moreover, to do things right, the logistic model that provides the PS estimates should be performed in a stepwise fashion and the model-building should be stopped when adequate covariates balance is reached.

Commentato [AF31]: Why do not you want to show the results of statistical tests together with the standardized difference (D)? This would mean focusing only on the results found in the sample without being able to generalize them to the whole population, through the inductive methods of the classical statistical inference theory. The result of the statistical test is fundamentally useful to corroborate the value of D: for example, let us consider the PS-matched sample. Since it is generally true that failure to reject the null hypothesis (i.e. $p \geq 0.05$) does not guarantee, by itself, a successful balance of covariates between the two groups (because of lack of statistical power) until the D value is revealed, on the other hand a relevant effect size (e.g. D>0.5) does not guarantee the covariate imbalance if the null hypothesis cannot be rejected (i.e. $p < 0.05$).

Commentato [AF32]: @Elisabetta please note that, since there are multiple causes of "censoring" of follow-up time in the user, then, rather than using the classical Cox model, it would have been more appropriate to use Fine & Gray's competitive hazards model (also known as "proportional subdistribution hazards model"). Unfortunately, for reasons related to the inability to retrieve death dates (?), this analysis would seem to be infeasible.

Commentato [PE33]: Are you also going to run a Cox multivariable outcome model for adjustment? Is this analysis necessary, if you are already planning to use PS-matching for adjustment?

Commentato [AF34R33]: This analysis is not strictly necessary but is advisable, first because in any case the multivariable Cox model will be run to estimate the effect of the active ingredient and therefore, for sake of consistency, it would be foolish not to be able to run the model that defines the main analysis. Second, it may often be the case that, in certain contexts, the multivariable model may give different results than the univariable model estimated in the PS-matched sample. One of these concerns the number of ...

Commentato [PE35]: Maybe explain the rationale for shifting the reference group to infliximab for this analysis.

Commentato [MC36R35]: We agree and we modified as follows: "using infliximab as the reference active ingredient, as it is generally considered the drug with higher risk of serious infection"

Commentato [PE37]: As background therapy during baseline or as co-initiation, or both?

Commentato [AS38R37]: Concomitant drugs

using both crude and fully-adjusted Cox Proportional-Hazards regression models in the unmatched cohort only. Risks will be reported as HRs along with their 95% CIs. The same covariates used for the propensity score matching procedure will be included in the fully-adjusted Cox model.

The assumption of proportionality of the hazards over time will be checked for each covariate included in the model by the Kolmogorov-Type Supremum test. In case of violation of this assumption, different strategies for dealing with the problem will be considered, such as stratification or the inclusion of a time-by-covariate interaction in the model as appropriate.

Sensitivity analyses

- For both primary and secondary objective analysis, censoring for switch to different bDMARDs or bDMARD discontinuation will not be performed and the exposure to drug categories will be considered as a time dependent variable.

Results plan

Patients' characteristics: The unmatched and the PS matched cohorts will be described for in terms of sex, median age, age bands (<18, 19-44, 45-64, 65-79, 80+ years), type of index drug (biosimilar or originator), concomitant use of medications, and comorbidities (**Table I**).

Table I. Characteristics of incident users of bDMARDs by drug class at the first date of bDMARD dispensing (i.e. index date) before and after the propensity-score (PS) matching

	PS unmatched cohort			**PS matched cohort**		
X	**TNF-alfa inhibitors**	**Anti-interleukin /IS**	**d before matching (*p* value)**	**TNF-alfa inhibitors**	**Anti-interleukin /IS**	**d after matching (*p* value)**
PS matching factors						
Sex: Female, n (%)						
Age (years), mean (SD)						
Age (bands), n (%)						
≤18						
19-44						
45-64						
65-79						
≥80						
Calendar year, n (%)						
…						
Previous use of csDMARDs, n (%)						
Previous use of corticosteroids, n (%)						
Other covariates						
Concomitant use of						
Methotrexate, n (%)						
Sulfasalazine, n (%)						
Leflunomide, n (%)						
Cyclosporine, n (%)						
Corticosteroids, n (%)						

Commentato [PE39]: Will all these covariates be used to estimate PS?

Commentato [MC40R39]: Yes, we agree, and we have now added this information in the text

Commentato [AF41]: I would include the p-value from statistical tests

Commentato [AF42]: idem

Charlson comorbidity index, mean (SD)						
Comorbidities						
Previous serious infections, n (%)						
Diabetes, n (%)						
COPD, n (%)						
Rheumatoid arthritis, n (%)						
Ankylosing spondylitis, n (%)						
Systemic lupus erythematosus, n (%)						
Celiac disease, n (%)						
Multiple sclerosis , n (%)						
Crohn's disease, n (%)						
Ulcerative colitis, n (%)						
Hidradenitis suppurativa, n (%)						

Abbreviations: bDMARDs: Disease-Modifying Antirheumatic Drugs; COPD: Chronic Obstructive Pulmonary Disease; csDMARDs: conventional synthetic Disease-Modifying Antirheumatic Drugs; SD: Standard Deviation; PS: Propensity Score; d: Standardized Difference

Time to onset: Time to onset of serious infections will only be computed among patients with the outcome (i.e. excluding the times of censored users) by drug class (TNF-alpha inhibitors, anti-IL, and selective immunosuppressant) and median, along with interquartile range, will be estimated. This calculation will also be performed by active ingredient and by concomitant medications. Kaplan Meier analysis will also be performed in the matched and unmatched cohorts, considering the entire follow-up period.

Incidence of serious infection (**Table II**): The incidence of serious infections will be calculated among the drug class (TNF-alfa as reference) in the unmatched and matched cohorts as detailed in the statistical analysis plan. Moreover, a sensitivity analysis by active ingredient will be performed (results will not be reported in **Table II**). Moreover, a risk analysis will be performed evaluating bDMARDs vs bDMARDs and the combination with csDMARDs and/or corticosteroids (**Table III**).

Table II. Incidence of serious infections occurring after index date (primary objective)

	PS unmatched (original) cohort					**PS matched cohort**
Exposure	**N events**	**Person-years**	**N events per 100 person-years**	**Crude HR and 95CI%**	**Adj HR* and 95CI%**	**HR (PS matched cohorts) and 95CI%**

TNF-α antagonists				REF	REF	REF
Anti-interleukins /IS						

Table III. Incidence of serious infections occurring after index date (secondary objective)

Exposure	**N events**	**Person-years**	**N events per 100 person-years**	**HR (Unadjusted Cox model) CI95%**	**HR (Adjusted Cox model) CI95%***
bDMARDs alone				REF	REF
bDMARDs + corticosteroids					
bDMARDs + csDMARDs					
bDMARDs + csDMARDs + corticosteroids					
bDMARDs + csDMARDs or corticosteroids					

*models will be adjusted for the following covariates: age at the index date, sex, calendar year, region, previous use of drugs (immunosuppressant as well as other classes), and comorbidities (please see "Other variables" section).

Abbreviations: bDMARDs: Disease-Modifying Antirheumatic Drugs; csDMARDs: conventional synthetic Disease-Modifying Antirheumatic Drugs; HR: Hazard Ratio; CI: Confidence Interval; PS: Propensity Score

Limitations

Information regarding duration of the disease is missing. Additionally, we were unable to determine whether a drug was prescribed for PsO or PsA. Although the disease's severity (e.g., Psoriasis Area Severity Index) was unavailable, the patients were affected by moderate to serious PsO or PsA due to the cohort selection criteria (patients taking bDMARDs).

Ethics Statement

This retrospective study protocol was notified to the Ethical Committees of the Academic Hospital of Messina and Verona, according to the current national law [Ministero della Salute, 2007]. The manuscript does not contain clinical studies or patient data. Formal consent is not required for this type of study.

References (AMA format)

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Appendix

Table A1. bDMARDs (originator/biosimilars) for the treatment of PsO/PsA by mechanism of action

Class	Drug - ATC	Indication	Condition	Original (bold) and biosimilars approved by EMA
TNF-alpha inhibitors	Infliximab - L04AB02	PsO	Adults: moderate to severe disease not responders to MTX, ciclosporin or PUVA	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
		PsA	Adults: active and progressive disease not responders to csDMARDs	**Remicade®,** Inflectra®, Remsima®, Flixabi®, Zessly®
	Etanercept - L04AB01	PsO	Adults: Moderate to severe disease not responders or intolerant to systemic therapy (ciclosporin, MTX, PUVA) Pediatric (6+): Chronic disease inadequately controlled or intolerant to systemic therapy or phototherapy	**Enbrel®,** Benepali®, Erelzi®, Nepexto®
		PsA	Adults: active and progressive disease not responders to csDMARDs Pediatric (12+): not responders or intolerant to MTX	**Enbrel®,** Benepali®, Erelzi®, Nepexto®
	Adalimumab - L04AB04	PsO	Adults: moderate to severe disease who are candidate to systemic therapy	**Humira®,** Hulio®, Hyrimoz®, Amgevita® Idacio® Imraldi®

			Pediatric (4+): Severe chronic disease not responders to topical therapy or phototherapy	Yuflyma® Hefiya® Libmyris® Amsparity®
		PsA	Adults: active and progressive disease not responders to csDMARDs	**Humira®,** Hyrimoz®, Amgevita® Idacio® Imraldi® Imraldi® Yuflyma® Hefiya® Libmyris® Amsparity®
	Certolizumab – L04AB05	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Cimzia®**
		PsA	Adults: active and progressive disease not responders to csDMARDs	**Cimzia®**
	Golimumab L04AB06	PsA	Adults: active and progressive disease not responders to csDMARDs	**Simponi®**
Interleukin-17 Receptor Antagonists	Brodalumab - L04AC12	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Kyntheum®**
Interleukin-17 antagonists	Ixekinumab - L04AC13	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Taltz®**
		PsA	Adults: active disease not responders to csDMARDs	**Taltz®**
	Secukinumab - L04AC10	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Cosentyx®**

		PsA	Adults: active disease not responders to csDMARDs	**Cosentyx®**
	Bimekizumab - L04AC21	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Bimzelx®**
IL-23 antagonists	Guselkumab - L04AC16	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Tremfya®**
		PsA	Adults: active disease not responders or intolerant to csDMARDs	**Tremfya®**
	Risankizumab - L04AC18	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Skyrizi®**
		PsA	Adults: active disease not responders or intolerant to csDMARDs	**Skyrizi®**
	Tildrakizumab - L04AC17	PsO	Adults: Moderate to severe disease candidates to systemic therapy	**Ilumetri®**
IL-12/IL-23 antagonists	Ustekinumab - L04AC05	PsO	Adults: Moderate to severe disease not responders or intolerant to systemic therapy (ciclosporin, MTX, PUVA) Pediatric (6+): Moderate to severe disease inadequately controlled or intolerant to systemic therapy or phototherapy	**Stelara®**
		PsA	Adults: active disease not responders to csDMARDs	**Stelara®**

T cell modulator	Abatacept – L04AA24	PsA	Adults: active disease not responders or intolerant to csDMARDs or MTX (addiotional systemic therapy not required)	**Orencia®**

Abbreviations: DMARDs: disease-modifying antirheumatic drugs; MTX: Methotrexate; PUVA: psoralen and ultraviolet-A light

Table A2. Articles by reference number: disease, study design, study drugs and findings

Articles (by reference number)	**Study Design**	**Disease**	**Study drugs**	**Findings**
Yiu ZZN, Ashcroft DM, Evans I, et al	Prospective cohort study	chronic plaque psoriasis	Infliximab vs nonbiologic systemic therapies	Infliximab: increased risk of serious infections
Yiu ZZN, Smith CH, Ashcroft DM, et al	Retrospective cohort study	moderate to severe psoriasis	etanercept, adalimumab, ustekinumab vs non-biologic systemic therapies	No significant increases in the risk of serious infection
Grijalva CG, Chen L, Delzell E, et al	Retrospective cohort study	rheumatoid arthritis, IBD, psoriasis, psoriatic arthritis, ankylosing spondylitis	TNF-α antagonists vs nonbiologic comparators	Not association with an increased risk of hospitalizations for serious infections
Li X, Andersen KM, Chang HY, Curtis JR, Alexander GC	Retrospective cohort study	Psoriasis and psoriatic arthritis	IL-17 (ixekizumab or secukinumab) vs IL-12/23 (ustekinumab) vs TNF (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) antagonists	Relative to TNF and IL-17, IL-12/23 inhibitors were associated with a reduced risk of serious infection

Jin Y, Lee H, Lee MP, et al	Retrospective cohort study	Psoriasis and psoriatic arthritis	ustekinumab versus other bDMARDs or apremilast	Other bDMARDs and apremilast were associated with a 1.4- to 3-times higher risk of hospitalization for serious infections when compared to ustekinumab
Penso L, Dray-Spira R, Weill A, Pina Vegas L, Zureik M, Sbidian E	Retrospective cohort study	moderate to severe psoriasis	tumor necrosis factor inhibitor, interleukin (IL) 12/23 inhibitor, IL-17 inhibitor, IL-23 inhibitor, apremilast	risk of serious infections was increased in infliximab and adalimumab vs etanercept, whereas ustekinumab had lower risk and no differences for IL-17 and IL-23 inhibitors or apremilast
Kalb RE, Fiorentino DF, Lebwohl MG, et al	Prospective cohort study	Psoriasis	ustekinumab, infliximab, adalimumab, etanercept, and nonbiologics	higher risk of serious infections with adalimumab and infliximab compared with nonmethotrexate and nonbiologic therapies. No increased risk was observed with ustekinumab or etanercept
Dávila-Seijo P, Dauden E, Descalzo MA, et al	Prospective cohort study	Psoriasis	bDMARDs (infliximab, etanercept, adalimumab, and ustekinumab) and nonbiological drugs (acitretin, cyclosporine, and methotrexate)	overall infections was significantly increased in the groups treated with adalimumab with methotrexate, infliximab, cyclosporine, and ustekinumab combined with methotrexate. Cyclosporine was the

				only drug that showed a significant increased risk of serious infections compared with methotrexate. Adalimumab in combination with methotrexate had the highest risk of infection recurrence
van der Schoot, LS, Groenewoud, HJMM, van Gelder, MMHJ, Otero, ME, Arnold, WP, Berends, MAM, et al	Prospective cohort study	Psoriasis and psoriatic arthritis	adalimumab, apremilast, certolizumab, etanercept, golimumab, ixekizumab, secukinumab, ustekinumab	Other bDMARDs and apremilast were associated with a 1.4- to 3-times higher risk of hospitalization for serious infections compared to ustekinumab
Wang J, Geng X, Zhang X, Xiao Y, Wang W	Retrospective cohort study	Patients in ustekinumab treatment	Ustekinumab vs Hepatitis B Virus Reactivation and Mycobacterial Infections	Apparently no harm
Egeberg A, Ottosen MB, Gniadecki R, et al	Retrospective cohort study	moderate-to-severe plaque psoriasis treated with bDMARDs	adalimumab, etanercept, infliximab, secukinumab and ustekinumab (also comparing originator vs biosimilars	highest rate of infections occurred with secukinumab, infliximab had a lower incidence of infections which may reflect that patients with high risk of infections are not started on this therapy

Menter A, Tyring SK, Gordon K, et al	Multicenter RCT	moderate to severe psoriasis	adalimumab (40 mg) vs placebo	nonserious infectious were greater among adalimumab-treated patients, serious infections were comparable
Gordon KB, Strober B, Lebwohl M, et al	Multicenter RCT	moderate-to-severe chronic plaque psoriasis	150 mg risankizumab, 45 mg or 90 mg ustekinumab (weight-based per label), or placebo	infections were more frequently reported in patients receiving risankizumab or ustekinumab compared with those receiving placebo

Table A3. Coding algorithm to identify the PsO/PsA indications for use of bDMARDs from regional claims databases.

	Source	Criteria
Algorithm (PsA e PsO)	*HDR | ETP*	696.0 **OR** 696.1
		OR
	EXE	045 (045.696.0 045.696.1) **OR** 696.0 **OR** 696.1
		OR
	pharmacy claims	Adalimumab
		OR
	pharmacy claims	Certolizumab
		OR
	pharmacy claims	Efalizumab
		OR
	pharmacy claims	Etanercept
		OR
	pharmacy claims	Golimumab
		OR
	pharmacy claims	Infliximab
		OR
	pharmacy claims	Secukinumab
		OR
	pharmacy claims	Ustekinumab
		OR
	pharmacy claims	Brodalumab
		OR
	pharmacy claims	Guselkumab
		OR
	pharmacy claims	Tildrakizumab
		OR
	pharmacy claims	Risankizumab
		OR
	pharmacy claims	Ixekizumab
		OR

		≥ 2 drug dispensing:
	pharmacy claims	Acitretin
		OR
	pharmacy claims	Cyclosporine
		OR
	pharmacy claims	MTX
		OR
	pharmacy claims	Betamethasone **AND** Salicylic acid
		OR
	pharmacy claims	Calcipotriol
		OR
	pharmacy claims	Calcipotriol **AND** Betamethasone
		OR
	pharmacy claims	Tacalcitol (≥ 2 drug dispensing in the last year)
		OR
	pharmacy claims	Tazarotene ((≥ 2 drug dispensing in the last year)
		OR
	Specialist consultation registry	Outpatient specialist consultation code: 99.82 ((≥ 2 in the last year)
		AND NOT
	pharmacy claims	Anti-TNFα **OR** MTX **OR** Cyclosporine
		AND
	HDR | *EXE* | *ETP*	720.0 **OR** 054
		OR
	SDO | *EXE* | *ETP*	555 **OR** 556 **OR** 009
		OR
	Specialist consultation registry	Phototherapy
		AND
	HDR | *EXE* | *ETP*	Atopic dermatitis **OR** Lymphoma **OR** Systemic corticosteroids
		OR
	EXE	045.696.0 **OR** 045.696.1
		AND
	HDR | *EXE* | *ETP*	714* **OR** 716.9

Abbreviations: HDR : Hospital Discharge Records, EXE : Exemptions, ETP: Electronic Therapeutic Plan, MTX: methotrexate

Table A4. Severe infectious diseases variables in HDRs: ICD-9 codes

Variable	Codes	Description
Herpes simplex	054	Herpes simplex
Herpes zoster	053	Herpes zoster
Primary tuberculosis	010	Primary tuberculous infection
Pulmonary tuberculosis	011, 012	Pulmonary tuberculosis and other respiratory tuberculosis
Extra-pulmonary tuberculosis	013, 014, 015, 016, 017, 018, 137	Tubercolosis of meninges and central nervous system, tuberculosis of intestines, peritoneum, and mesenteric glands, tuberculosis of bones and joints, tuberculosis of genitourinary system, tuberculosis of other organs, miliary tuberculosis
Non-invasive candidiasis	1120, 1121, 1122, 1223	Candidiasis of the skin, nails and mucosa
Invasive candidiasis	1124, 1125, 1228, 1129	Candidiasis of the lung, other organs or disseminated
Sepsis	99591, 99592, 78552, 7907, 038	Sepsis, septic shock
Endocarditis	03642, 07422, 0932, 09884, 421, 42292	Endocarditis (mainly infectious)
Viral hepatitis	070	Viral hepatitis (A, B, C, others)
Pneumonia	480-486, 07889	Viral pneumonia, bacterial pneumonia
	4870	Influenza with pneumonia
Non-invasive fungal infections	0390, 0394	Fungal infections infections of the skin, scalp and nails (except Candida albicans)

Invasive fungal infections	0391, 0392, 0393, 0398, 0399, 114, 115, 116, 117, 118, 4846, 4847, 7116	Visceral fungal infections (except Candida albicans)
Infections of conjunctiva	077	Infections of conjunctiva
Infections of the eye	3731, 3732, 3734, 3735, 3736	Infections of the eye, except diseases of conjunctiva
COVID-19	4803, 07982	With or without pneumonia, but severe disease
Osteomyelitis/ infection of joints	730, 711, 00323, 05671, 0985, 00324, 37603, 5264	Osteomyelitis, periostitis, infection of joints
Cystitis (UTI)	5950, 5954, 597, 5990	Cystitis
Infections of kidney	590	Pyelonephritis
Infections of skin and subcutaneous tissue	686, 035, 0400, 56961, 681, 682, 72886, 7854	Severe infections of skin and subcutaneous tissue
Intestinal infectious diseases	001-009	Intestinal infectious diseases
	567	Peritonitis and retroperitoneal infections
	566	Abscess of anal and rectal regions

Table 5: ATC codes of antibiotics searched on claims databases.

ATC Codes	Description	ATC Specific Drug Codes	Active Ingredient
J01A	Tetracyclines	J01AA01	Demeclocycline
		J01AA02	Doxycycline
		J01AA03	Chlortetracycline
		J01AA04	Lymecycline
		J01AA05	Metacycline
		J01AA07	Tetracycline
		J01AA08	Minocycline
		J01AA12	Tigecycline
		J01AA13	Eravacycline
J01B	Amphenicols	J01BA01	Chloramphenicol
		J01BA02	Thiamphenicol
J01C	Beta-Lactam Antibacterials, Penicillins	J01CA01	Ampicillin
		J01CA03	Carbenicillin
		J01CA04	Amoxicillin
		J01CA06	Bacampicillin
		J01CA08	Pivmecillinam
		J01CA09	Azlocillin
		J01CA10	Mezlocillin
		J01CA12	Piperacillin
		J01CA17	Temocillin
		J01CE01	Benzylpenicillin
		J01CE02	Phenoxymethylpenicillin
		J01CE03	Propicillin
		J01CE08	Benzathine Benzylpenicillin
		J01CE30	Combinations
		J01CF01	Dicloxacillin
		J01CF02	Cloxacillin
		J01CF03	Meticillin
		J01CF04	Oxacillin
		J01CF05	Flucloxacillin
		J01CR01	Ampicillin And Beta-Lactamase Inhibitor
		J01CR02	Amoxicillin And Beta-Lactamase Inhibitor
		J01CR03	Ticarcillin And Beta-Lactamase Inhibitor
		J01CR04	Sultamicillin
		J01CR05	Piperacillin And Beta-Lactamase Inhibitor
		J01CR50	Combinations Of Penicillins
J01D	Other Beta-Lactam Antibacterials	J01DA01	Cefalexin
		J01DA02	Cefaloridine
		J01DA04	Cefazolin
		J01DA06	Cefuroxime
		J01DA07	Cefamandole
		J01DA09	Cefadroxil

		J01DA17	Cefonicid
		J01DA18	Latamoxef
		J01DA21	Cefatrizine
		J01DA31	Cefradine
		J01DA32	Cefoperazone
		J01DA36	Ceftezole
		J01DB01	Cefalexin
		J01DB03	Cefalothin
		J01DB04	Cefazolin
		J01DB05	Cefadroxil
		J01DB07	Cefatrizine
		J01DB08	Cefapyrin
		J01DB09	Cephradine
		J01DB12	Ceftezole
		J01DC01	Cefuroxime
		J01DC02	Cefamandole
		J01DC03	Cefaclor
		J01DC04	Cefotetan
		J01DC05	Cefonicid
		J01DC06	Loracarbef
		J01DC08	Cefmetazole
		J01DC09	Cefprozil
		J01DC10	Cefotaxime
		J01DD01	Ceftazidime
		J01DD02	Ceftriaxone
		J01DD04	Latamoxef
		J01DD06	Ceftizoxime
		J01DD07	Cefixime
		J01DD08	Cefodizime
		J01DD09	Cefetamet
		J01DD10	Cefoperazone
		J01DD12	Cefpodoxime
		J01DD13	Ceftibuten
		J01DD14	Cefditoren
		J01DD16	Ceftazidime And Beta-Lactamase Inhibitor
		J01DD52	Cefepime
		J01DE01	Cefpirome
		J01DE02	Aztreonam
		J01DF01	Meropenem
		J01DH02	Ertapenem
		J01DH03	Doripenem
		J01DH04	Imipenem And Cilastatin
		J01DH51	Meropenem And Vaborbactam
		J01DH52	Imipenem, Cilastatin, And Relebactam
		J01DH56	Ceftobiprole Medocaril
		J01DI01	Ceftaroline Fosamil
		J01DI02	Ceftolozane And Beta-Lactamase Inhibitor

		J01DI54	Cefuroxime
J01E	Sulfonamides And Trimethoprim	J01EA02	Brodimoprim
		J01EB02	Sulfamethizole
		J01EC02	Sulfadiazine
		J01ED01	Sulfadimethoxine
		J01ED02	Sulfalene
		J01ED06	Sulfaperine
		J01ED09	Sulfamazone
		J01EE01	Sulfamethoxazole And Trimethoprim
		J01EE02	Sulfadiazine And Trimethoprim
		J01EE03	Sulfamethylo And Trimethoprim
		J01EE04	Sulfamoxole And Trimethoprim
		J01EE06	Sulfadiazine And Tetroxoprim
J01F	Macrolides, Lincosamides And Streptogramins	J01FA01	Erythromycin
		J01FA02	Spiramycin
		J01FA03	Midecamycin
		J01FA06	Roxithromycin
		J01FA07	Josamycin
		J01FA08	Troleandomycin
		J01FA09	Clarithromycin
		J01FA10	Azithromycin
		J01FA11	Miocamycin
		J01FA12	Rokitamycin
		J01FA13	Dirithromycin
		J01FA14	Flurithromycin
		J01FA15	Telithromycin
		J01FF01	Clindamycin
		J01FF02	Lincomycin
		J01FG02	Quinupristin/Dalfopristin
J01G	Aminoglycoside Antibacterials	J01GA01	Streptomycin
		J01GB01	Tobramycin
		J01GB03	Gentamicin
		J01GB04	Kanamycin
		J01GB06	Amikacin
		J01GB07	Netilmicin
		J01GB08	Sisomicin
		J01GB09	Dibekacin
		J01GB10	Ribostamycin
		J01GB11	Isepamicin
J01M	Quinolone Antibacterial	J01MA01	Ofloxacin
		J01MA02	Ciprofloxacin
		J01MA03	Pefloxacin
		J01MA04	Enoxacin
		J01MA06	Norfloxacin
		J01MA07	Lomefloxacin
		J01MA08	Fleroxacin
		J01MA10	Rufloxacin
		J01MA11	Grepafloxacin

		J01MA12	Levofloxacin
		J01MA14	Moxifloxacin
		J01MA17	Prulifloxacin
		J01MA23	Delafloxacin
		J01MB01	Rosoxacin
		J01MB02	Nalidixic Acid
		J01MB03	Piromidic Acid
		J01MB04	Pipemidic Acid
		J01MB05	Oxolinic Acid
		J01MB06	Cinoxacin
		J01MB07	Flumequine
J01R	Combinations Of Antibacterials	J01RA01	Penicillins, Combinations With Other Antibacterials
		J01RA02	Sulfonamides, Combinations With Other Antibacterials (Excl. Trimethoprim)
J01X	Other Antibacterials	J01XA01	Vancomycin
		J01XA02	Teicoplanin
		J01XA03	Telavancin
		J01XA04	Dalbavancin
		J01XA05	Oritavancin
		J01XB01	Colistin
		J01XC01	Fusidic Acid
		J01XD01	Metronidazole
		J01XD03	Ornidazole
		J01XE01	Nitrofurantoin
		J01XE02	Nifurtoinol
		J01XX01	Fosfomycin
		J01XX03	Clofocotol
		J01XX04	Spectinomycin
		J01XX08	Linezolid
		J01XX09	Daptomycin
		J01XX11	Tedizolid
		J01XX12	Lefamulin

Table 6: ATC codes of proton pump inhibitors searched on claims databases.

ATC Codes	**Active Ingredient**
A02BC01	Omeprazole
A02BC02	Pantoprazole
A02BC03	Lansoprazole
A02BC04	Rabeprazole
A02BC05	Esomeprazole
A02BC06	Dexlansoprazole

Table 7: ATC codes of non-steroidal anti-inflammatory drugs searched on claims databases.

ATC codes	Active Ingredient
M01AA01	Phenylbutazone
M01AB01	Indomethacin
M01AB02	Sulindac
M01AB03	Tolmetin
M01AB05	Diclofenac
M01AB08	Etodolac
M01AB10	Fentiazac
M01AB11	Acemetacin
M01AB13	Oxametacin
M01AB14	Proglumetacin
M01AB15	Ketorolac
M01AB16	Aceclofenac
M01AB55	Diclofenac Combinations
M01AC01	Piroxicam
M01AC02	Tenoxicam
M01AC05	Lornoxicam
M01AC06	Meloxicam
M01AE01	Ibuprofen
M01AE02	Naproxen
M01AE03	Ketoprofen
M01AE04	Fenoprofen
M01AE05	Fenbufen
M01AE09	Flurbiprofen
M01AE11	Tiaprofenic Acid
M01AE12	Oxaprozin
M01AE13	Ibuproxam
M01AE14	Dexibuprofen
M01AE15	Flunoxaprofen
M01AE17	Dexketoprofen
M01AE51	Ibuprofen Combinations
M01AE52	Naproxen And Esomeprazole
M01AE53	Ketoprofen Combinations
M01AG01	Mefenamic Acid
M01AG04	Meclofenamic Acid
M01AH01	Celecoxib
M01AH02	Rofecoxib
M01AH03	Valdecoxib
M01AH04	Parecoxib
M01AH05	Etoricoxib
M01AX01	Nabumetone
M01AX02	Niflumic Acid
M01AX05	Glucosamine
M01AX07	Benzydamine
M01AX17	Nimesulide
M01AX21	Diacerein

M01AX22	Morniflumate
M01AX25	Chondroitin Sulfate

Table A8. Definition of the Charlson comorbidity index [Charlson ME et al, 2022], ICD-9 codes.

Disease	ICD-9 codes
Myocardial infarction	410.x, 412.x
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4 - 425.9, 428.x
Peripheral vascular disease:	093.0, 437.3, 440.x, 441.x, 443.1 - 443.9, 447.1, 557.1, 557.9, V43.4
Cerebrovascular disease	362.34, 430.x - 438.x
Dementia	290.x, 294.1, 331.2
Chronic pulmonary disease	416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8
Rheumatic disease	446.5, 710.0 - 710.4, 714.0 - 714.2, 714.8, 725.x
Peptic ulcer disease	531.x - 534.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7
Diabetes without chronic complication	250.0 - 250.3, 250.8, 250.9
Diabetes with chronic complication	250.4 - 250.7
Haemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0 - 344.6, 344.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0 - 583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin	140.x - 172.x, 174.x - 195.8, 200.x - 208.x, 238.6
Moderate or severe liver disease	456.0 - 456.2, 572.2- 572.8
Metastatic solid tumour	196.x - 199.x
HIV/AIDS	042.x - 044.x

Table A9. Other variables, ICD-9 codes.

Variable	ICD-9	Description
Obesity		
Diabetes mellitus	250, 3572, 3620, 36641, 6488, 7751, 79029, 2490-2499	Diabetes mellitus including type 1, congenital diabetes, gestational diabetes, diabetes complications.
COPD	491	Chronic bronchitis and chronic obstructive pulmonary disease
Infections	See Table A4 for complete list of ICD-9 codes	Infections requiring hospitalization
HIV	042	Human Immunodeficiency Virus infection
Rheumatoid arthritis	714	Rheumatoid arthritis
Ankylosing spondylitis	720	Ankylosing spondylitis
Systemic lupus	7100, 6954	Systemic lupus erythematosus, Lupus erythematosus including erythematodes (discoid) and erythematosus (discoid) not disseminated
Celiac disease	5790	Celiac disease
Multiple sclerosis	340	Multiple sclerosis
Autoimmune hepatitis	57142	Autoimmune hepatitis
Crohn's disease	555	Regional enteritis Includes: Crohn's disease, Granulomatous enteritis
Ulcerative colitis	556	Ulcerative colitis
Hidradenitis suppurativa	70583	Hidradenitis suppurativa