The Association Between Chronic Immune-Mediated Inflammatory Diseases and Cardiovascular Risk

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Abstract

Objective To examine the association between chronic immune-mediated diseases (rheumatoid arthritis, systemic lupus erythematosus, or the following chronic immune-mediated inflammatory diagnoses groups: inflammatory bowel diseases, inflammatory polyarthropathies, systemic connective tissue disorders and spondylopathies) and the 6-year coronary artery disease, stroke, cardiovascular disease incidence and overall mortality; and to estimate the population attributable fractions for all four end-points for each chronic immune-mediated inflammatory disease.

Methods Cohort study of individuals aged 35-85 years, with no history of cardiovascular disease from Catalonia (Spain). The coded diagnoses of chronic immune-mediated diseases and cardiovascular diseases were ascertained and registered using validated codes, and date of death was obtained from administrative data. Cox regression models for each outcome according to exposure were fitted to estimate hazard ratios (HR) in two models: (1) after adjustment for sex, age, cardiovascular risk factors and (2) further adjusted for drug use. Population attributable fractions were estimated for each exposure.

Results Data were collected from 991,546 participants. The risk of cardiovascular disease was increased in systemic connective tissue disorders [Model 1: HR=1.38 (95% confidence interval=1.21-1.57) and 2: HR=1.31 (1.15-1.49)], rheumatoid arthritis [HR=1.43 (1.26-1.62) and HR=1.31 (1.15-1.49)] and inflammatory bowel diseases [HR=1.18 (1.06-1.32) and HR=1.12 (1.01-1.25)]. The effect of anti-inflammatory treatment was significant in all instances [HR=1.50 (1.24-1.81); HR=1.47 (1.23-1.75); HR=1.43 (1.19-1.73), respectively]. The population attributable fractions for all three disorders were 13.4%, 15.7%, and 10.7%, respectively.

Conclusion Systemic connective tissue disorders and rheumatoid arthritis conferred the highest cardiovascular risk and population impact, followed by inflammatory bowel diseases.

Keywords Cardiovascular disease, Inflammation, Arthritis, Connective Tissue Diseases, Spondylarthritis, Inflammatory Bowel Diseases

Key messages

What is already known on this subject?

Individuals diagnosed chronic immune-mediated inflammatory diseases present with increased CVD risk.

There are no comparable indicators to ascertain the cardiovascular risk associated with each chronic immune-mediated inflammatory disease due to the different inclusion criteria used in previous publications.

What might this study add?

Cardiovascular events and overall mortality risk was particularly pronounced in individuals diagnosed with systemic connective tissue disorders [HR=1.31 (95% confidence interval=1.15-1.49) and HR=1.30 (1.17-1.44), respectively] and rheumatoid arthritis [HR=1.31 (1.15-1.49) and HR=1.31 (1.18-1.46), respectively]. This risk was not explained by the higher prevalence of cardiovascular risk factors, nor by the use of DMARDs and anti-inflammatory drugs.

How might this impact on clinical practice?

The development of new tools for the prediction of cardiovascular events, which could incorporate CIID activity biomarkers, may help to reduce the incidence of such events.

INTRODUCTION

The primary prevention of cardiovascular diseases (CVD) is a paramount priority of the public health agenda because it is the main cause of death in the developed world and is increasing in developing countries.[1] The common basis of CVD is atherosclerosis, an inflammatory degenerative process present throughout a person's lifetime.[2] The pathogenesis of CVD in patients with chronic immune-mediated inflammatory diseases (CIID) is multi-factorial and is thought to result from an interaction of inflammation, metabolic factors, therapy, and disease-related factors.[3]

Individuals diagnosed with inflammatory bowel diseases,[4] rheumatoid arthritis,[5] systemic lupus erythematosus (SLE),[6] systemic sclerosis,[7] or ankylosing spondylitis[8] have shown an increased CVD risk. However, straightforward comparison of the studies is difficult owing to the different inclusion criteria used. Better understanding of the association between these conditions and cardiovascular morbidities can help in early assessment and management of risk factors and may help to improve long-term outcomes in patients with CIID.

The objectives of the study were: (1) to ascertain whether 6-year risk of coronary artery disease, stroke, CVD incidence and overall mortality are associated with the diagnosis of rheumatoid arthritis, SLE, or the following CIID diagnoses groups: inflammatory bowel diseases, inflammatory polyarthropathies, systemic connective tissue disorders, and spondylopathies; and (2) to estimate the population-based burden of coronary artery disease, stroke, CVD, and mortality attributable to each of the studied CIID.

METHODS

Data sources

The System for the Development of Research in Primary Care (SIDIAP) is an electronic medical records database derived from general practices of the Catalan Institute of Health in Catalonia (Spain). Data on approximately 5.8 million patients are recorded by general practitioners as part of patients' clinical records. Since approximately 80% of the population is registered with a general practitioner of the Catalan Institute of Health, SIDIAP is considered representative of the population in Catalonia.[9] The International Classification of Diseases 10th Edition (ICD-10) is used to code diagnoses and the Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of drugs. SIDIAP is also linked with hospital admissions data.

SIDIAP^{Q} is the subsample of individuals assigned to the 40% of general practitioners periodically selected to provide researchers with the best quality registry data and has been validated for the study of the epidemiology of CVD. The methodology for selecting this subsample has been explained elsewhere.[9] The present study was approved by the local ethics committees.

Study design

We conducted a cohort study of individuals included in SIDIAP^{Q}. The inclusion period spanned 1 January 2007 through 31 December 2012. Participants were 35 to 85 years old and those who had a record documenting a past history of myocardial infarction, angina, stroke, transient ischemic attack, intermittent claudication or coronary revascularization procedures prior to the inclusion were excluded. Patients were followed up until they experienced the outcomes of interest, died, left the SIDIAP^{Q}

database (e.g. change of address) or the follow-up ended (31 December 2012), whichever came first.

Definition of chronic immune-mediated inflammatory disease

A pre-specified list of ICD-10 codes, set a priori and based on previous work in the field,[10 11] was used to screen SIDIAP^{Q} records in order to identify all patients with CIID and classify them in four groups: (1) inflammatory bowel disease, (2) inflammatory polyarthropathies, (3) systemic connective tissue disorders, and (4) spondylopathies (see the disorders included in each group in Supplementary Table 1). In addition, a complementary analysis was performed for the most prevalent single diagnoses: (5) rheumatoid arthritis and (6) SLE. We included individuals without a registered diagnosis who required a continued prescription for a medication that would normally be used to treat inflammatory bowel disease, rheumatoid arthritis or SLE, based on evidence-based recommendations.[12-15] If an individual presented with more than two diagnoses, we considered the oldest one for the purpose of this analysis. Individuals who developed CIID during follow-up were considered non-exposed. Since the CIID considered in this study have physical features, adverse prognosis and the database has been previously validated[10 11] diagnoses are expected to be accurately recorded.

Identification of outcomes

The end-points considered were: (1) coronary artery disease: incident myocardial infarction or angina; (2) incident stroke; (3) cardiovascular disease: coronary artery disease or stroke; and (4) all-cause mortality (Supplementary Table 2). All end-points were identified from the SIDIAP and Hospital Discharge registries. The methodology

for case-finding used in the SIDIAP database has shown high validity and good representativeness of the population for use in epidemiological studies of CVD.[9]

Assessment of covariates

Data were obtained from electronic records on sex, age, systolic and diastolic blood pressure, glucose, triglycerides, total, high density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, glycaemia, weight, and height at baseline. Presence of cardiovascular risk factors was based on the presence of relevant codes with a date prior to the inclusion of each participant: (1) Diabetes mellitus: ICD-10 categories E11, E12, E14, and subcategories thereof; (2) Hypertension: ICD-10 categories I10, I15, and subcategories thereof; (3) Hypercholesterolemia: ICD-10 category E78 and its subcategories, except for E78.3 and E78.6; (4) Smoking: ICD-10 category F17 for smokers or Z72.0 for exsmokers and (5) Obesity: ICD-10 category E66 and subcategories except for E66.1 and E66.2 [9]. Coronary artery disease risk was estimated in participants aged 35 to 74 years with the Framingham-REGICOR function validated for the Spanish population.[16] Participants were categorized into three treatment groups: disease-modifying anti-rheumatic drugs including biologic therapies (DMARD), anti-inflammatory drugs (i.e. non-steroidal anti-inflammatory drugs, glucocorticoids, other non-inflammatory drugs), and non-users of DMARD and anti-inflammatory drugs. Lipid-lowering and antihypertensive treatments were also considered. The drugs included in each group are summarized in Supplementary Table 3, 4 and 5.

Statistical analysis

We used 10 multiple imputations by chained equations[17] to replace missing baseline values for cholesterol (total, HDL, LDL), triglycerides, glycemia, systolic and diastolic blood pressure, height, weight, and MEDEA index (a deprivation index designed to capture sex-related inequalities). In addition to incorporating the missing-at-random assumption, we compared case-complete results alone with the multiple imputations as a sensitivity analysis.

Continuous variables were summarized as mean (standard deviation) or median [interquartile range] when their distribution departed from normal, and categorical variables as proportions. The incidence of coronary artery disease, stroke and CVD events and overall mortality was estimated. We plotted the Kaplan-Meier curves for all four end-points by CIID diagnoses and in population with no CIID and we performed log-rank tests to estimate the differences between each diagnosis and CIID-free individuals. Bonferroni correction for multiple comparisons was applied, considering as significant a p-value <0.002.

To assess the association between the CIID diagnoses and the 6-year incidence of coronary artery disease, stroke and CVD events or death, we adjusted two Cox regression models for each outcome. The first was adjusted for sex, age, systolic and diastolic blood pressure, total and HDL cholesterol, diabetes and smoking. The second was further adjusted for lipid-lowering, antihypertensive and rheumatic-specific drug use divided in three categories. The proportionality assumption was tested for all models (Supplementary Table 6). To test the robustness of case-definition, we performed several sensitivity analyses. In the first, we excluded patients with no record of a diagnosis but who required continued prescription of a medication normally used to

treat inflammatory bowel disease, rheumatoid arthritis, or SLE, based on evidence-based recommendations. The second sensitivity analysis excluded those individuals who were receiving anti-inflammatory treatment (NSAIDs or DMARDs) before the CIID diagnosis. The third excluded those individuals with chronic diseases that may be related with both inflammation and cardiovascular risk (e.g., chronic kidney disease, sleep disorders, and liver disease). The fourth excluded those individuals with a CVD diagnosis in the 12 months after the study start date to minimize the possibility of prevalent CVD. Also, as a sensitivity analysis, model 2 was adjusted using the Fine and Gray method for coronary artery disease, stroke and CVD outcomes and considering death as a competing event.

Finally, to estimate the burden of CVD and mortality attributable to each CIID, the PAF were estimated for all four end-points, using Levin's formula. We used the adjusted hazard ratios (HR) according to model 2 and the prevalence of every CIID diagnosis observed in our cohort.

All calculations were made with R statistical package (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We included 991,546 individuals in our analysis, 467,494 (47.1%) men, mean age 53 years (standard deviation=13). Inflammatory polyarthropathies was the most prevalent CIID diagnosis (2.3%), followed by inflammatory bowel diseases (1.0%), systemic connective tissue disorders (0.5%) and spondylopathies (0.2%) (Figure 1). Additionally, 5552 (0.6%) presented with rheumatoid arthritis and 664 (0.07%) with SLE. Individuals with CIID were older, and more often presented with diabetes, hypertension,

dyslipidemia and higher 10-year cardiovascular risk than those without CIID. Finally, the individuals with CIID were more frequently on treatment with statins, aspirin and DMARDs (Table 1).

Annual incidence rates for all end-points showed significantly higher rates in those diagnosed with CIID (Table 2). Additionally, the Kaplan-Meier curves showed significantly lower disease-free time (i.e., coronary artery disease, cerebrovascular diseases and CVD) and survival for all CIID diagnoses compared with CIID-free population, except for SLE and spondylopathies. Indeed, the latter only presented with higher risk for death (Figure 2).

The multivariable models showed that systemic connective tissue disorders and rheumatoid arthritis increased the risk of all end-points considered, particularly coronary artery disease for the first [HR=1.37; (95% confidence interval: 1.15-1.65)] and stroke for the latter [HR=1.33 (1.11-1.60)]. Among individuals with SLE, only the risk of mortality was significantly higher [HR=1.50; (1.03-2.18)], even though the group in which this disease is included (i.e. systemic connective tissue disorders) conferred an increased risk for all end-points. On the other hand, the group of inflammatory polyarthropathies only showed a marginally significant association with stroke [HR=1.09; (0.99-1.19)]. Finally, inflammatory bowel diseases had a significant association with stroke and with overall mortality [HR=1.23; (1.06-1.43) and HR=1.64; (1.51-1.76), respectively]. The association between inflammatory bowel diseases and overall mortality did not meet the proportionality assumption. We stratified the follow-up in three periods: [0-1yea], [1y-4y], [>4y] and the proportionality assumption was met. The hazards ratios were HR=2.9 (2.49-3.39), HR=1.60 (1.42-1.80), and HR= 1.22

(1.06-1.41), respectively (Figure 3). No significant differences were found between the main analysis and any sensitivity analysis performed (Supplementary Tables 7-13).

The CIIDs with significant population impact on coronary artery disease, stroke and CVD were systemic connective tissue disorders (15.6%, 9.1%, and 13.4%, respectively) and rheumatoid arthritis (14.4%, 16.5%, and 15.7%, respectively). In addition, inflammatory bowel diseases presented significant PAF for stroke (18.7%) and for cardiovascular diseases (10.7%). Finally, the population impact on overall mortality was significant for all CIIDs, except for the spondylopathies, although the magnitude ranged from 39.0% for inflammatory bowel diseases to 3.4% for SLE (Figure 4).

DISCUSSION

Diagnoses of CIID conferred an increased risk of cardiovascular disease and overall mortality in this cohort study. This risk was particularly pronounced in individuals diagnosed with systemic connective tissue disorders and rheumatoid arthritis. Overall mortality risk was increased in both groups of diseases. This greater risk was not explained by aging, the higher prevalence of cardiovascular risk factors observed in CIID individuals, nor by the use of DMARDs and anti-inflammatory drugs, which may have a role in the modulation of cardiovascular risk. Indeed, the differences in the estimated cardiovascular risk did not reflect higher incidence in individuals with CIID compared to those without, pointing out the effect of other variables not included in such estimates. Additionally, inflammatory bowel diseases raised the risk of stroke and the overall mortality risk.

Risk of cardiovascular disease in chronic immune-mediated inflammatory disease

Individuals with CIID were older and had a worse cardiovascular risk factor profile; however, the multivariable analysis adjusted for the relevant variables showed an added risk not explained by these cardiovascular risk-related variables. A previous study, which also analyzed data from electronic medical records, showed similar coronary artery disease and stroke incidence in individuals with systemic connective disorders, inflammatory polyarthropathies, and inflammatory bowel diseases.[18] Additionally, we performed the same analysis separately for rheumatoid arthritis and for SLE, the most prevalent diseases within both groups, and therefore the most reported in the literature. As previously described, rheumatoid arthritis showed a significant risk in all four end-points, even after adjustment for drug therapy.[19] Lazzerini et al. pointed out that a higher risk of rhythm disturbances, particularly tachiarrythmias, in such individuals may significantly contribute to the high cardiovascular morbidity and mortality.[20] SLE only showed a significant association with overall mortality. The systematic review by Schoenfeld et al. showed that SLE at least doubled cardiovascular risk; however, the authors also pointed out the discrepancies found within the literature.[21] Concurring with Andersohn et al., individuals with inflammatory bowel diseases presented higher risk of stroke.[22] On the other hand, the association between these diseases and coronary artery disease has not been totally clarified. Similar to previous reports, we did not find an increased risk of coronary artery disease in these individuals;[18] however, this association was significant in the analysis of a nation-wide, population-based Danish cohort.[23] Finally, individuals with spondylopathies did not present with significantly higher risk for any of the end-points analyzed.

Prevention of cardiovascular disease in chronic immune-mediated inflammatory disease

The most-used treatments for controlling CIID, and particularly rheumatoid arthritis, the most thoroughly described, may have antagonistic effects on cardiovascular risk. The DMARDs drugs may confer a cardioprotective effect mostly attributed to the inhibition of systemic inflammation.[24] However, Aviña-Zubieta et al. described a dual effect of glucocorticoids on myocardial infarction risk in individuals with rheumatoid arthritis: an immediate effect mediated through current dosage and a long-term effect of cumulative exposure.[25] In addition, del Rincón et al. pointed out that daily doses higher than 8 mg were associated with higher cardiovascular and overall mortality in such individuals.[26] Recently, O'Neill et al. showed in a randomized clinical trial the beneficial effect of certain anti-inflammatory treatments that modulate the tumour necrosis factor-α pathway (e.g. methortrexate + infliximab), to restore the beneficial effects of HDL on the vasculature.[27]

To minimize the confounder effect of such variables, Model 2 of the present analysis was adjusted for drug use, divided in three categories (DMARDs, anti-inflammatory drugs, and non-DMARD non-anti-inflammatory drugs). Indeed, further pharmacoepidemiology studies are needed to ascertain the effect of antirheumatic treatments in all CIID diagnoses.

A reduction in the number of individuals diagnosed with systemic connective tissue disorders and rheumatoid arthritis may have a moderate population impact on preventing coronary artery disease, stroke and CVD. However, the diagnosis of such CIIDs together with an adverse cardiovascular profile may have an additive effect on the risk of coronary artery disease and CVD. The most recent European League Against

Rheumatism (EULAR) guideline promotes a proactive management of cardiovascular risk in individuals with inflammatory polyarthritis and spondylopathies. The objective is to control not only systemic inflammation, but also cardiovascular risk factors.[28] These recommendations have also been proposed for individuals with SLE[29] but could probably be extended to individuals with any systemic connective tissue disorder. In addition, the development of new tools for the prediction of cardiovascular events, which could incorporate CIID activity biomarkers, may help to reduce the incidence of such events.[24 30]

Characteristics and limitations of the study

The results of our study confirm the high cardiovascular risk conferred by previous studies exploring CIID incidence with lower sample sizes.[4 6-8 22] However, some biases inherent to the observational design of the study should be considered. First, reverse causality is not likely to be present in our study because the design meets the temporality criteria and the individuals with a history of CVD were excluded at recruitment. In addition, the results of the sensitivity analysis excluding those who presented with a CVD event within the first 12 months of follow-up did not differ from the main analysis. To avoid misclassification bias, we used the medical diagnosis of CIID extracted from SIDIAP, a primary care database. Although this source of data may contain underreporting, the validity of SIDIAP coding for ICD-10 diagnosis of cardiovascular and rheumatic diseases has been documented.[10 11] Indeed, the results of the sensitivity analyses confirmed the robustness of the case-definition. In addition, the representativeness of data ensures the generalizability of the results. The covariates of the present analysis had missing values (ranging from 9% to 78%) that could influence

the results. To avoid selection bias, wherever the population with missing data differed from those with complete data, we imputed the missing values for continuous variables instead of excluding records with missing data. The appropriateness of performing multiple imputations depends not only on the percentage and mechanism of missing values but also on the number of complete observations used in the imputation process. In our study, 218,140 complete cases were available to impute variables with missing values. Exposure variables (i.e. CIID diagnoses) and outcomes had no missing values. We selected the two most frequent single CIID diagnoses (rheumatoid arthritis and SLE) in the population and in the literature for analysis. In addition, we provided broad definitions of CIID diagnosis (i.e., inflammatory bowel diseases, inflammatory polyarthropathies, systemic connective tissue disorders, and spondylopathies). This approach, proposed by Dregan et al., allowed for comparison of results.[18] Finally, the present analysis did not consider variables such as severity or elapsed time between CIID diagnosis and the incidence of cardiovascular events or death. The use of broad CIID definitions may complicate the use of such variables due to the number and heterogeneity of the diseases included in each group. Finally, to minimize confounding by indication bias, all our analyses were adjusted for any medication with potential effects on inflammation and cardiovascular risk (DMARDs, antihypertensive treatments, and statins). Despite all our efforts, however, residual confounding is likely to exist. Thus, pharmacoepidemiology studies considering each CIID's specific variables are needed to ascertain the best way to prevent cardiovascular diseases in such individuals.

CONCLUSION

Systemic connective tissue disorders and rheumatoid arthritis were the CIID diagnoses with the highest 6-year risk of coronary artery disease or any cardiovascular event and the greatest population impact. Diagnosis of inflammatory bowel diseases (i.e. ulcerative colitis and Crohn disease) conferred a significant risk and PAF for stroke. Regarding overall mortality, all CIID diagnoses except spondylopathies increased 6-year mortality.

Conflict of interest statement The authors report no conflict of interest

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Author’s contributions JMBD, MGG, MCC, RR, and MG conceived and designed the study. JMBD, MGG, MCC, RR, DPA, RE and MG acquired, analyzed, or interpreted the data. JMBD, BS, IRD and MG drafted the manuscript. MGG, MCC and JP carried out the statistical analysis. JMBD and MG supervised the study. MG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval Parc de Salut Mar Ethics Committee.

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Figure legends

Figure 1 Participants flow-chart. CAD: Coronary artery disease. CIID: Chronic immune mediate inflammatory disease. CVD: Cardiovascular disease.

Figure 2 Survival curves for 6-year incidence of coronary artery disease (A), cerebrovascular disease (B), cardiovascular disease (C), and overall mortality (D) according to CIID diagnoses and in CIID-free population. Log-rank test p-values have been computed for each CIID diagnosis and CIID-free individuals.

Figure 3 Hazard ratios for 6-year incidence of coronary artery disease (A), cerebrovascular disease (B), cardiovascular disease (C), and overall mortality (D) among participants with CIID diagnosis compared with those without CIID.
Model 1 has been adjusted by age, sex, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure, and diastolic blood pressure. Model 2 has been further adjusted for statins, hypertensive drugs, and 3 categories of exposure to antirheumatic-specific treatments: disease-modifying antirheumatic drugs, other anti-inflammatory drugs, no exposure.

Figure 4 Population attributable fraction for 6-year incidence of coronary artery disease (A), cerebrovascular disease (B), cardiovascular disease (C), and overall mortality (D) for different chronic immune-mediated diseases. Bars are ordered according to the magnitude of the population-attributable fraction for each group of chronic immune-mediated disease diagnoses.

Table 1 Baseline characteristics of participants according to diagnosis of chronic immune-mediated inflammatory diseases

	Inflammatory bowel diseases	Inflammatory polyarthropathies	Systemic connective tissue disorders	Spondylopathies	CIID-free
N (%)	9544 (1.0)	22 779 (2.3)	4491 (0.5)	2243 (0.2)	952 489 (96.1)
Age, mean (SD)	56 (14)	60 (12)	63 (14)	55 (12)	52 (13)
Sex (men), n (%)	4162 (44)	14371 (63)	890 (20)	1185 (53)	446 886 (47)
Diabetes, n (%)	807 (10)	2806 (13)	437 (11)	205 (10)	61 131 (7)
Glycemia (mg/dl), median [IQR]	92 [82-104]	95 [85-108]	91 [82-102]	92 [83-104]	91 [82-103]
Hypertension, n (%)	2760 (29)	9633 (42)	1801 (40)	664 (30)	182 170 (19)
Systolic blood pressure (mmHg), mean (SD)	129 (16)	133 (17)	131 (17)	129 (16)	128 (16)
Diastolic blood pressure (mmHg), mean (SD)	77 (10)	78 (10)	76 (9)	77 (10)	77 (10)
Dyslipidemia, n (%)	2645 (28)	8068 (35)	1493 (33)	581 (26)	174 995 (18)
Total cholesterol (mg/dl), mean (SD)	206 (37)	208 (37)	208 (37)	207 (37)	206 (36)
HDL cholesterol (mg/dl), mean (SD)	57 (15)	55 (15)	61 (15)	56 (15)	57 (15)
Smoker, n (%)	3448 (36)	8763 (38)	998 (22)	921 (41)	294 541 (31)
Body mass index, mean (SD)	28.0 (4.8)	28.9 (4.8)	28.1 (4.9)	28.1 (4.7)	27.6 (4.6)
Statins, n (%)	1246 (13)	3870 (17)	903 (20)	296 (13)	85 201 (9)
Aspirin, n (%)	425 (4)	1468 (6)	395 (9)	103 (5)	28 281 (3)
DMARD, n (%)	737 (8)	1248 (5)	592 (13)	121 (5)	2013 (0.2)
DMARD + NSAIDs*, n (%)	242 (10)	980 (10)	352 (14)	93 (4)	874 (34)
DMARD + Corticosteroids*, n (%)	229 (11)	764 (37)	304 (45)	31 (2)	720 (35)
DMARD + NSAIDs + Corticosteroids*, n (%)	96 (8)	634 (52)	188 (16)	23 (19)	270 (22)
Anti-hypertensive treatment, n (%)	2683 (28)	9006 (40)	1844 (41)	634 (28)	171 004 (18)
10-year cardiovascular risk (%), median [IQR]	2.4 [1.3-4.4]	3.6 [2.0-6.6]	2.3 [1.4-4.0]	2.7 [1.5-4.9]	2.1 [1.1-3.7]

CIID, Chronic immune-mediated inflammatory disease; DMARD, Disease-modifying antirheumatic drugs; IQR, Interquartile range; NSAID, Non-steroidal anti-inflammatory drugs; SD, Standard deviation. *In individuals treated with DMARDs

Table 2 Annual incidence rates for cardiovascular end-points and overall mortality according to different CIID diagnoses per 1,000 person-year (95% confidence interval) compared with the general population.

	Inflammatory bowel diseases N=9544		Inflammatory polyarthropathies N=22 779		Systemic connective tissue disorders N=4491		Spondylopathies N=2243		CIID-free N=952 489	
	n	Annual incidence (95% CI)	n	Annual incidence (95% CI)	n	Annual incidence (95% CI)	n	Annual incidence (95% CI)	n	Annual incidence (95% CI)
Coronary artery disease	174	3.23 (2.75 to 3.71)	597	4.61 (4.24 to 4.98)	122	4.84 (3.98 to 5.70)	43	3.34 (2.34 to 4.34)	12 841	2.35 (2.31 to 2.39)
Stroke	177	3.28 (2.80 to 3.77)	519	3.99 (3.65 to 4.34)	118	4.66 (3.82 to 5.50)	29	2.24 (1.43 to 3.06)	10 665	1.95 (1.91 to 1.99)
Cardiovascular disease	344	6.43 (5.75 to 7.11)	1090	8.49 (7.99 to 9.00)	237	9.49 (8.28 to 10.70)	71	5.54 (4.25 to 6.83)	23 009	4.24 (4.18 to 4.29)
Overall mortality	650	11.96 (11.04 to 12.88)	1403	10.69 (10.13 to 11.25)	362	14.16 (12.70 to 15.62)	95	7.31 (5.84 to 8.78)	28 723	5.23 (5.17 to 5.29)

CIID, Chronic immune-mediated inflammatory disease

Figure 1.

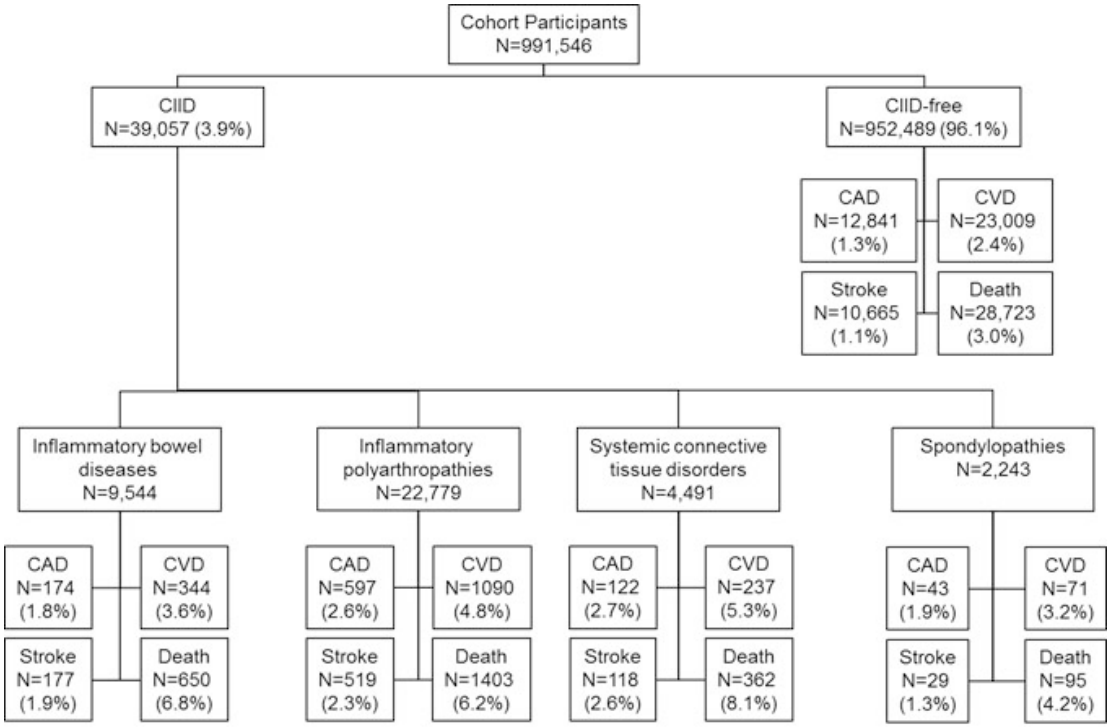

Cohort Participants
N=991,546
CIID
N=39,057 (3.9%)
CIID-free
N=952,489 (96.1%)
CAD
N=12,841
(1.3%)
CVD
N=23,009
(2.4%)
Stroke
N=10,665
(1.1%)
Death
N=28,723
(3.0%)
Inflammatory bowel diseases
N=9,544
Inflammatory polyarthropathies
N=22,779
Systemic connective tissue disorders
N=4,491
Spondylopathies
N=2,243
CAD
N=174
(1.8%)
CVD
N=344
(3.6%)
Stroke
N=177
(1.9%)
Death
N=650
(6.8%)
CAD
N=597
(2.6%)
CVD
N=1090
(4.8%)
Stroke
N=519
(2.3%)
Death
N=1403
(6.2%)
CAD
N=122
(2.7%)
CVD
N=237
(5.3%)
Stroke
N=118
(2.6%)
Death
N=362
(8.1%)
CAD
N=43
(1.9%)
CVD
N=71
(3.2%)
Stroke
N=29
(1.3%)
Death
N=95
(4.2%)

Figure 2.

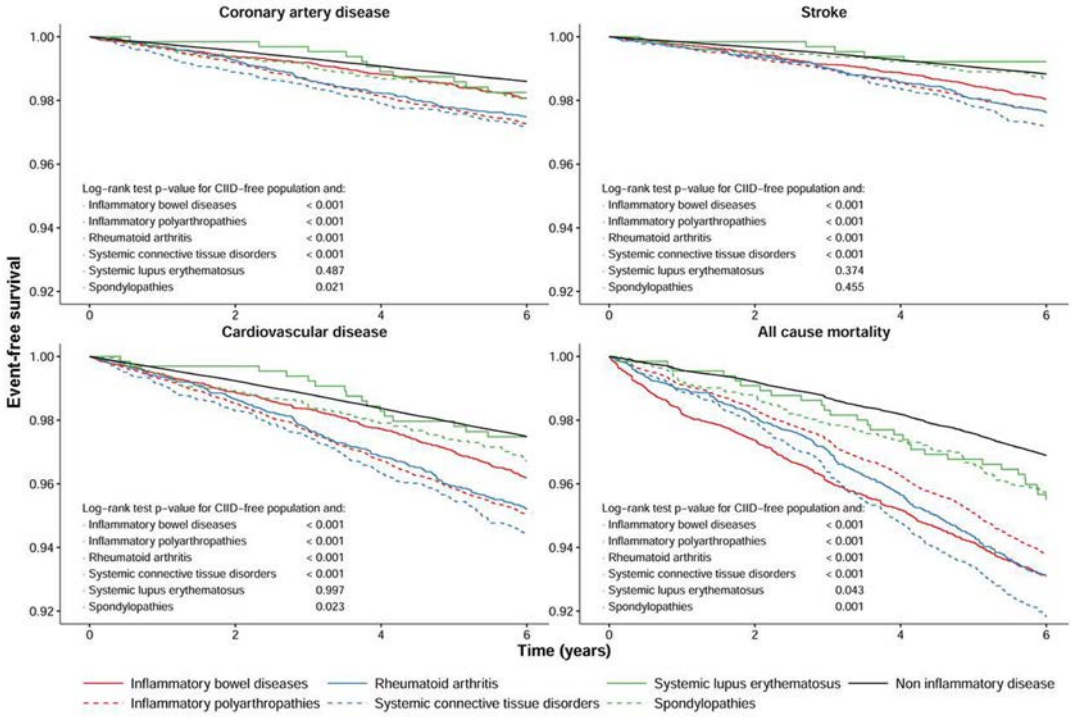

Coronary artery disease
Log-rank test p-value for CIID-free population and:
Inflammatory bowel diseases < 0.001
Inflammatory polyarthropathies < 0.001
Rheumatoid arthritis < 0.001
Systemic connective tissue disorders < 0.001
Systemic lupus erythematosus 0.487
Spondylopathies 0.021
Stroke
Log-rank test p-value for CIID-free population and:
Inflammatory bowel diseases < 0.001
Inflammatory polyarthropathies < 0.001
Rheumatoid arthritis < 0.001
Systemic connective tissue disorders < 0.001
Systemic lupus erythematosus 0.374
Spondylopathies 0.455
Cardiovascular disease
Log-rank test p-value for CIID-free population and:
Inflammatory bowel diseases < 0.001
Inflammatory polyarthropathies < 0.001
Rheumatoid arthritis < 0.001
Systemic connective tissue disorders < 0.001
Systemic lupus erythematosus 0.997
Spondylopathies 0.023
All cause mortality
Log-rank test p-value for CIID-free population and:
Inflammatory bowel diseases < 0.001
Inflammatory polyarthropathies < 0.001
Rheumatoid arthritis < 0.001
Systemic connective tissue disorders < 0.001
Systemic lupus erythematosus 0.043
Spondylopathies 0.001
Event-free survival
1.00
0.98
0.96
0.94
0.92
0
2
4
6
Time (years)
Inflammatory bowel diseases
Inflammatory polyarthropathies
Rheumatoid arthritis
Systemic connective tissue disorders
Systemic lupus erythematosus
Spondylopathies
Non inflammatory disease

Figure 3.

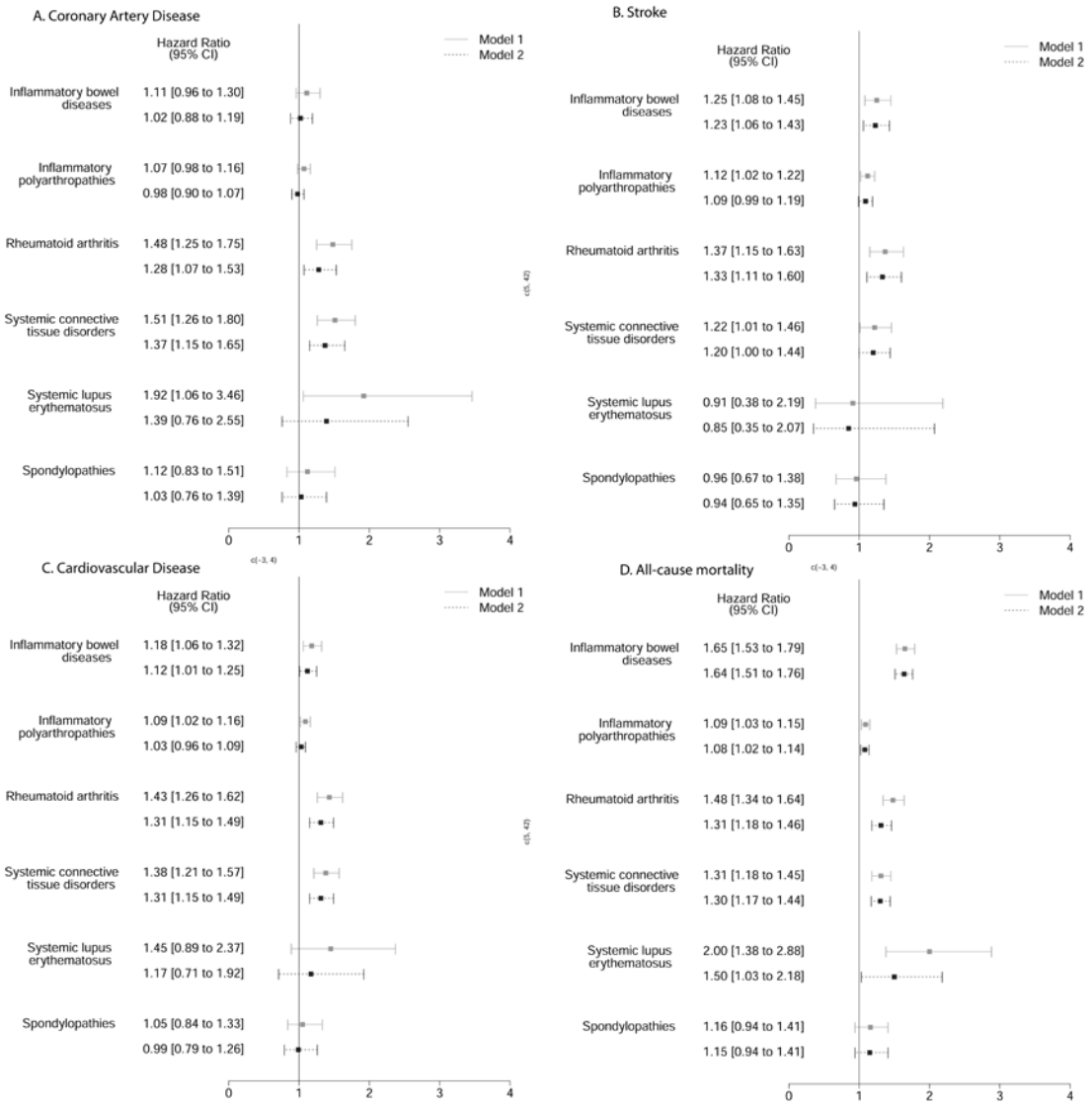
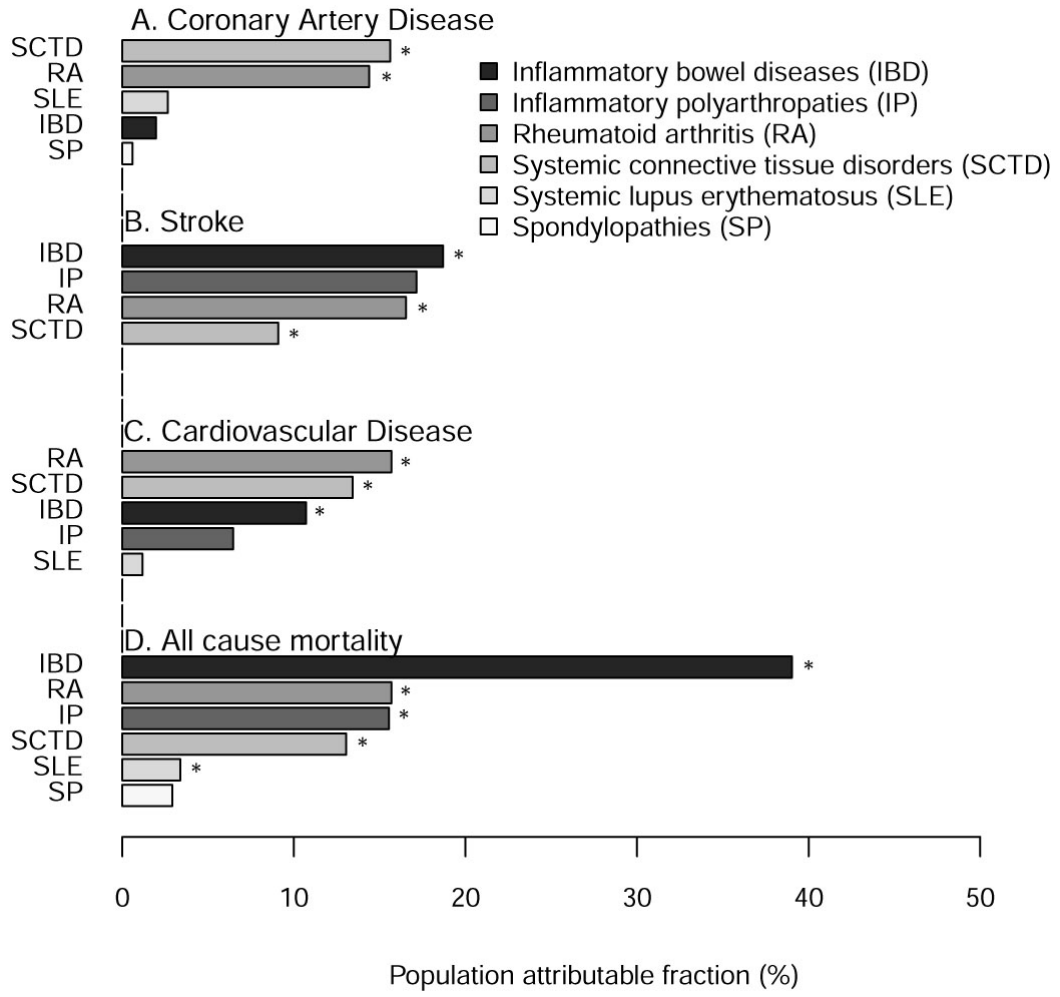

A. Coronary Artery Disease
Hazard Ratio (95% CI)
Model 1
Model 2
Inflammatory bowel diseases
1.11 [0.96 to 1.30]
1.02 [0.88 to 1.19]
Inflammatory polyarthropathies
1.07 [0.98 to 1.16]
0.98 [0.90 to 1.07]
Rheumatoid arthritis
1.48 [1.25 to 1.75]
1.28 [1.07 to 1.53]
Systemic connective tissue disorders
1.51 [1.26 to 1.80]
1.37 [1.15 to 1.65]
Systemic lupus erythematosus
1.92 [1.06 to 3.46]
1.39 [0.76 to 2.55]
Spondylopathies
1.12 [0.83 to 1.51]
1.03 [0.76 to 1.39]
0
1
2
3
4
B. Stroke
Hazard Ratio (95% CI)
Model 1
Model 2
Inflammatory bowel diseases
1.25 [1.08 to 1.45]
1.23 [1.06 to 1.43]
Inflammatory polyarthropathies
1.12 [1.02 to 1.22]
1.09 [0.99 to 1.19]
Rheumatoid arthritis
1.37 [1.15 to 1.63]
1.33 [1.11 to 1.60]
Systemic connective tissue disorders
1.22 [1.01 to 1.46]
1.20 [1.00 to 1.44]
Systemic lupus erythematosus
0.91 [0.38 to 2.19]
0.85 [0.35 to 2.07]
Spondylopathies
0.96 [0.67 to 1.38]
0.94 [0.65 to 1.35]
0
1
2
3
4
C. Cardiovascular Disease
Hazard Ratio (95% CI)
Model 1
Model 2
Inflammatory bowel diseases
1.18 [1.06 to 1.32]
1.12 [1.01 to 1.25]
Inflammatory polyarthropathies
1.09 [1.02 to 1.16]
1.03 [0.96 to 1.09]
Rheumatoid arthritis
1.43 [1.26 to 1.62]
1.31 [1.15 to 1.49]
Systemic connective tissue disorders
1.38 [1.21 to 1.57]
1.31 [1.15 to 1.49]
Systemic lupus erythematosus
1.45 [0.89 to 2.37]
1.17 [0.71 to 1.92]
Spondylopathies
1.05 [0.84 to 1.33]
0.99 [0.79 to 1.26]
0
1
2
3
4
D. All-cause mortality
Hazard Ratio (95% CI)
Model 1
Model 2
Inflammatory bowel diseases
1.65 [1.53 to 1.79]
1.64 [1.51 to 1.76]
Inflammatory polyarthropathies
1.09 [1.03 to 1.15]
1.08 [1.02 to 1.14]
Rheumatoid arthritis
1.48 [1.34 to 1.64]
1.31 [1.18 to 1.46]
Systemic connective tissue disorders
1.31 [1.18 to 1.45]
1.30 [1.17 to 1.44]
Systemic lupus erythematosus
2.00 [1.38 to 2.88]
1.50 [1.03 to 2.18]
Spondylopathies
1.16 [0.94 to 1.41]
1.15 [0.94 to 1.41]
0
1
2
3
4

Figure 4.


A. Coronary Artery Disease
SCTD
RA
SLE
IBD
SP
B. Stroke
IBD
IP
RA
SCTD
C. Cardiovascular Disease
RA
SCTD
IBD
IP
SLE
D. All cause mortality
IBD
RA
IP
SCTD
SLE
SP
Inflammatory bowel diseases (IBD)
Inflammatory polyarthropaties (IP)
Rheumatoid arthritis (RA)
Systemic connective tissue disorders (SCTD)
Systemic lupus erythematosus (SLE)
Spondylopathies (SP)
0
10
20
30
40
50
Population attributable fraction (%)

Supplementary Material

Supplementary Table 1 Diagnoses included in each group

ICD-10 Code	Title
K50-K52	**Inflammatory bowel diseases**
K50	Crohn disease (regional enteritis)
K51	Ulcerative colitis
K52	Other noninfective gastroenteritis and colitis
M05-M14, L40.5	**Inflammatory polyarthropathies**
M05	Seropositive rheumatoid arthritis
M06	Other rheumatoid arthritis
M07	Psoriatic and enteropathic arthropathies
M08	Juvenile arthritis
M09	Juvenile arthritis in diseases classified elsewhere
M10	Gout
M11	Other crystal arthropathies
M12	Other specific arthropathies
M13	Other arthritis
L40.5	Arthropathic psoriasis
M30-M35, G635	**Systemic connective tissue disorders**
M30	Polyarteritis nodosa and related conditions
M31	Other necrotizing vasculopathies
M32	Systemic lupus erythematosus
M33	Dermatopolymyositis
M34	Systemic sclerosis
M35	Other systemic involvement of connective tissue
G63.5	Polyneuropathy in systemic connective tissue disorders
M45-M46	**Spondylopathies**
M45	Ankylosing spondylitis
M46	Other inflammatory spondylopathies

Supplementary Table 2 Outcomes considered in the follow-up

ICD-10 Code	Title
I20-I23, I25	**Ischemic heart diseases**
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I25	Chronic ischaemic heart disease
I60-I64	**Cerebrovascular diseases**
I60	Subarachnoid hemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction

Supplementary Table 3 DMARDS and anti-inflammatory drugs included in each treatment group

ATC Code	Drug
	DMARD
A07EC01	Sulfasalazine
A07EC02	Mesalazine
A07EC03	Olsalazine
A07EC04	Balsalazide
L01AA01	Cyclophosphamide
L01BA04	Pemetrexed
L01BB01	Azathioprine
L01XC02	Rituximab
L04AA06	Mycophenolic acid
L04AA13	Leflunomide
L04AA24	Abatacept
L04AA26	Belimumab
L04AB01	Etanercept
L04AB02	Infliximab
L04AB04	Adalimumab
L04AB05	Certolizumab pegol
L04AB06	Golimumab
L04AC07	Tocilizumab
L04AD01	Cyclosporine
L04AX01	Azathioprine
L04AX03	Methotrexate
M01CB01	Sodium aurothiomalate
M01CB02	Sodium aurothiosulfate
M01CB03	Auranofin
M01CB04	Aurothioglucose
M01CB05	Aurotioprol
P01BA01	Chloroquine
P01BA02	Hydroxychloroquine
	Glucocorticoids
H02AB01	Betamethasone
H02AB02	Dexamethasone
H02AB03	Fluocortolone
H02AB04	Methylprednisolone
H02AB05	Paramethasone
H02AB06	Prednisolone
H02AB07	Prednisone
H02AB08	Triamycinolone
H02AB09	Hydrocortisone
H02AB10	Cortisone
H02AB11	Prednylidene
H02AB12	Rimexolone
H02AB13	Deflazacort
H02AB14	Cloprednol
H02AB15	Meprednisone
H02AB17	Cortivazol

	Non-steroidal anti-inflammatory drugs
M01AB	Acetic acid derivatives and related substances
M01AC	Oxicams
M01AE	Propionic acid derivatives
M01AG	Fenamates
M01AH	Coxibs
M01AX	Other anti-inflammatory and antirheumatic agents, non-steroids
N02BA01	Acetylsalicylic acid
N02BA06	Salsalate
N02BA11	Diflunisal
	Other anti-inflammatory drugs
A07EA06	Budesonide
A14AA07	Prasterone
L01XD01	Porfimer sodium
L04AA10	Sirolimus
L04AA23	Natalizumab
L04AD02	Tacrolimus
R03AB03	Orciprenaline
R03AC02	Salbutamol
R03AC03	Terbutaline
R03AC08	Pirbuterol
R03AC12	Salmeterol
R03AC13	Formoterol
R03BA01	Beclometasone
R03BA02	Budesonide
R03BA05	Fluticasone
R03BA07	Mometasone
R03BA08	Ciclesonide
R03BB01	Ipratropium bromide
R03BB04	Tiotropium bromide
R03CB03	Orciprenaline
R03CC02	Salbutamol
R03CC03	Terbutaline
R03DA04	Theophylline
R03DA05	Aminophylline
R03DX07	Roflumilast
V03AN01	Oxygen

Supplementary Table 4 Lipid-lowering drugs included

ATC Code	Drug
C10AA01	Simvastatin
C10AA02	Lovastatin
C10AA03	Pravastatin
C10AA04	Fluvastatin
C10AA05	Atorvastatin
C10AA06	Cerivastatin
C10AA07	Rosuvastatin
C10AA08	Pitavastatin

Supplementary Table 5 Antihypertensive drugs included

ATC Code	Drug
C07	Beta blocking agents
C08	Calcium channel blockers
C09	Agents acting on the renin-angiotensin system

Supplementary Table 6 p-values for proportionality assumption

End-point	CIID	p-value (Model 1)	p-value (Model 2)
Cardiovascular disease	Rheumatoid arthritis	0.3090	0.2473
Cardiovascular disease	Inflammatory polyarthropaties	0.1854	0.0928
Cardiovascular disease	Systemic lupus erythematosus	0.4605	0.4446
Cardiovascular disease	Inflammatory bowel disease	0.0419	0.0293
Cardiovascular disease	Systemic connective tissue disorders	0.4612	0.3532
Cardiovascular disease	spondylopathies	0.8322	0.7925
Coronary artery disease	Rheumatoid arthritis	0.9632	0.8202
Coronary artery disease	Inflammatory polyarthropaties	0.3384	0.2494
Coronary artery disease	Systemic lupus erythematosus	0.2038	0.2512
Coronary artery disease	Inflammatory bowel disease	0.1531	0.1673
Coronary artery disease	Systemic connective tissue disorders	0.2187	0.2259
Coronary artery disease	spondylopathies	0.6315	0.6577
Death	Rheumatoid arthritis	0.1306	0.6424
Death	Inflammatory polyarthropaties	0.7740	0.5989
Death	Systemic lupus erythematosus	0.4243	0.2011
Death	Inflammatory bowel disease	0.0000	0.0000
Death	Systemic connective tissue disorders	0.3090	0.7109
Death	spondylopathies	0.4159	0.6325
Stroke	Rheumatoid arthritis	0.1956	0.0880
Stroke	Inflammatory polyarthropaties	0.4498	0.2869
Stroke	Systemic lupus erythematosus	0.5520	0.6969
Stroke	Inflammatory bowel disease	0.1919	0.1149
Stroke	Systemic connective tissue disorders	0.0363	0.0192
Stroke	spondylopathies	0.9790	0.8970

Supplementary Table 7 Baseline characteristics of participants according to diagnosis of chronic immune-mediated inflammatory diseases. Case-complete analysis and percentage of missings

	Inflammatory bowel diseases	Inflammatory polyarthropathies	Systemic connective tissue disorders	Spondylopathies	No inflammatory disease
N (%)	9,544 (1.0)	22,779 (2.3)	4,491 (0.5)	2,243 (0.2)	952,489 (96.1)
Age, mean (SD)	56 (14)	60 (12)	63 (14)	55 (12)	52 (13)
Sex (men), n (%)	4162 (44)	14371 (63)	890 (20)	1185 (53)	446886 (47)
Diabetes, n (%)	956 (10)	3058 (13)	466 (10)	221 (10)	62436 (7)
Glycemia (mg/dl), median [IQR]	92 [84-105] (NA: 56.96%)	96 [87-110] (NA: 51.47%)	91 [83-103] (NA: 51.44%)	93 [85-104] (NA: 56.13%)	93 [85-104] (NA: 69.81%)
Hypertension, n (%)	2760 (29)	9633 (42)	1801 (40)	664 (30)	182170 (19)
Systolic blood pressure (mmHg), mean (SD)	130 (18) (NA: 52.80%)	135 (18) (NA: 45.84%)	133 (18) (NA: 43.02%)	130 (17) (NA: 51.89%)	131 (17) (NA: 67.54%)
Diastolic blood pressure (mmHg), mean (SD)	77 (10) (NA: 53.34%)	79 (10) (NA: 46.57%)	77 (9) (NA: 43.80%)	78 (10) (NA: 52.65%)	78 (10) (NA: 67.91%)
Dyslipidemia, n (%)	2645 (28)	8068 (35)	1493 (33)	581 (26)	174995 (18)
Total cholesterol (mg/dl), mean (SD)	207 (40) (NA: 57.42%)	209 (38) (NA: 51.88%)	209 (39) (NA: 52.13%)	209 (39) (NA: 57.24%)	210 (38) (NA: 69.90%)
HDL cholesterol (mg/dl), mean (SD)	58 (16) (NA: 69.09%)	54 (15) (NA: 62.71%)	61 (16) (NA: 65.66%)	57 (16) (NA: 68.39%)	58 (15) (NA: 77.28%)
LDL cholesterol (mg/dl), mean (SD)	129 (34) (NA: 69.34%)	128 (33) (NA: 63.27%)	129 (34) (NA: 66.09%)	132 (34) (NA: 68.57%)	131 (33) (NA: 77.31%)
Triglycerides (mg/dl), median [IQR]	107 [78-151] (NA: 65.74%)	124 [89-178] (NA: 59.81%)	105 [78-143] (NA: 62.17%)	106 [76-152] (NA: 65.89%)	105 [76-148] (NA: 75.64%)
Smoker, n (%)	3448 (36)	8763 (38)	998 (22)	921 (41)	294541 (31)
Obesity, n (%)	1431 (15)	4587 (20)	733 (16)	336 (15)	96996 (10)
Body mass index, mean (SD)	28.94 (5.17) (NA: 70.13%)	29.98 (4.89) (NA: 65.11%)	28.86 (4.91) (NA: 63.19%)	29.10 (4.97) (NA: 71.47%)	29.03 (5.11) (NA: 79.73%)
Statins, n (%)	1246 (13)	3870 (17)	903 (20)	296 (13)	85201 (9)
Aspirin, n (%)	425 (4)	1468 (6)	395 (9)	103 (4)	28281 (3)
Disease-modifying antirheumatic drugs, n (%)	737 (8)	1248 (5)	592 (13)	121 (5)	2013 (0.2)
10-year cardiovascular risk (%), median [IQR]	3.3 [2.0-6.3] (NA: 77.90%)	5.0 [2.8-8.7] (NA: 72.13%)	2.8 [1.8-4.8] (NA: 73.64%)	3.7 [2.2-6.7] (NA: 77.49%)	3.3 [2.0-5.9] (NA: 84.24%)

IQR, Interquartile range; NA, Not available; SD, Standard deviation

Supplementary Table 8 Hazard ratios for coronary artery disease, stroke, cardiovascular disease and overall mortality in individuals with chronic immune-mediated inflammatory disease. Case-complete analysis

	Coronary Artery Disease		Stroke		Cardiovascular Disease		Overall Mortality	
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Inflammatory bowel disease	1.07 (0.83-1.40)	1.05 (0.75-1.49)	1.22 (0.95-1.57)	1.40 (1.02-1.94)	1.16 (0.96-1.39)	1.23 (0.97-1.56)	1.52 (1.31-1.77)	1.32 (1.02-1.69)
Inflammatory polyarthropathies	1.11 (0.97-1.27)	0.91 (0.75-1.11)	1.17 (1.01-1.35)	1.17 (0.97-1.43)	1.13 (1.02-1.25)	1.05 (0.92-1.21)	1.16 (1.05-1.28)	1.01 (0.87-1.18)
Rheumatoid arthritis	1.21 (0.87-1.68)	1.17 (0.75-1.83)	1.34 (0.98-1.84)	1.41 (0.92-2.18)	1.28 (1.01-1.60)	1.32 (0.97-1.80)	1.60 (1.31-1.96)	1.42 (1.03-1.97)
Systemic connective tissue disorders	1.33 (0.97-1.82)	1.24 (0.81-1.92)	1.18 (0.87-1.61)	1.14 (0.73-1.78)	1.28 (1.02-1.59)	1.23 (0.90-1.67)	1.50 (1.25-1.80)	1.60 (1.21-2.12)
Systemic lupus erythematosus	0.88 (0.12-6.22)	*	*	*	0.46 (0.06-3.25)	*	1.85 (0.69-4.94)	2.60 (0.63-10.74)
Spondylopathies	1.11 (0.66-1.88)	0.69 (0.29-1.67)	0.69 (0.33-1.44)	0.40 (0.10-1.58)	0.90 (0.58-1.40)	0.59 (0.28-1.23)	1.37 (0.95-1.97)	1.37 (0.78-2.42)

*Unable to estimate due to low sample size

Supplementary Table 9 Hazard ratios for coronary artery disease, stroke, cardiovascular disease and overall mortality in individuals with registered diagnosis of chronic immune-mediated inflammatory disease

	Coronary artery disease		Stroke		Cardiovascular disease		Death	
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Inflammatory bowel disease	1.10 (0.95, 1.28)	1.02 (0.87, 1.18)	1.23 (1.06, 1.43)	1.22 (1.05, 1.42)	1.17 (1.05, 1.30)	1.11 (1.00, 1.24)	1.65 (1.52, 1.78)	1.64 (1.51, 1.77)
Inflammatory polyarthropathies	1.07 (0.98, 1.16)	0.98 (0.90, 1.07)	1.12 (1.02, 1.22)	1.09 (0.99, 1.19)	1.09 (1.02, 1.16)	1.03 (0.96, 1.09)	1.09 (1.03, 1.15)	1.08 (1.02, 1.14)
Rheumatoid arthritis	1.48 (1.25, 1.75)	1.28 (1.07, 1.53)	1.37 (1.15, 1.63)	1.33 (1.11, 1.60)	1.43 (1.26, 1.62)	1.31 (1.15, 1.49)	1.48 (1.34, 1.64)	1.31 (1.18, 1.46)
Systemic connective tissue disorders	1.50 (1.25, 1.79)	1.37 (1.14, 1.65)	1.20 (1.00, 1.44)	1.19 (0.99, 1.43)	1.37 (1.20, 1.56)	1.30 (1.14, 1.48)	1.30 (1.17, 1.44)	1.29 (1.16, 1.44)
Systemic lupus erythematosus	1.92 (1.06, 3.46)	1.39 (0.76, 2.55)	0.91 (0.38, 2.19)	0.85 (0.35, 2.07)	1.45 (0.89, 2.37)	1.17 (0.71, 1.92)	2.00 (1.38, 2.88)	1.50 (1.03, 2.18)
Spondylopathies	1.12 (0.83, 1.51)	1.03 (0.76, 1.39)	0.96 (0.67, 1.38)	0.94 (0.65, 1.35)	1.05 (0.84, 1.33)	0.99 (0.79, 1.26)	1.16 (0.94, 1.41)	1.15 (0.94, 1.41)

Model 1 has been adjusted by age, sex, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure and diastolic blood pressure. Model 2 has been further adjusted for statins, hypertensive drugs and rheumatic disease-specific treatments divided in 3 categories: DMARDs users, other anti-inflammatory drugs, not exposed to any of them.

Supplementary Table 10 Hazard ratios for coronary artery disease, stroke, cardiovascular disease and overall mortality in individuals with diagnosis of chronic immune-mediated inflammatory disease and no anti-inflammatory treatments (NSAIDs or DMARDs) before the diagnosis.

	Coronary artery disease		Stroke		Cardiovascular disease		Death	
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Inflammatory bowel disease	1.12 (0.95, 1.32)	1.08 (0.91, 1.28)	1.34 (1.14, 1.57)	1.32 (1.13, 1.55)	1.24 (1.10, 1.39)	1.21 (1.07, 1.36)	1.74 (1.60, 1.90)	1.80 (1.66, 1.96)
Inflammatory polyarthropathies	1.05 (0.96, 1.14)	0.99 (0.90, 1.07)	1.11 (1.02, 1.22)	1.09 (0.99, 1.19)	1.08 (1.01, 1.15)	1.03 (0.97, 1.10)	1.04 (0.98, 1.10)	1.07 (1.01, 1.13)
Rheumatoid arthritis	1.40 (1.15, 1.70)	1.35 (1.11, 1.63)	1.38 (1.13, 1.67)	1.36 (1.12, 1.65)	1.40 (1.22, 1.61)	1.36 (1.19, 1.57)	1.27 (1.12, 1.44)	1.30 (1.15, 1.47)
Systemic connective tissue disorders	1.46 (1.20, 1.76)	1.40 (1.16, 1.69)	1.25 (1.04, 1.51)	1.24 (1.03, 1.50)	1.38 (1.21, 1.58)	1.34 (1.17, 1.53)	1.27 (1.14, 1.42)	1.33 (1.19, 1.48)
Systemic lupus erythematosus	1.48 (0.62, 3.56)	1.41 (0.59, 3.40)	1.28 (0.48, 3.41)	1.26 (0.47, 3.37)	1.41 (0.73, 2.71)	1.37 (0.71, 2.63)	2.02 (1.25, 3.27)	2.05 (1.27, 3.31)
Spondylopathies	1.13 (0.83, 1.53)	1.07 (0.78, 1.45)	0.93 (0.64, 1.36)	0.91 (0.63, 1.33)	1.04 (0.82, 1.32)	1.00 (0.79, 1.27)	1.15 (0.94, 1.42)	1.20 (0.97, 1.47)

Model 1 has been adjusted by age, sex, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure and diastolic blood pressure. Model 2 has been further adjusted for statins, hypertensive drugs and rheumatic disease-specific treatments divided in 3 categories: DMARDs users, other anti-inflammatory drugs, not exposed to any of them.

Supplementary Table 11 Hazard ratios for coronary artery disease, stroke, cardiovascular disease and overall mortality in individuals with diagnosis of chronic immune-mediated inflammatory disease and no chronic kidney disease, sleep disorders or liver disease.

	Coronary artery disease		Stroke		Cardiovascular disease		Death	
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Inflammatory bowel disease	1.10 (0.95, 1.28)	1.02 (0.88, 1.19)	1.24 (1.07, 1.44)	1.23 (1.06, 1.43)	1.17 (1.05, 1.30)	1.12 (1.01, 1.25)	1.60 (1.48, 1.73)	1.61 (1.49, 1.75)
Inflammatory polyarthropathies	1.05 (0.97, 1.14)	0.97 (0.90, 1.06)	1.11 (1.01, 1.21)	1.08 (0.99, 1.18)	1.07 (1.01, 1.14)	1.02 (0.96, 1.08)	1.05 (0.99, 1.11)	1.06 (1.00, 1.12)
Rheumatoid arthritis	1.47 (1.24, 1.74)	1.29 (1.08, 1.54)	1.36 (1.14, 1.62)	1.33 (1.11, 1.60)	1.42 (1.26, 1.61)	1.31 (1.15, 1.49)	1.46 (1.32, 1.62)	1.34 (1.21, 1.50)
Systemic connective tissue disorders	1.49 (1.25, 1.78)	1.37 (1.14, 1.64)	1.21 (1.01, 1.45)	1.20 (1.00, 1.44)	1.37 (1.20, 1.56)	1.30 (1.15, 1.48)	1.27 (1.14, 1.41)	1.28 (1.16, 1.43)
Systemic lupus erythematosus	1.88 (1.04, 3.40)	1.40 (0.77, 2.56)	0.90 (0.37, 2.16)	0.85 (0.35, 2.07)	1.43 (0.87, 2.33)	1.17 (0.71, 1.93)	1.93 (1.33, 2.78)	1.60 (1.10, 2.33)
Spondylopathies	1.12 (0.83, 1.51)	1.03 (0.76, 1.39)	0.96 (0.66, 1.38)	0.94 (0.65, 1.35)	1.05 (0.83, 1.32)	0.99 (0.79, 1.26)	1.13 (0.92, 1.38)	1.15 (0.94, 1.40)

Model 1 has been adjusted by age, sex, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure and diastolic blood pressure. Model 2 has been further adjusted for statins, hypertensive drugs and rheumatic disease-specific treatments divided in 3 categories: DMARDs users, other anti-inflammatory drugs, not exposed to any of them.

Supplementary Table 12 Hazard ratios for coronary artery disease, stroke, cardiovascular disease and overall mortality in individuals with chronic immune-mediated inflammatory disease. Competing risks analysis

	Coronary artery disease HR (95% CI)	Stroke HR (95% CI)	Cardiovascular disease HR (95% CI)
Inflammatory bowel disease	0.98 (0.84-1.14)	1.17 (1.01-1.36)	1.07 (0.96-1.19)
Inflammatory polyarthropathies	0.98 (0.90-1.06)	1.08 (0.99-1.18)	1.02 (0.96-1.08)
Rheumatoid arthritis	1.26 (1.05-1.50)	1.30 (1.08-1.55)	1.28 (1.13-1.45)
Systemic connective tissue disorders	1.34 (1.12-1.61)	1.17 (0.98-1.41)	1.28 (1.13-1.46)
Systemic lupus erythematosus	1.40 (0.77-2.57)	0.86 (0.35-2.08)	1.18 (0.71-1.94)
Spondylopathies	1.03 (0.76-1.38)	0.93 (0.65-1.35)	0.99 (0.79-1.25)