Autoimmune disorders and cardiovascular risk: A population-based study on 19 autoimmune disorders and 12 cardiovascular diseases in 22 million individuals.

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Abstract

Background: It has been suggested that some autoimmune disorders are associated with an increased risk of cardiovascular disease. Whether and the extent to which this is true for all autoimmune conditions is unknown.

Methods: We used linked primary and secondary electronic health records from 22 million individuals in the Clinical Practice Research Datalink (CPRD) to assemble a cohort of individuals newly diagnosed with any of 19 autoimmune disorders between 01/01/2000 and 31/12/2017 and free of cardiovascular disorders (CVD) up to 12 months after diagnosis, and up to five individuals matched on age, sex, socioeconomic status and region, with follow-up until 30/06/2019. We investigated the incidence of twelve cardiovascular outcomes and used Cox-proportional hazards models to examine differences in patients with and without autoimmune disorders. In sensitivity analyses, models were further adjusted for known cardiovascular risk factors.

Findings: We identified 446 449 individuals with autoimmune disorders and 2 102 830 matched controls. Of these, 68 413 people with and 231 410 without autoimmune disorders developed incident CVD during a median of 6.2 years of follow-up. Patients with one or more autoimmune disorder had a higher risk of cardiovascular outcomes than controls: hazard ratio (HR) [95% confidence interval (CI)] 1.56 [1.52, 1.59]. This relationship held for every individual cardiovascular disorder and increased progressively with the number of autoimmune disorders present. Among autoimmune disorders, systemic sclerosis (3.59 [2.81, 4.59]), Addison's disease (2.83 [1.96, 4.09]), systemic lupus erythematosus (2.82 [2.38, 3.33]) and type I diabetes (2.36 [2.21, 2.52]), presented with highest overall cardiovascular risk. Excess cardiovascular risk also affected rates of hospital admissions and death from cardiovascular causes, was highest in the very young (<45 years). Although accounting for blood pressure, BMI, smoking, cholesterol, and type 2 diabetes only modesty attenuated the strength of the associations, in many cases data on these additional cardiovascular risk factors were missing and may not have been fully adjusted for.

Interpretation: Autoimmune disorders are associated with a higher risk of developing cardiovascular outcomes. These findings warrant targeted cardiovascular prevention measures, in particular in younger patients with autoimmune disorders, and further research into pathophysiological mechanisms underlying these complications.

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Keywords: autoimmune disorders, cardiovascular diseases, risk factor, cohort study, epidemiology, CPRD.

Research in Context

Evidence before this study

We searched Pubmed, Embase and Web of Science for reports published between 1 January 2000 to 30 December 2021 related to “autoimmune disorders” (any of the 19 individual conditions investigated) and “cardiovascular risk” (any of the twelve individual conditions investigated), reviewed references of clinical practice guidelines and consulted with experts for relevant studies. Most studies investigated one autoimmune disorder at a time, generally more common autoimmune disorders, such as rheumatoid arthritis or psoriasis. Cardiovascular outcomes were largely focussed on coronary heart disease and stroke. Studies frequently referred to comparatively small sample sizes and insufficiently assessed independence from classical atherosclerotic cardiovascular risk factors, rendering adequate synthesis of these findings difficult. Evidence was particularly scarce for rarer autoimmune disorders and for non-atherosclerotic heart diseases. We found no study that reported associations between autoimmune disorders as a group of conditions and a broad range of cardiovascular outcomes.

With the exception of rheumatoid arthritis, inflammatory bowel disease, lupus, and psoriasis, current levels of evidence were insufficient to achieve consensus in the latest cardiovascular prevention guidelines or for risk estimators used in routine clinical practice.

Added value of this study

We provide evidence that patients with autoimmune disorders have a 1.4 - 3.6 times higher risk of developing cardiovascular disease than people without autoimmune disorder – an order of magnitude that is similar to the risk brought by type 2 diabetes. Excess risk was particularly high in the very young (<45 years) and was not explained by traditional cardiovascular risk factors, such as age, sex, socioeconomic status, blood pressure, BMI, smoking, cholesterol or type 2 diabetes. The 19 autoimmune disorders investigated in our study accounted for a population attributable fraction of cardiovascular disease of 6.3%.

Our study shows that, among 19 of the most common autoimmune disorders, all conditions were associated with increased cardiovascular risk, pointing towards a pattern that affects autoimmune disorders as a group of diseases, rather than individually. Importantly, excess cardiovascular risk also affected rates of hospital admissions and death from cardiovascular causes. Furthermore, increased cardiovascular risk was visible across the whole cardiovascular disease spectrum, beyond classical atherosclerotic disease, including infection-related heart disorders, heart inflammation, as well as thromboembolic and degenerative heart disorders.

Implications of all the available evidence

Patients with autoimmune disorders present with significantly increased risk of developing cardiovascular disorders.

Cardiovascular risk prevention deserves to be an integral part of the management of autoimmune diseases. Further research is needed to design and assess the effectiveness of cardiovascular prevention measures for patients with autoimmune disorders, such as screening programmes and early use of preventive treatments. Statins and some specific anti-inflammatory therapies have been shown to reduce the risk of cardiovascular events and the present findings call for more trials with novel anti-inflammatory therapies to reduce cardiovascular risk in autoimmune disease populations.

As of today, the precise pathophysiological links between the many different, and particularly the less common, autoimmune disorders, their treatments, and cardiovascular disease, are not entirely understood and require elucidation.

Introduction

Selected autoimmune disorders, such as rheumatoid arthritis, are associated with increased cardiovascular morbidity and mortality.[1] Chronic and systemic inflammation, largely attributed to the presence of pro-inflammatory cytokines and autoantibodies, is thought to be underlying the observed association. Rheumatoid arthritis is not the only nor the most common autoimmune disorder with inflammatory pathophysiology. This is the case for a range of autoimmune disorders such as multiple sclerosis or psoriasis, and many of the over 100 autoimmune disorders, which collectively affect 5 to 9% of the population.[2,3] Yet, individual diseases' contributions to cardiovascular risk, interactions with traditional cardiovascular risk factors and exact underlying biological mechanisms are still subject to much debate.[4]

To date, a particular challenge has been the relatively modest sized cohorts available to study, their limited duration of follow-up and small numbers of cardiovascular events.[5] Consequently, biomarkers or other surrogates have been relied upon to probe disease mechanisms and to inform the development of treatments.[4] There are also some studies of the association between selected inflammatory conditions and specific cardiovascular events,[1,6,7] but the impact of different conditions on various cardiovascular disorders has not been compared on a large scale. As a result, there is currently insufficient evidence for cardiovascular prevention guidelines to specifically address autoimmunity,[8] and only rheumatoid arthritis and systemic lupus erythematosus are typically used to predict cardiovascular risk in routine clinical practice.[9,10] Importantly, the contribution of autoimmune disorders to cardiovascular disease in the population may extend beyond atherosclerotic disease such as myocardial, valvular, conduction and other cardiac complications, as well as venous-thromboembolic problems, and the potential impact of autoimmune disorders on the broader spectrum of cardiovascular diseases is currently unknown.

To address these knowledge gaps, we used a large longitudinal database of linked primary and secondary care that provides information on millions of individuals' diagnoses with several years of follow-up,[11] and assessed the association between 19 of the most common autoimmune disorders and a broad range of cardiovascular outcomes accounting for known cardiovascular risk factors.

Methods

Data source

We used electronic health records from the Clinical Practice Research Datalink (CPRD, GOLD and AURUM datasets) from 1 January 1985 to 30 June 2019. The CPRD database contains anonymised patient data from approximately 20% of the current UK population and is broadly representative in terms of age, sex and ethnicity. CPRD is one of the largest databases of longitudinal medical records from primary care in the world and has been validated for epidemiological research for a broad range of conditions.[11] Primary care records from CPRD were linked to secondary care records from Hospital Episodes Statistics (HES admitted patient care and HES outpatient) data as well as death certificates from the Office for National Statistics (ONS). Linkage was available for a subset of English practices from 1 January 1998 onwards, covering approximately 50% of all CPRD records. Scientific approval for this study was given by the CPRD Independent Scientific Advisory Committee (ISAC).

Case identification

We investigated 19 of the most common autoimmune disorders (AID): Addison's disease; ankylosing spondylitis; coeliac disease; type 1 diabetes; Graves' disease; Hashimoto thyroiditis; inflammatory bowel disease (Crohn's disease or ulcerative colitis); multiple sclerosis; myasthenia gravis; pernicious anaemia; polymyalgia rheumatica; primary biliary cirrhosis; psoriasis; rheumatoid arthritis; Sjogren; systemic lupus erythematosus; systemic sclerosis; vasculitis (including temporal arteritis, giant cell arteritis, polyarteritis nodosa, and ANCA-positive vasculitis); and vitiligo[3,12,13] Diseases were considered individually and as a composite outcome of all autoimmune diseases combined. For the combined analyses, the first recorded autoimmune disease was used.

For each condition, a list of diagnostic codes from the ICD-10 (International Classification of Diseases 10th revision, used in secondary care and on death certificates), OPCS-4 (Classification of Interventions and

Procedures version 4, used in secondary care), and Read[14] (used in primary care) coding schemes was defined to identify diagnoses from electronic health records (**appendix**). Incident diagnoses were defined as the first record of that condition in primary or secondary care records from any diagnostic position.

Study endpoints

The primary endpoints for the analysis were the initial presentation of fatal and non-fatal cardiovascular disorders (CVD). To best characterize the broad spectrum of CVD, we examined the following twelve conditions: aortic aneurysm; cardiac arrhythmias (atrial fibrillation and flutter, and supraventricular arrhythmias) and conduction system disease; heart failure; ischaemic heart disease; myocarditis and pericarditis (of non-infectious origin); peripheral arterial disease; infective endocarditis; stroke (ischaemic, haemorrhagic) and transient ischemic attack; valve disorders (excluding congenital and rheumatic); and venous thromboembolism or pulmonary embolism. Diseases were considered individually and as a composite outcome of all twelve CVD combined. For the combined analyses, the first recorded CVD was used. Incident diagnoses were defined as the first record of that condition in primary care, secondary care or death certificates from any diagnostic position.

To test whether observed associations could be due to increased medical attention leading to higher rates of diagnoses in individuals regularly followed-up for a chronic condition, we performed sensitivity analyses that restricted CVD to diagnoses recorded as the primary reason for hospital admission as well as mortality with CVD listed as the first cause of death.

Study population

The general population cohort included all men and women with records labelled as 'acceptable' by CPRD quality control[11], approved for HES and ONS linkage, and registered with their general practice for at least 12 months during the study period (01/01/2000 to 30/06/2019).

Among these, we defined an autoimmune disease cohort consisting of patients with incident AID (any of the 19 conditions investigated) between 01/01/2000 and 31/12/2017, up to 80 years of age at diagnosis, and free of CVD until 12 months after incident AID. The 12-months CVD-free period was defined to minimise risks of reverse causality. The index date was defined as the date of incident AID diagnosis plus 12 months. To ensure inclusion of incident AID diagnoses only, we excluded patients with an AID diagnosis before 01/01/2000 or within the first 12 months of registration with their general practice.

A comparison group was defined consisting of up to five individuals matched on age (±5 years), calendar time (individuals contributing to data within ±2 years of the matched individual's incident AID diagnosis), sex, socioeconomic status and region, randomly selected amongst individuals free of AID at any time. The index date was defined as the latest of the patient's practice registration date + 12 months and the matched individual diagnosis date. Similarly to the AID cohort, individuals with CVD before the index date were excluded.

Time at risk was defined to start on the individual's index date and to end on the earliest of the study end date (30/06/2019), patients' transfer out of practice date, practice's last collection date, incident CVD, and patient death as listed in the ONS record. Time at risk was calculated separately for each cardiovascular disease investigated.

Covariates

Covariates were selected to account for known cardiovascular risk factors. Baseline characteristics (systolic and diastolic blood pressure, smoking status, cholesterol (total cholesterol/high-density lipoprotein ratio) and body mass index (BMI)) were abstracted from electronic health records as the most recent measurement within 2 years before the index date. We further present prevalence of type 2 diabetes, as the percentage of patients with a diagnosis recorded in their primary care or hospital discharge record, prior to their index date. Socioeconomic status was defined as the Index of Multiple Deprivation (IMD) 2015 quintile,[15] a composite measure of relative deprivation at a small area level, covering an average population of 1500 people, ranked in ascending order of deprivation score and grouped in equal fifths, with quintiles 1 and 5 representing the least and most deprived areas, respectively. Finally, we extracted information on cardiovascular prevention

therapies, including statins and aspirin, as the number of patients with at least 3 prescriptions of that specific drug class, within 5 years after index date.

Statistical analyses

Baseline characteristics are presented as frequencies (%) for categorical data, medians and interquartile range (IQR) for non-normally distributed continuous data, or means and standard deviation (SD) for normally distributed continuous data for each cohort.

Missing values of blood pressure, smoking status, cholesterol, and BMI were imputed using multiple imputation by chained equations (MICE) with 5 imputed datasets.[16] Covariates values outside of the 2 years prior to index date were used as predictor variables in the imputation model. For clinical diagnoses, if no mention of a specific disease was ever recorded, then the patient was assumed to be free from the disease. Other variables (age, sex, socioeconomic status, region and practice registration dates) were complete in the studied dataset.

Incidence rates of CVD events per 1 000 years at risk were calculated in patients with and without autoimmune disease, overall as well as by subgroup of age, sex, socioeconomic status and calendar year. We used Cox proportional hazards models and calculated hazard ratios (HR) and corresponding 95% confidence intervals (CI) to compare the risk of incident CVD in patients with autoimmune disorders and matched controls. Models were clustered by matching sets. The proportional hazards assumption was evaluated using Schoenfeld residuals. Cumulative incidence plots were created using the Kaplan-Meier method and censored for time at risk. In sensitivity analyses, we adjusted models for blood pressure, smoking status, cholesterol, and BMI, as well as age and time-at-risk strata. Estimates and standard errors of adjusted analyses were obtained using Rubin's rules to combine the results of the separate analyses of individual imputed data sets.

Referring to the general population cohort, we further calculated the population attributable fraction of cardiovascular disorders attributable to autoimmune disease (any of the disorders investigated in this study) using the Miettinen formula[17] and the hazard ratio adjusted for blood pressure, smoking status, cholesterol, and BMI.

Study findings are reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) recommendations.[18] Statistical analyses were performed in R, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among the 22 009 375 individuals included in the study, we identified a total of 758 961 patients with a newly diagnosed autoimmune disorder between 01/01/2000 and 31/12/2017. Of those, 446 449 individuals were younger than 80 years of age at diagnosis, free of CVD until 12 months after incident AID, and constituted the final autoimmune cohort. The mean (SD) age at AID diagnosis was 47.2 (19.8) years, and 61% were women. The matched cohort comprised 2 102 830 individuals and presented with similar baseline characteristics. Among participants, 1 155 652 (45.3%) had missing data on blood pressure, 1 272 310 (49.9%) on smoking status, 1 595 420 (62.6%) for BMI, and 2 089 295 (82.0%) for cholesterol. Rates of missing data were higher in the control group compared to the autoimmune disease cohort (**Table 1**).

Incidence of cardiovascular disorders by age, sex, socioeconomic group and over time

Incidence rates of CVD per 1 000 patient-years were 23.3 among patients with AID and 15.0 among those without AID (HR: 1.56 [1.52, 1.59]). Higher risk of CVD was visible across all subgroups of sex, age, socioeconomic status and time, but affected younger individuals more than older people (HR in patients <45 years: 2.33 [2.16, 2.51] vs. HR in patients aged >75 years: 1.30 [1.24, 1.36]). This excess risk was seen to a similar extent in men and women and did not appear to have changed over time (**Figure 1**). Although excess

risk attenuated with longer follow-up time, it did so only modestly (HR at 1 year: 1.60 [1.56, 1.64]; 5 years: 1.49 [1.48, 1.51]; 10 years: 1.44 [1.42, 1.45]; 15 years: 1.48 [1.46, 1.51]).

Among those who developed cardiovascular disease, individuals with AID did so at a significantly younger age (age at first CVD presentation: 67.7 (14.1) years vs. 70.4 (13.2) years in individuals with and without AID respectively) and people with AID had a considerably higher risk of developing CVD before the age of 65 (HR 1.97 [1.90,2.05]).

Trends and patterns by individual disease

A total of 41 902 (9.3%) patients with AID were diagnosed with two or more autoimmune conditions, and cardiovascular risk gradually increased with the number of autoimmune disorders (HR for one, two, and three or more autoimmune disorders: 1.41 [1.37, 1.45], 2.63 [2.49, 2.78], 3.79 [3.36, 4.27], respectively). Among individual autoimmune disorders, the highest cardiovascular risk was seen in systemic sclerosis (HR: 3.59 [2.81, 4.59]), Addison's disease (HR: 2.83 [1.96, 4.09]), systemic lupus erythematosus (HR: 2.82 [2.38, 3.33]) and type I diabetes (2.36 [2.21, 2.52]) (**Figure 2**).

The association between autoimmunity and cardiovascular risk was significant for each individual cardiovascular disorder and was highest for myocarditis and pericarditis (HR: 2.34 [1.86, 2.94]), peripheral artery disease (HR: 2.09 [1.97, 2.22]), and infective endocarditis (HR: 1.85 [1.54, 2.23]) (**Figure 3**).

Classical cardiovascular risk factors

In adjusted analyses, traditional cardiovascular risk factors did not appear to explain the observed associations. Although data on covariates was partly missing, adjusting for blood pressure, smoking, BMI, cholesterol and type 2 diabetes, only slightly attenuated the excess risk related to AID (adjusted HR of CVD among patients with AID compared to those without AID: 1.40 [1.37, 1.44]) (**Figure 1**).

Hospitalisations and death from cardiovascular causes

Sensitivity analyses further showed that patients with autoimmune disorders also had a higher risk of hospital admissions for cardiovascular causes (HR: 1.33 [1.29, 1.36]) as well as higher mortality from cardiovascular causes (HR: 1.23 [1.16, 1.30]), compared to individuals without an autoimmune disorder.

Population attributable fraction

Among the 22 009 375 individuals who constituted the general population cohort, 2 834 671 (12.8%) developed a first cardiovascular event during the study period. Among those, 596 960 (21.1%) had a record of autoimmune disease (any of the 19 autoimmune disorders investigated in this study), and the fraction of cardiovascular disorders in the general population that was attributable to autoimmune disorders was 6.3%.

Discussion

Our large-scale population-based study provides several insights into the cardiovascular burden of autoimmune disorders, its variation by individual diseases, and its relation to traditional cardiovascular risk factors.

Our findings confirm evidence from previous studies showing increased cardiovascular risk associated with selected autoimmune disorders, such as rheumatoid arthritis,[1] inflammatory bowel disease,[19] or psoriasis,[20] and show that patients with autoimmune disorders have a higher cardiovascular risk than people without an autoimmune disorder, with hazard ratios ranging from 1.4 to 3.6. These compared to hazard ratios of 1.26, 1.29 and 1.62 for a 20 mmHg increase in systolic blood pressure, 5 kg/m^2 increase in BMI and diagnosis of type 2 diabetes, respectively, previously reported in the CRPD dataset.[21–23] Most importantly, our study shows that, among 19 of the most common autoimmune disorders, all were associated with increased cardiovascular risk, indicating that autoimmunity per se, rather than any individual condition is the risk factor and that the potential contribution of these disorders to cardiovascular disease in the population is far greater than previously recognised. Yet, as of today, there is little awareness of this relationship and thus most patients with autoimmune disease do not receive cardiovascular prevention measures that could help lower this burden or undergo screening to detect cardiovascular disease.

Further insights into the importance of autoimmune diseases as a cardiovascular risk factor come from our stratified analyses. Although the excess cardiovascular risk was largely consistent across sexes, and socioeconomic groups and did not change significantly over time, the age-stratified analyses show that excess risk related to autoimmunity was significantly greater in younger (<45 years) compared with older individuals. This is likely because cardiovascular disease is typically rare in healthy individuals at such a young age, whereas in older age groups, cardiovascular disorders become more prevalent due to accumulation of classical cardiovascular risk factors and senescence. Consequently, autoimmune diseases are particularly important in causing premature cardiovascular disease, with the potential to result in a disproportionate loss of years of life and disability.

Importantly, the observed excess cardiovascular risk was not explained by traditional cardiovascular risk factors, such as age, sex, socioeconomic status, blood pressure, BMI, smoking, or cholesterol. These findings are consistent with the inflammatory hypothesis and clinical trial data, which have shown that inhibiting chronic inflammation, even without altering lipids or other risk factors, lowers rates of cardiovascular events.[24–26] Statin therapy has also shown to improve cardiovascular outcomes among individuals with elevated inflammatory markers, even in subgroups with no other risk factors.[27] While the present findings argue for trials testing the effects of novel anti-inflammatory agents on cardiovascular outcomes in patients with autoimmune disease, it could be argued that the JUPITER trial already supports the use of statins in these patients, and the use of statins in the patients studied was low.[27]

Yet, another key finding was that excess cardiovascular risk was reflected in a whole range of cardiovascular disorders beyond atherosclerotic disease, in which involvement of chronic inflammation is well established. The risk of infection-related heart disorders was particularly elevated, possibly due to treatments of autoimmune disorders, which might make patients more susceptible to infections and their consequences on the cardiovascular system. The risk of inflammatory cardiac disorders, including pericarditis and myocarditis, was also elevated substantially, as was venous thromboembolism, and degenerative heart disease, such as non-rheumatic valve disorders and heart failure. These findings suggest that the potential effects of autoimmunity on cardiovascular health are likely to be much broader than originally thought, likely as a consequence of effects on connective tissue and small vessels, cardiomyocytes, and possibly some of the treatments commonly used to treat autoimmunity. Further studies are needed to investigate cardiovascular side effects of autoimmune drug therapy such as corticosteroids, anti-rheumatic medication, NSAIDs or biologics, and the complex interplay between beneficial effects, such as on inflammation with improved cardiovascular fitness, the need to preserve organ function in acute instances, and damaging side effects.

Our disease-specific analyses provide further insights into individual autoimmune disorders and their effect on cardiovascular risk. Although as a group, connective tissue and organ-specific autoimmune diseases presented with similar rates of cardiovascular disease, autoimmune conditions directly associated with inflammation, autoantibody mediated pathology and endothelial dysfunction, such as systemic lupus erythematosus and systemic sclerosis, were associated with the highest overall cardiovascular risk. The cardiovascular pathophysiology of systemic lupus erythematosus is perhaps the best studied of all, and is often complex due to the wide variety of associated autoantibodies capable of triggering a number of different pro-inflammatory and pathophysiological pathways. For example, autoantibodies to protein antigens, nucleic acids and to complexed lipids have been shown to variously participate in immune complex-associated endothelial damage and vasculitis, thrombocytopaenia, venous or arterial thrombosis and interference with lipid profiles. Increased rates of conventional risk factors such as family history, hypertension and blood biochemistry disturbances, as well as treatment with corticosteroids are all also likely to contribute to the high cardiovascular risk in these patients.[28,29] By contrast, conditions with very localised impact, such as vitiligo, which is largely restricted to the skin, appeared to present less risk to cardiovascular health.

Finally, the question as to whether observed associations might be due to increased medical attention in patients regularly followed-up for a chronic condition must be considered. While reliance on routine clinical data means that one cannot fully exclude that possibility, several elements attest of the robustness of our findings. Results from sensitivity analyses showing that patients with autoimmune disease were more also likely to be admitted to hospital for cardiovascular reasons, and more likely to die from cardiovascular

disease; concordance with independent studies that were not reliant on routine clinical data; and well-studied pathophysiological explanations, as well as the reduction in cardiovascular events seen in recent trials of antiinflammatory drugs, all point towards the fact that results are unlikely to be due to increased medical attention alone.

A major strength of this study is the selection of a large and representative cohort from primary and secondary care, with information on clinical diagnoses and cardiovascular risk factors and an extensive longitudinal follow-up. The very large size of our cohort also allowed us to perform stratified analyses of unprecedented granularity, over a broad spectrum of conditions, as well as allowing examination of age, sex, and socioeconomic subgroups, and trends over time. The use of routinely reported diagnoses captured the burden of disease as experienced by physicians and health services, and likely increases the generalizability of findings. One of the key limitations of our study was the inability to account for the effect of concomitant drug therapy, such as antirheumatic drugs, NSAIDs, or steroids, on the association between autoimmune disease and cardiovascular risk. Such analyses of non-randomised treatment would be highly confounded and unlikely to be clinically meaningful. The significant amounts of missingness in blood pressure, smoking, BMI or cholesterol measurements, which may not be missing at random, and the unavailability of additional data relevant to cardiovascular risk, such as information on exercise undertaken or inflammatory biomarkers, mean that our adjusted sensitivity analyses must be interpreted with caution. Research using electronic health records databases is also reliant on the accuracy of clinical coding carried out during consultations and hospital admissions. The validity of diagnoses underlying our study has therefore been carefully assessed and was considered appropriate in light of the over two hundred independent studies that have investigated the validity of diagnoses recorded in CPRD which reported an average positive predictive value of about 90% for a broad range of conditions.[30] Results from our sensitivity analyses restricted to cardiovascular diseases diagnosed in secondary care further confirm the validity and robustness of our findings. Finally, a large number of tests and subgroup analyses within one study must be interpreted with caution. However, the present case, the results are internally consistent with very small p-values and no suggestion of spurious findings due to the random paly of chance."

Our findings have important implications for health care resource planning and preventive strategies. The substantial cardiovascular risk observed in patients with autoimmune disorders, particularly in younger age groups, suggests that strategies to reduce cardiovascular risk should become a routine part of autoimmune disease management. While approaches to prevent atherosclerotic disease and stroke such as controlling blood pressure and reducing cholesterol are well established, the causes of cardiovascular conditions associated with autoimmune diseases, and their potential treatments, require further research.

Contributions

NC, JMM, JCM, GV, GM and JV conceived and designed the study. NC, GV, GM and JV contributed to acquiring the data, designed the statistical analysis plan and performed the statistical analysis. NC, LG, JV, JMM and JCM compiled diagnostic code lists. All authors - NC, GV, GM, LG, TC, GC, JCM, KR, JMM, and JV - contributed to interpreting the results, drafting the manuscript and the revisions. NC, JV, GV and GM had full access to the data in the study and had final responsibility for the decision to submit for publication. All authors gave final approval of the version to be published.

Declarations of interest

None.

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Prof Justin Mason died shortly before publication of this work. He was widely recognised as an outstanding clinician and academic, a gifted leader, and a friend to many. Justin was an international authority on large vessel vasculitis and his care for his patients and contributions to the vasculitis community will continue to make a significant difference for many years to come.

Data sharing

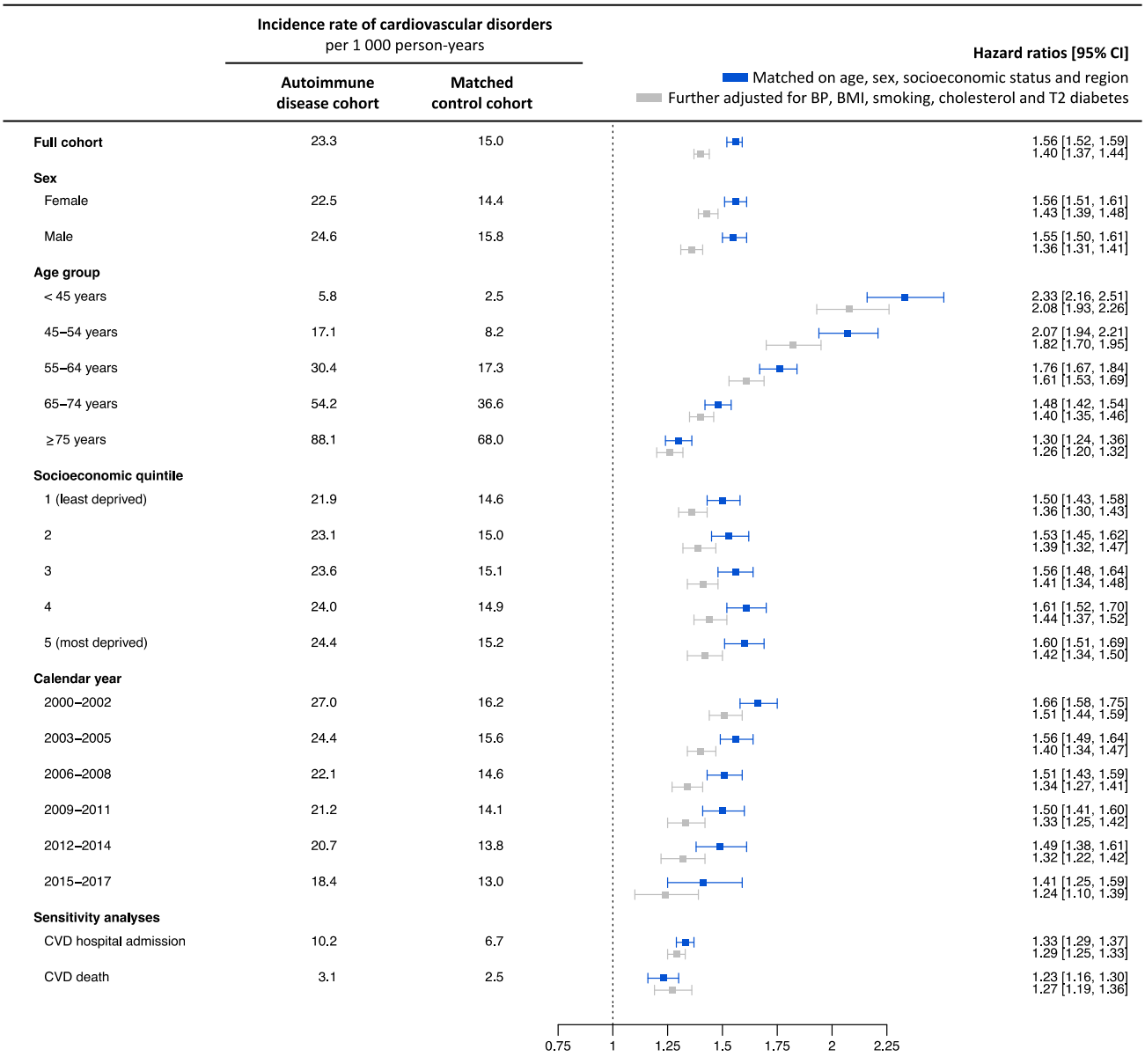
Access to CPRD data is subject to a license agreement and protocol approval process that is overseen by CPRD's Independent Scientific Advisory Committee (ISAC). A guide to access is provided on the CPRD website.

Table1: Baseline characteristics of patients with incident autoimmune disease and matched control cohort.

	Autoimmune disease cohort (N= 446 449)	**Matched control cohort (N= 2 102 830)**	**Overall (N= 2 549 279)**
Age at index (years)			
Mean (SD)	47.2 (19.8)	47.6 (19.7)	47.5 (19.7)
Female sex	271 410 (60.8%)	1 283 478 (61.0%)	1 554 888 (61.0%)
Socioeconomic status quintile			
1	100 276 (22.5%)	476 458 (22.7%)	576 734 (22.6%)
2	91 757 (20.6%)	433 519 (20.6%)	525 276 (20.6%)
3	88 470 (19.8%)	415 916 (19.8%)	504 386 (19.8%)
4	85 138 (19.1%)	398 967 (19.0%)	484 105 (19.0%)
5	80 808 (18.1%)	377 970 (18.0%)	458 778 (18.0%)
Number of autoimmune disorders			
0	0 (0%)	2 102 830 (100%)	2 102 830 (82.5%)
1	404 547 (90.6%)	0 (0%)	404 547 (15.9%)
2	37 226 (8.3%)	0 (0%)	37 226 (1.5%)
3 or more	4 676 (1.0%)	0 (0%)	4 676 (0.2%)
Time at risk (years)			
Median [IQR]	5.6 [2.4, 9.9]	6.4 [2.8, 11.3]	6.2 [2.7, 10.8]
Systolic blood pressure (mmHg)			
Mean (SD)	130 (17.6)	130 (18.0)	130 (17.9)
Missing (%)	160 466 (35.9%)	995 186 (47.3%)	1 155 652 (45.3%)
Diastolic blood pressure (mmHg)			
Mean (SD)	77.3 (10.1)	77.8 (9.87)	77.7 (9.92)
Missing (%)	160 536 (36.0%)	995 255 (47.3%)	1 155 791 (45.3%)
Body mass index (kg/m^2)			
Mean (SD)	27.9 (6.48)	27.1 (5.72)	27.3 (5.88)
Missing (%)	267 125 (59.8%)	1 328 295 (63.2%)	1 595 420 (62.6%)
Cholesterol (total cholesterol/high-density lipoprotein ratio)			
Mean (SD)	3.78 (1.22)	3.78 (1.20)	3.78 (1.20)
Missing (%)	339 607 (76.1%)	1 749 688 (83.2%)	2 089 295 (82.0%)
Smoking status			
Ex	60 403 (13.5%)	220 958 (10.5%)	281 361 (11.0%)
No	120 924 (27.1%)	577 478 (27.5%)	698 402 (27.4%)
Yes	61 787 (13.8%)	235 419 (11.2%)	297 206 (11.7%)
Missing (%)	203 335 (45.5%)	1 068 975 (50.8%)	1 272 310 (49.9%)
Type 2 diabetes	31 252 (7.0%)	66 830 (3.2%)	98 082 (3.8%)
Cardiovascular prevention therapy			
Aspirin	37 824 (8.5%)	119 335 (5.7%)	157 159 (6.2%)
Statins	85 246 (19.1%)	275 873 (13.1%)	361 119 (14.2%)

For variables with missing entries, summary statistics present observed values alongside the percentage of missing values (missing within two years prior to index). Socioeconomic status was defined as the Index of Multiple Deprivation (IMD) 2015 quintile.

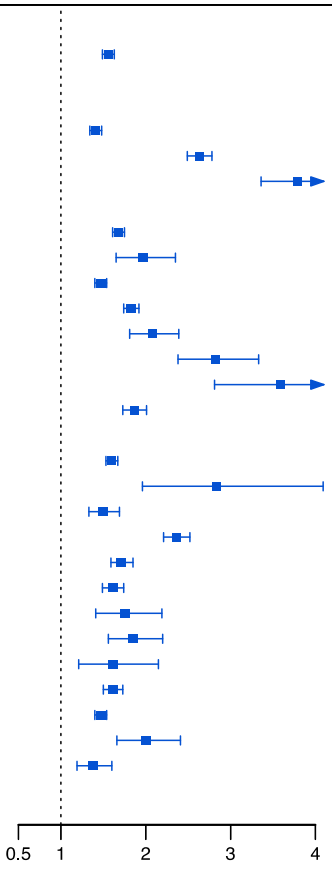
Figure 1: Incidence rates and hazard ratios of cardiovascular disorders among patients with autoimmune disease and matched controls



Socioeconomic status (SES) refers to Index of Multiple Deprivation (IMD) 2015 quintile, with 1 referring to the most affluent and 5 to the most deprived quintile. Calendar year refers to the year individuals were included in the study. CVD hospital admission refers to hospital admissions with cardiovascular disease (CVD) as the primary admission diagnosis. CVD death refers to death with cardiovascular disease listed as the primary cause of death. Abbreviations BP = systolic and diastolic blood pressure; BMI = Body Mass Index; T2 diabetes = type 2 diabetes.

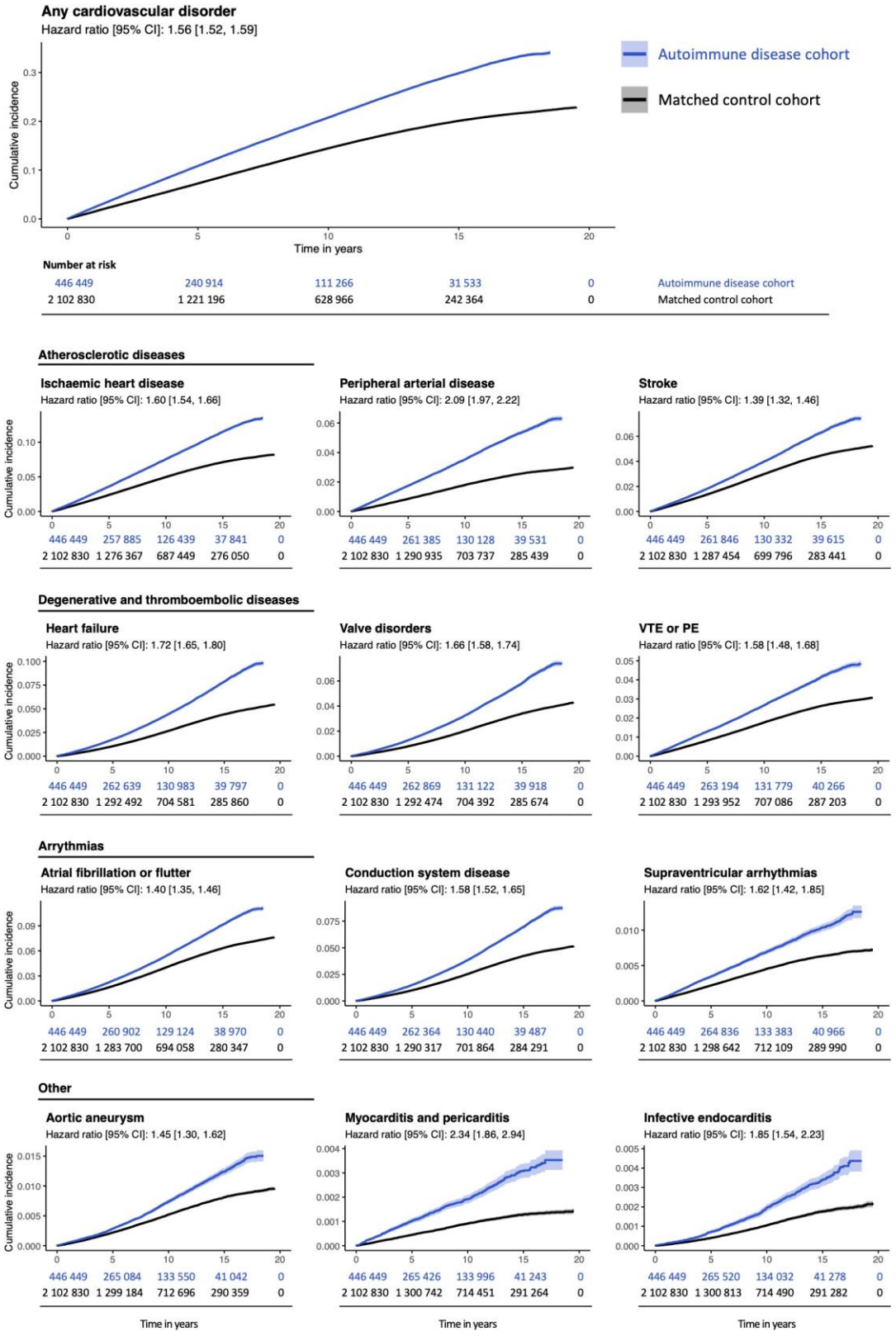
Figure 2: Hazard ratios and 95% CI for incident cardiovascular disease among patients with autoimmune disorders compared to matched controls. Stratified by the individual autoimmune disorder.

	Cohort		Events		Hazard ratios [95% CI]
	AID	Controls	AID	Controls	
Any autoimmune disorder	446 449	2 102 830	68 413	231 410	1.56 [1.52, 1.59]
Number of autoimmune disorders					
1	404 547	1 902 682	55 301	198 769	1.41 [1.37, 1.45]
2	37 226	177 676	11 005	28 570	2.63 [2.49, 2.78]
3 or more	4 676	22 472	2 107	4 071	3.79 [3.36, 4.27]
Connective tissue disorders	160 217	761 918	36 846	118 391	1.68 [1.63, 1.74]
Ankylosing spondylitis	9 864	46 121	1 423	3 822	1.97 [1.65, 2.35]
Polymyalgia rheumatica	48 102	231 802	15 390	55 870	1.47 [1.40, 1.54]
Rheumatoid arthritis	66 796	318 456	15 520	46 594	1.83 [1.74, 1.92]
Sjogren	9 933	47 330	2 327	6 139	2.08 [1.81, 2.39]
Systemic lupus erythematosus	10 483	49 402	2 204	4 227	2.82 [2.38, 3.33]
Systemic sclerosis	2 159	10 310	752	1 320	3.59 [2.81, 4.59]
Vasculitis	37 940	178 494	7 839	22 658	1.87 [1.73, 2.01]
Organ–specific disorders	407 078	1 909 992	53 706	175 205	1.60 [1.56, 1.64]
Addison	2 548	12 055	604	1 218	2.83 [1.96, 4.09]
Coeliac	24 895	115 692	2 507	8 618	1.50 [1.33, 1.69]
Type 1 Diabetes	50 264	235 540	9 697	23 568	2.36 [2.21, 2.52]
Inflammatory Bowel Disease	49 214	230 236	6 470	19 532	1.71 [1.59, 1.85]
Graves	44 001	207 508	6 409	20 535	1.61 [1.49, 1.74]
Hashimoto	7 630	35 650	822	2 364	1.76 [1.41, 2.19]
Multiple sclerosis	12 006	56 523	1 356	3 876	1.85 [1.56, 2.20]
Myasthenia gravis	2 171	10 319	544	1 812	1.61 [1.21, 2.15]
Pernicious anaemia	32 910	156 887	8 228	27 099	1.61 [1.50, 1.73]
Psoriasis	185 178	869 184	21 197	73 465	1.47 [1.41, 1.53]
Primary biliary cirrhosis	4 612	21 973	1 086	3 060	2.00 [1.66, 2.41]
Vitiligo	23 709	109 914	1 791	6 526	1.38 [1.19, 1.60]



AID refers to the autoimmune disease cohort. Patients with autoimmune disorders were compared to up to five individuals matched on age (±5 years), calendar year (±2 years), sex, socioeconomic status and region, free of AID at any time. Hazard ratios and corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazards models clustered by matching set. Cardiovascular diseases investigated included: aortic aneurysm; cardiac arrhythmias (atrial fibrillation and flutter, and supraventricular arrhythmias) or *conduction system disease; heart failure; ischaemic heart disease; myocarditis and pericarditis (of non-infectious origin); peripheral arterial disease; infective endocarditis; stroke (ischaemic, haemorrhagic) and transient ischemic attack); valve disorders; and venous thromboembolism or pulmonary embolism.*

Figure 3: Cumulative incidence of cardiovascular disease among patients with autoimmune disorders compared to matched controls. Stratified by individual cardiovascular disorders.



Hazard ratios and corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazards models clustered by matching set, and compared incident cardiovascular disease among patients with autoimmune disorders compared to controls *matched for age, calendar year, sex, socioeconomic status, and region.*

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