



# Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK

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## Summary

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**Background** A rise in the incidence of some autoimmune disorders has been described. However, contemporary estimates of the overall incidence of autoimmune diseases and trends over time are scarce and inconsistent. We aimed to investigate the incidence and prevalence of 19 of the most common autoimmune diseases in the UK, assess trends over time, and by sex, age, socioeconomic status, season, and region, and we examine rates of co-occurrence among autoimmune diseases.

**Methods** In this UK population-based study, we used linked primary and secondary electronic health records from the Clinical Practice Research Datalink (CPRD), a cohort that is representative of the UK population in terms of age and sex and ethnicity. Eligible participants were men and women (no age restriction) with acceptable records, approved for Hospital Episodes Statistics and Office of National Statistics linkage, and registered with their general practice for at least 12 months during the study period. We calculated age and sex standardised incidence and prevalence of 19 autoimmune disorders from 2000 to 2019 and used negative binomial regression models to investigate temporal trends and variation by age, sex, socioeconomic status, season of onset, and geographical region in England. To characterise co-occurrence of autoimmune diseases, we calculated incidence rate ratios (IRRs), comparing incidence rates of comorbid autoimmune disease among individuals with a first (index) autoimmune disease with incidence rates in the general population, using negative binomial regression models, adjusted for age and sex.

**Findings** Among the 22 009 375 individuals included in the study, 9 788 722 had a new diagnosis of at least one autoimmune disease between Jan 1, 2000, and June 30, 2019 (mean age 54·0 years [SD 21·4]). 6 258 799 (63·9%) of these diagnosed individuals were female and 3 529 933 (36·1%) were male. Over the study period, age and sex standardised incidence rates of any autoimmune diseases increased (IRR 2017–19 vs 2000–02 1·04 [95% CI 1·00–1·09]). The largest increases were seen in coeliac disease (2·19 [2·05–2·35]), Sjogren's syndrome (2·09 [1·84–2·37]), and Graves' disease (2·07 [1·92–2·22]); pernicious anaemia (0·79 [0·72–0·86]) and Hashimoto's thyroiditis (0·81 [0·75–0·86]) significantly decreased in incidence. Together, the 19 autoimmune disorders examined affected 10·2% of the population over the study period (1 912 200 [13·1%] women and 668 264 [7·4%] men). A socioeconomic gradient was evident across several diseases, including pernicious anaemia (most vs least deprived area IRR 1·72 [1·64–1·81]), rheumatoid arthritis (1·52 [1·45–1·59]), Graves' disease (1·36 [1·30–1·43]), and systemic lupus erythematosus (1·35 [1·25–1·46]). Seasonal variations were observed for childhood-onset type 1 diabetes (more commonly diagnosed in winter) and vitiligo (more commonly diagnosed in summer), and regional variations were observed for a range of conditions. Autoimmune disorders were commonly associated with each other, particularly Sjogren's syndrome, systemic lupus erythematosus, and systemic sclerosis. Individuals with childhood-onset type 1 diabetes also had significantly higher rates of Addison's disease (IRR 26·5 [95% CI 17·3–40·7]), coeliac disease (28·4 [25·2–32·0]), and thyroid disease (Hashimoto's thyroiditis 13·3 [11·8–14·9] and Graves' disease 6·7 [5·1–8·5]), and multiple sclerosis had a particularly low rate of co-occurrence with other autoimmune diseases.

**Interpretation** Autoimmune diseases affect approximately one in ten individuals, and their burden continues to increase over time at varying rates across individual diseases. The socioeconomic, seasonal, and regional disparities observed among several autoimmune disorders in our study suggest environmental factors in disease pathogenesis. The inter-relations between autoimmune diseases are commensurate with shared pathogenetic mechanisms or predisposing factors, particularly among connective tissue diseases and among endocrine diseases.

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## Research in context

### Evidence before this study

We searched PubMed and Embase in August, 2022, for reports published in English between Jan 1, 2000, to July 30, 2022, related to “autoimmune disorders” (any of the 19 individual conditions investigated) and “incidence”, reviewed references of clinical practice guidelines, and consulted with experts for relevant studies. Most studies investigated one autoimmune disorder at a time. In general, studies investigated the more common autoimmune disorders, such as type 1 diabetes or psoriasis. Studies generally relied on a small number of cases and presented different designs, case identification, and diagnostic methods, rendering adequate synthesis and the calculation of pooled estimates and temporal trends difficult. Evidence was particularly scarce for rare autoimmune disorders (eg, Addison’s disease). We found no study that reported large-scale disease incidence and temporal trends of autoimmune disorders as a group of conditions.

### Added value of this study

We present age and sex standardised incidence rates derived from a large, representative, general UK population cohort, setting a baseline for international comparison, monitoring of prevention strategies, and the design of public health policies. Temporal trends across a broad range of autoimmune diseases do not support the idea of a rapidly increasing incidence of autoimmune diseases, and provide valuable reference rates for future studies investigating population-level effects of newly introduced risk factors, such as the COVID-19 pandemic. We provide robust evidence of socioeconomic, seasonal,

and regional disparities for several autoimmune diseases (particularly Graves’ disease, pernicious anaemia, rheumatoid arthritis, systemic lupus erythematosus, and childhood-onset type 1 diabetes). Such variations are unlikely to be attributable to genetic differences alone and suggest involvement of potentially modifiable risk factors in the pathogenesis of autoimmune diseases. We also show important inter-relations between many autoimmune diseases, and our data suggest that co-occurrence of autoimmune disease is common, yet orders of magnitude differ widely between diseases. Associations were highest among connective tissue diseases, and for individuals with childhood-onset type 1 diabetes and Addison’s disease, coeliac disease, and thyroid diseases. More generally, increased risk of developing Addison’s disease was observed after almost every autoimmune disease investigated. Multiple sclerosis stood out as having low rates of co-occurrence with other autoimmune diseases, suggesting a distinct pathophysiology.

### Implications of all the available evidence

The burden of autoimmune disorders appears higher than previous estimates, and continues to increase over time, albeit at varying rates across individual diseases. Socioeconomic, seasonal, and regional disparities in disease incidence point to potentially preventable factors involved in the pathogenesis of autoimmune diseases. Co-occurrences of diseases point to common genetic and environmental risk factors that interact and operate variably across these diseases. Further research is needed to elucidate the pathophysiological mechanism underlying the associations observed in this study.

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## Introduction

Autoimmune diseases arise when immune dysregulation causes host tissue damage.<sup>1</sup> A wide range of autoimmune diseases are described that present with variable age of onset, tissue distribution, and clinical and functional effects.<sup>1</sup> Most of these diseases are incurable and require lifelong treatment.

Adequate public health and service delivery planning requires reliable information about contemporary, population-level disease incidence. However, estimates of autoimmune disease incidence rates and their temporal trends, even in high-income countries, are scarce and inconsistent.<sup>1</sup> Some autoimmune disorders, such as type 1 diabetes, are reported to have increased over the past three decades, raising the question as to whether the overall incidence of autoimmune disorders is on the rise, driven perhaps by common environmental factors or behavioural changes. Even for type 1 diabetes, the incidence of which is among the best studied within autoimmune diseases, reports rely on relatively small cohorts,<sup>2,3</sup> and estimates vary by a factor of ten between studies in Europe alone.<sup>4,5</sup> For many other autoimmune diseases, evidence concerning disease incidence and prevalence is more scarce than for diabetes. The relatively

modest absolute numbers of people affected by individual autoimmune diseases is a major challenge to investigators and hinders adequate synthesis across studies.<sup>6</sup> As a result, reliable estimates of disease incidence and how they evolve over time, particularly for autoimmune diseases as a group, are not available.

Commonalities and differences between individual diseases are also not well understood and continue to be subject to much research. Although emerging evidence has suggested that autoimmune diseases tend to co-occur within individuals, large-scale investigations across a broad spectrum of autoimmune diseases that could provide clues about shared pathogenesis and risk factors are not currently available.<sup>7,8</sup>

To address these knowledge gaps, we analysed a large longitudinal database of primary and secondary care records in the UK that provides information on millions of individuals’ diagnoses with several years of follow-up.<sup>9,10</sup> We aimed to investigate the incidence and prevalence for 19 of the most common autoimmune diseases, assess trends over time, by sex, age, socioeconomic status, season, and UK region, and examine rates of co-occurrence among autoimmune diseases.

## Methods

### Data source

See Online for appendix

In this population-based observational study, we used electronic health records from the GOLD and Aurum datasets of the Clinical Practice Research Datalink (CPRD) from Jan 1, 1985, to June 30, 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.<sup>9</sup> Primary care records from CPRD were linked to secondary care records from Hospital Episodes Statistics (HES) data (HES admitted patient care data and HES outpatient data). Linkage was available for a subset of English practices from Jan 1, 1998, onwards, covering approximately 50% of all CPRD records. The CPRD Group has ethical approval from a National Research Ethics Service Committee for all purely observational research using anonymised CPRD data. Scientific approval for this study was given by the CPRD Independent Scientific Advisory Committee.

### Study population

Individuals who were eligible for inclusion in the study were men and women (no age restriction) with records labelled as acceptable for research purposes by the CPRD, approved for HES and Office of National Statistics linkage, and registered with their general practice for at least 12 months during the study period (Jan 1, 2000, to June 30, 2019). For incidence calculations, we excluded all individuals who had a diagnosis of the disease of interest before the study start date (Jan 1, 2000), or within the first 12 months of registration with their general practice.

### Case identification

We investigated 19 of the most common autoimmune disorders: Addison's disease, ankylosing spondylitis, coeliac disease, childhood-onset type 1 diabetes, Graves' disease, Hashimoto's thyroiditis, inflammatory bowel disease (Crohn's disease or ulcerative colitis), multiple sclerosis, myasthenia gravis, pernicious anaemia, polymyalgia rheumatica, primary biliary cholangitis, psoriasis, rheumatoid arthritis (including its specific subtypes such as Still disease, Caplan syndrome, rheumatoid spondylitis, and others), Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, vasculitis, and vitiligo.<sup>11–13</sup>

Although some of these diseases remain debated in terms of their autoimmune causes and might be more appropriately described as immune-mediated inflammatory diseases, we refer to this group of conditions as autoimmune diseases to assist readability.

For each condition, we identified diagnoses from primary care or secondary care records based on diagnostic codes from the International Classification of

Diseases, tenth revision (used in secondary care), and Read<sup>14</sup> and SNOMED<sup>15</sup> coding schemes (used in primary care). Furthermore, we identified some conditions by the prescription of specific drugs (appendix p 11). Specifically, individuals with childhood-onset type 1 diabetes were identified as those with at least one diagnostic code referring to type 1 or insulin-dependent diabetes, at least one insulin prescription, and who were 19 years or younger at first diagnosis. Individuals with Hashimoto's thyroiditis were identified as those with at least one levothyroxine prescription and no history of hyperthyroidism, pituitary disease, thyroid surgery, or thyroid-altering medication (eg, amiodarone, lithium, sodium valproate, carbimazole, propylthiouracil, thalidomide, or sunitinib). When conflicting arthritis diagnoses (ie, ankylosing spondylitis and rheumatoid arthritis) were recorded in the same individual, the most recent recorded diagnosis was used. Incident diagnoses were defined as the first record of that condition in primary or secondary care records from any diagnostic position.

### Covariates

Smoking status and BMI were abstracted from electronic health records as the most recent measurement within 2 years before diagnosis of an autoimmune disease. Socioeconomic status was defined as the Index of Multiple Deprivation 2015 quintile,<sup>16</sup> a composite measure of relative deprivation for small areas, covering an average population of 1500 people, ranked in ascending order of deprivation score and grouped in equal fifths, with quintile one representing the least deprived areas and quintile five representing the most deprived areas. Data on sex are as reported by the patient when they registered with their general practitioner. Ethnicity data were extracted from both primary and secondary care records. When ethnicity differed between primary and secondary care records, secondary care data were used.

### Statistical analysis

Baseline characteristics are presented as frequencies for categorical data, medians and IQR for non-normally distributed continuous data, and mean and SD for normally distributed continuous data. These data are presented for the whole autoimmune disease cohort and stratified by sex, socioeconomic quintile, and period of diagnosis. Number and percentage of records with missing data are displayed for variables with missing entries.

Observed incidence rates were computed by dividing the number of incident cases by the number of patient-years in the cohort. Category-specific rates were computed separately for subgroups of age, sex, socioeconomic status, region, calendar year of diagnosis, and season of diagnosis. Winter was defined as the period from January to March, and summer was defined as the period from June to August. Time at risk was calculated to start at the latest of patient's registration date plus 12 months, birth year, or study start

date; and stopped at the earliest of death, transfer out of practice, practice's last collection date, incidence of the disease of interest, or study end date. Observed prevalence was computed considering all people ever diagnosed with autoimmune disease (numerator) among those who were alive and registered with a general practitioner on June 30 in each year (denominator). To allow comparison with other studies, we further calculated incidence and prevalence of childhood-onset type 1 diabetes restricting the denominator to those who were 19 years or younger (appendix p 8). We also performed some sensitivity analyses using more restrictive disease definitions and present these analyses in the appendix (p 2). Diseases were considered individually and as a composite outcome of all autoimmune disorders combined. For the combined analyses, we calculated primary incidence (first recorded autoimmune disorder, reflecting the number of people affected by autoimmune disorders) and cumulative incidence (all recorded autoimmune disorders, reflecting the cumulative number of autoimmune disorder diagnoses).

Standardised rates were computed by applying direct age and sex standardisation<sup>17</sup> to the 2013 European Standard Population<sup>18</sup> using 5-year age bands up to age 90 years.

Negative binomial regression models were used to examine overall and category-specific incidence rate ratios (IRRs) and corresponding 95% CIs. Models were adjusted for calendar year, age (categorised into 5-year age-bands), sex, socioeconomic status, and region. Negative binomial models were chosen over Poisson models to account for overdispersion in the data. Sensitivity analyses comparing Poisson and negative binomial models showed very similar results.

To characterise the co-occurrence of autoimmune diseases, we ran a series of cohort studies to calculate IRRs for the development of a second (comorbid) autoimmune disease according to disease status of a first (index) autoimmune disease. IRRs were calculated using negative binomial regression models adjusted for age, sex, and calendar year. We performed separate analyses for each pair and sequence of autoimmune diseases, following methods by Somers and colleagues.<sup>7</sup> For these analyses, time at risk started at the latest date of patient registration plus 12 months or diagnosis of the index disease, and stopped at the earliest date of the incidence of the comorbid autoimmune disease, death, the patient ceasing registration with the general practice, the practice's last collection date, or the end of the study.

Study findings are reported in accordance with the RECORD recommendations.<sup>19</sup> Statistical analyses were performed in R (version 3.6.2) and validated with SAS (version 9.4).

#### Role of the funding source

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

## Results

Between Jan 1, 2000, and Dec 31, 2019, a total of 22 009 375 individuals in the CPRD database met study population criteria, with 135 691 152 patient-years of follow-up. Among these individuals, we identified 1123789 new diagnoses of autoimmune diseases, affecting a total of 978 872 individuals. The mean age when an autoimmune disease was diagnosed was 54.0 years (SD 21.4), and 625 879 (63.9%) of these individuals were women (table).

The number of people newly diagnosed with one (or more) autoimmune diseases increased only modestly during the study period (IRR 2017–19 vs 2000–02 1.04 [95% CI 1.00–1.09]; figure 1). The number of new autoimmune disease diagnoses increased by 22% during the study period (2017–19 vs 2000–02 IRR 1.22 [1.18–1.28]), largely due to an increasing number of secondary autoimmune disease diagnoses among individuals already affected by a first autoimmune disease (ie, primary incidence only increased by 4%; figure 1). Coeliac disease, Graves' disease, and Sjogren's syndrome showed the largest increases, whereas Hashimoto's thyroiditis and pernicious anaemia declined modestly during the study period (figure 1). The observed increase in coeliac disease, Graves' disease, and Sjogren's syndrome was largely driven by a higher number of diagnoses in women than in men over time from 2000 to 2019. The increase in Graves' disease was largely driven by an increase in the number of diagnoses in very old individuals (aged  $\geq 80$  years), whereas the increase in coeliac disease was largely driven by an increase in the number of diagnoses in younger individuals (aged  $\leq 40$  years), when comparing incidence over time (appendix p 5).

Autoimmune disorders developed at any age (ie, age 0–95 years). Median age at first autoimmune disease presentation varied greatly among individual autoimmune diseases. For many conditions, incidence increased with age; this was the case for Graves' disease, pernicious anaemia, and rheumatoid arthritis. Only six conditions were commonly diagnosed before the age 5 years: Addison's disease, coeliac disease, childhood-onset type 1 diabetes, psoriasis, vitiligo, and vasculitis (largely due to Henoch–Schönlein purpura, Kawasaki disease, and glomerulonephritis; appendix p 9). For other conditions, such as multiple sclerosis, psoriasis, and systemic lupus erythematosus, the incidence peaked in middle age. Furthermore, some conditions showed a bimodal age distribution, with a peak in childhood or early adulthood and another peak later in life, which was the case for coeliac disease, inflammatory bowel disease, and vasculitis (figure 2).

Most autoimmune disorders were more common in women than in men (figure 3). Thyroid disorders, Sjögren's syndrome, lupus, and systemic sclerosis had the highest IRR in women compared with men (figure 3). Only three diseases were more common in men than in

	All patients (n=978 872)		Socioeconomic status quintile					Time period	
	Sex	Male (n=352 993)	Least deprived (n=220 047)	Most deprived (n=170 856)	2000-02 (n=141 951)	2017-19 (n=123 420)			
Mean age at diagnosis, years	Female (n=625 879)	54.4 (21.1)	53.3 (22.0)	55.5 (21.0)	51.0 (22.0)	55.7 (20.7)	52.6 (22.0)		
Sex	54-4 (21.4)	54-4 (21.1)	53.3 (22.0)	55.5 (21.0)	51.0 (22.0)	55.7 (20.7)	52.6 (22.0)		
Female	625 879 (63.9%)	NA	NA	139 694 (63.5%)	110 322 (64.6%)	95 166 (67.0%)	76 917 (62.3%)		
Male	352 993 (36.1%)	NA	NA	80 353 (36.5%)	60 534 (35.4%)	46 785 (33.0%)	46 503 (37.7%)		
Ethnicity	17 257/933 814 (1.8%)	11 732/601 805 (1.9%)	5525/322 009 (1.7%)	751/209 672 (0.4%)	7652/165 422 (4.6%)	1471/130 283 (1.1%)	2970/119 583 (2.5%)		
African or Caribbean	46 621/933 814 (5.0%)	29 458/601 805 (4.9%)	17 163/322 009 (5.2%)	6695/209 672 (3.2%)	123 757/652 165 422 (7.5%)	3686/130 283 (2.8%)	8362/119 583 (7.0%)		
Asian	45 363/933 814 (4.9%)	27 201/601 805 (4.5%)	18 162/322 009 (5.5%)	10 202/209 672 (4.9%)	79 257/652 165 422 (4.8%)	3843/130 283 (2.9%)	8267/119 583 (6.9%)		
Mixed or other*	824 573/933 814 (88.3%)	533 414/601 805 (88.6%)	291 159/322 009 (87.7%)	189 790/209 672 (91.5%)	1 374 707/652 165 422 (83.1%)	121 283/130 283 (93.1%)	99 984/119 583 (83.6%)		
White	45 058 (4.6%)	24 074 (3.8%)	20 984 (5.9%)	10 375 (5.1%)	5434 (3.2%)	11 668 (8.2%)	3837 (3.1%)		
Missing									
Socioeconomic status quintile	One	220 047 (22.5%)	80 353 (22.8%)	NA	NA	32 134 (22.6%)	28 215 (22.9%)		
Two	204 731 (20.9%)	129 945 (20.8%)	74 786 (21.2%)	NA	NA	30 146 (21.2%)	25 591 (20.7%)		
Three	197 109 (20.1%)	125 845 (20.1%)	71 264 (20.2%)	NA	NA	28 870 (20.3%)	24 498 (19.8%)		
Four	186 129 (19.0%)	120 073 (19.2%)	66 056 (18.7%)	NA	NA	26 957 (19.0%)	23 421 (19.0%)		
Five	170 856 (17.5%)	110 322 (17.6%)	60 534 (17.1%)	NA	NA	23 844 (16.8%)	21 695 (17.6%)		
Number of autoimmune disorders	One	833 157 (85.1%)	311 062 (88.1%)	187 435 (85.2%)	145 738 (85.3%)	112 615 (79.3%)	112 712 (91.3%)		
Two	124 742 (12.7%)	87 678 (14.0%)	37 064 (10.5%)	28 024 (12.7%)	21 449 (12.6%)	24 147 (17.0%)	9 698 (7.9%)		
Three or more	20 973 (2.1%)	16 106 (2.6%)	4867 (1.4%)	4588 (2.1%)	3669 (2.1%)	5189 (3.7%)	1010 (0.8%)		
BMI, kg/m <sup>2</sup>	Mean (SD)	27.8 (6.33)	27.7 (5.55)	27.1 (5.75)	28.5 (6.99)	27.3 (5.90)	28.1 (6.71)		
Missing	509 139 (52.0%)	316 940 (50.6%)	192 199 (54.4%)	120 581 (54.8%)	82 763 (48.4%)	102 926 (72.5%)	56 660 (45.9%)		
Smoking status	Current smoker	126 240/608 581 (20.7%)	77 046/391 340 (19.7%)	49 194/217 241 (22.6%)	18 463/130 792 (14.1%)	33 855/111 889 (30.3%)	10 029/40 454 (24.8%)		
Former smoker	167 829/608 581 (27.6%)	92 501/391 340 (23.6%)	75 328/217 241 (34.7%)	37 139/130 792 (28.4%)	28 250/111 889 (25.2%)	91 514/40 454 (22.6%)	23 176/77 984 (29.7%)		
Never smoker	314 512/608 581 (51.7%)	221 793/391 340 (56.7%)	92 719/217 241 (42.7%)	75 190/130 792 (57.5%)	49 784/111 889 (44.5%)	21 274/40 454 (52.6%)	40 754/77 984 (52.3%)		
Missing	370 291 (37.8%)	234 539 (37.5%)	135 752 (38.5%)	89 255 (40.6%)	58 967 (34.5%)	101 497 (71.5%)	45 436 (36.8%)		

Data are n (%), n/N (%), or mean (SD). Socioeconomic status was defined as the Index of Multiple Deprivation 2015 quintile, with one referring to the least deprived socioeconomic quintile and five to the most deprived socioeconomic quintile. For variables with missing entries, category percentages are calculated out of participants with complete data (as shown by denominators), and percentages for missing data are calculated out of total participants. NA=not applicable. \*Mixed or other is a composite category in which we included participants whose race or ethnicity is different to any of the categories already listed in this table, as well as people who are from two or more different races or ethnic backgrounds.

**Table: Baseline characteristics of patients with incident autoimmune disease from 2000 to 2019**

women, namely ankylosing spondylitis, childhood-onset type 1 diabetes, and myasthenia gravis (figure 3).

Overall, the most deprived socioeconomic groups had a higher incidence of autoimmune diseases than the least deprived socioeconomic groups (figure 4). A marked socioeconomic gradient was visible across several individual diseases, including Graves' disease, pernicious anaemia, rheumatoid arthritis, and systemic lupus erythematosus (figure 4; appendix p 4). For other diseases, such as Hashimoto's thyroiditis and inflammatory bowel disease, no difference in incidence was observed among socioeconomic groups despite relatively large numbers of cases; for coeliac disease and polymyalgia rheumatica, disease incidence was highest in the least deprived group (figure 4; appendix p 4).

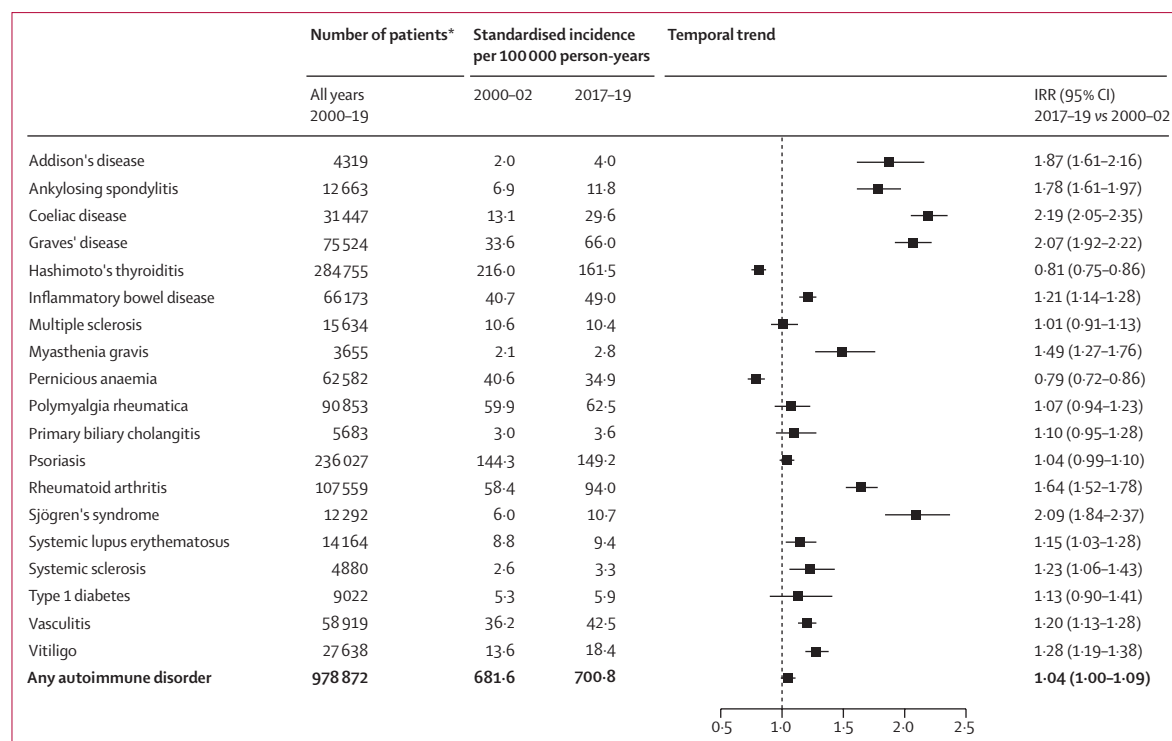
Overall, variation by geographical region was modest. However, polymyalgia rheumatica, type 1 diabetes, and coeliac disease were considerably more common outside of London, and pernicious anaemia was most common in northern regions of England (appendix p 6). Sjögren's syndrome, lupus, and vitiligo had lower incidence rates outside of London (appendix p 6).

Most autoimmune diseases were diagnosed throughout the year with no significant differences between winter and summer months (appendix p 7). Seasonal variation was observed only for type 1 diabetes, which was more commonly diagnosed during the winter months

(January to March) compared with the summer months (June to August), and for vitiligo, which was more commonly diagnosed during the summer months compared with the winter months (appendix p 7).

Autoimmune disorders were commonly associated with each other. Increased risk of developing a second autoimmune disorder was seen across many autoimmune diseases, but orders of magnitude differed widely between diseases (figure 5). Associations were generally highest among connective tissue diseases, particularly between Sjögren's syndrome, systemic lupus erythematosus, and systemic sclerosis (figure 5). Individuals with childhood-onset type 1 diabetes also had significantly higher rates of Addison's disease (IRR 26.5 [95% CI 17.3–40.7]), coeliac disease (28.4 [25.2–32.0]), and thyroid disease (Hashimoto's thyroiditis 13.3 [11.8–14.9] and Graves' disease 6.7 [5.1–8.8]). More generally, Addison's disease occurred at a considerably higher incidence among people with pre-existing autoimmune disease than in the general population (figure 5). Multiple sclerosis stood out as having low rates of co-occurrence with other autoimmune diseases and even showed an inverse association with some autoimmune disorders, but this was only significant for vitiligo (figure 5; appendix p 10).

The combined prevalence of the 19 autoimmune disorders investigated in this study, standardised by age



**Figure 1: Incidence of autoimmune disorders over time from 2000 to 2019**

Incidence rates are per 100 000 person-years at risk and are age and sex standardised to the 2013 European Standard Population. Any autoimmune disorder refers to the primary incidence of the 19 autoimmune disorders investigated in this study (ie, the number of patients first diagnosed with one autoimmune disease). IRR=incidence rate ratio. \*The number of patients newly diagnosed with autoimmune disease during the study period.

and sex, was 10·2% (N=1912 200, 13·1% for women [N=1243 936] and 7·4% for men [N=668 264]). Prevalence increased over time from 7·7% (N=697 236) in 2000–02 to 11·0% (N=1050 995) in 2017–19 (RR 2017–19 vs 2000–02 1·41 [95% CI 1·37–1·44]).

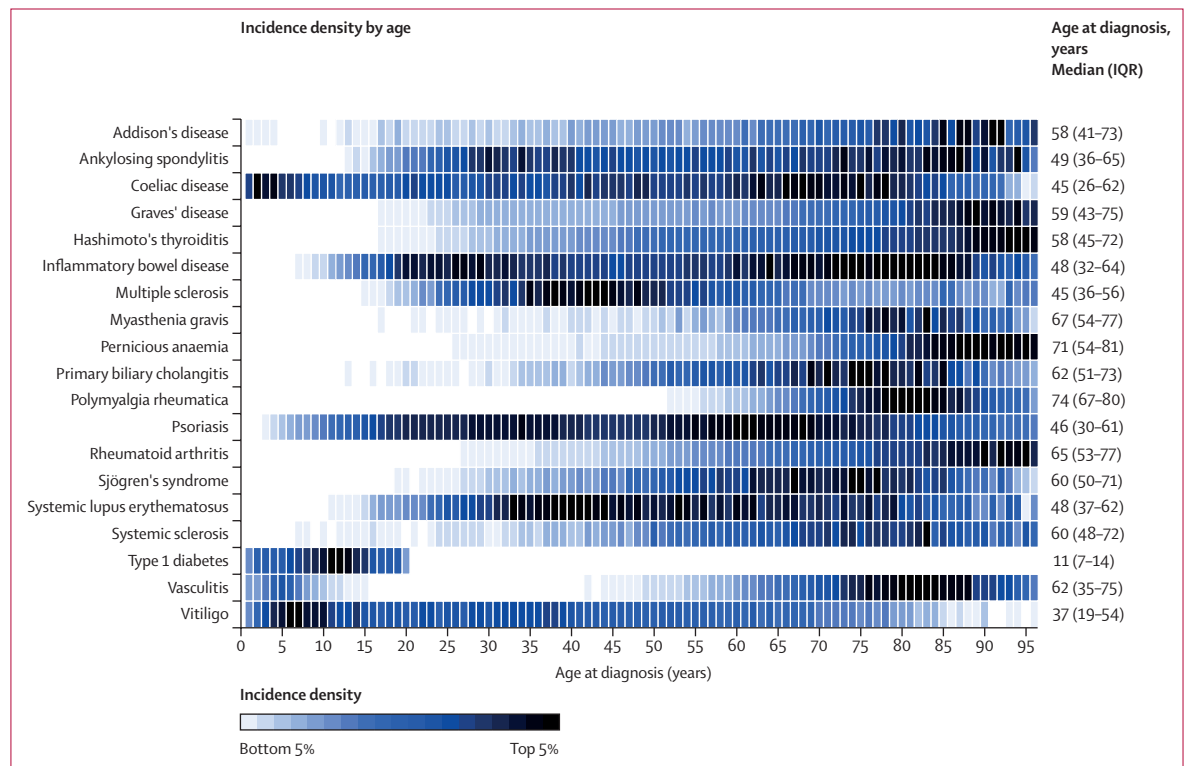
**Discussion**

Our large-scale, population-based study provides several novel insights into the burden of autoimmune disorders, its variation over time, and its variation by individual diseases and patient subgroups of age, sex, and socioeconomic status. Our findings support and extend evidence from previous studies showing an increasing incidence of several autoimmune disorders,<sup>20</sup> and show that the increase was particularly pronounced for Graves’ disease, coeliac disease, and rheumatic disorders. Our results reflect disease incidence based on diagnostic criteria, screening practices, availability, and accuracy of diagnostic tests in place at that precise time and hence must be interpreted within this context. As such and in consideration of the increasing awareness for some of these conditions, improved coding practices, and earlier recognition of these conditions over the past two decades, the observed increase remains modest.

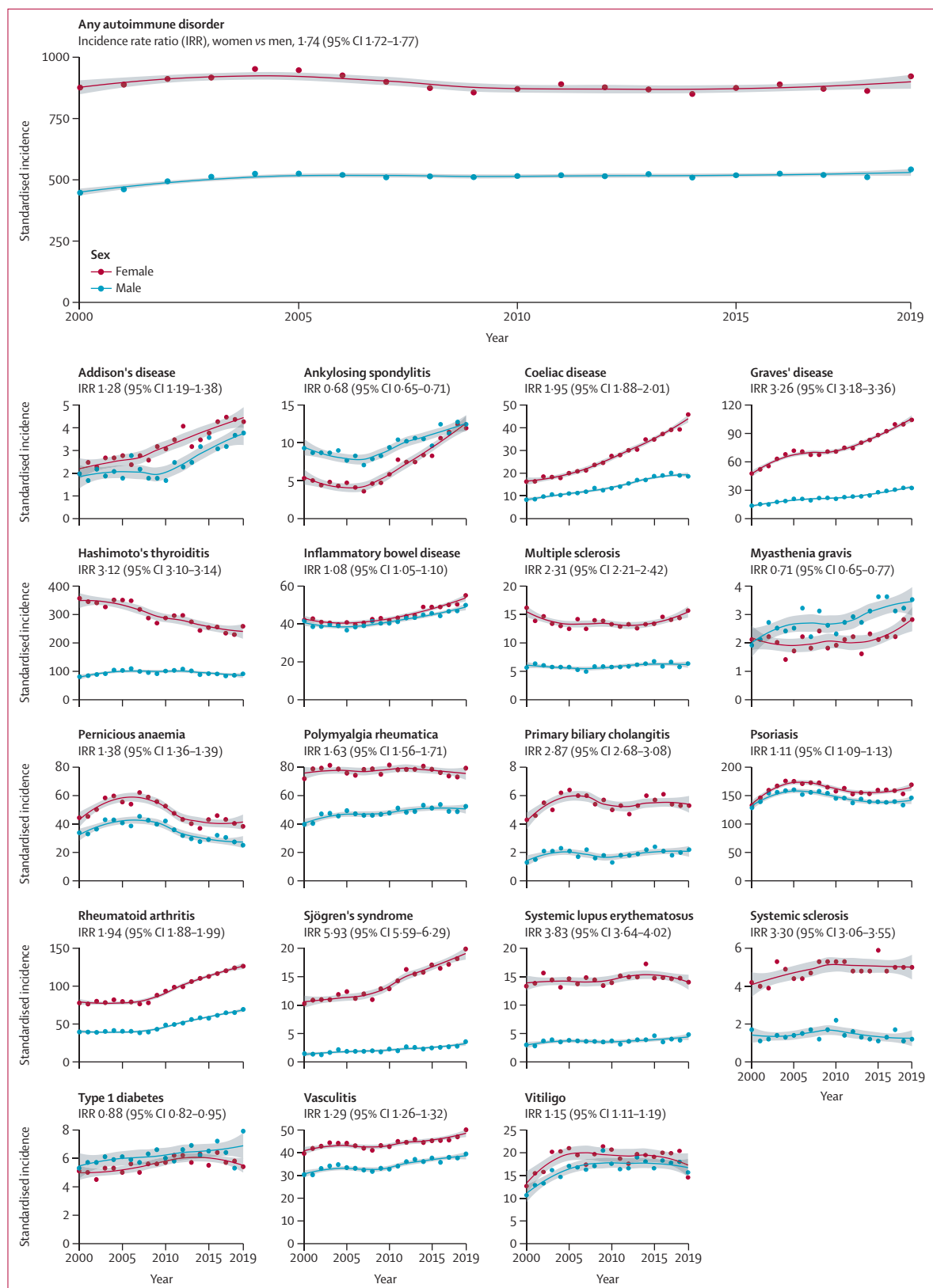
The epidemiology of type 1 diabetes is perhaps the best studied of all autoimmune disorders. Previous studies had

reported varying estimates and trends over time,<sup>4,5</sup> and several surveys from Scandinavian countries have reported steep increases of the incidence of type 1 diabetes since the 1950s with a plateau since the mid-2000s.<sup>21,22</sup> In our study, we observed only a modest increase in the incidence of type 1 diabetes over the past two decades. Overall estimates were similar to estimates from a simulation study on the incidence of type 1 diabetes<sup>23</sup> in western Europe and similar to those reported by the International Diabetes Federation Atlas for the UK,<sup>24,25</sup> but were lower than those reported in northern European countries.<sup>21,26</sup> Another key finding was the reduction in Hashimoto’s thyroiditis over time, which could be due to more careful initiation of levothyroxine in older people with subclinical hypothyroidism after trials showing little benefit of the drug in this population.<sup>27,28</sup> Pernicious anaemia also showed an apparent decline in incidence over time, a decline that appears to coincide with increased use of dietary supplements over the same period, and possibly a more widespread recognition of other causes of vitamin B12 deficiency such as *Helicobacter pylori* infection, although no causal inference can be made from our data.<sup>29</sup>

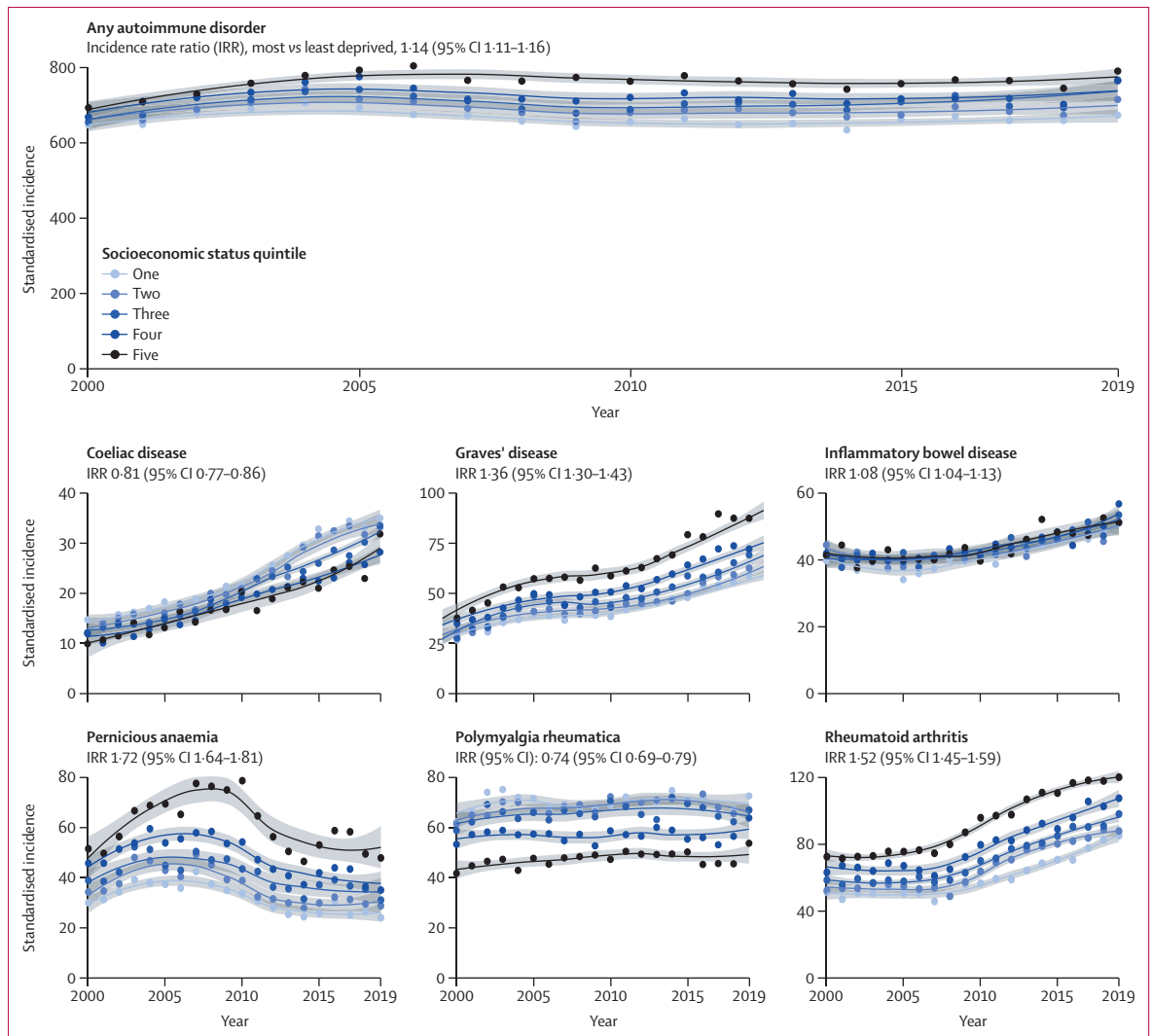
The observed increase in incidence of rheumatic diseases will probably have important implications for health services and the substantial medication expenditures linked to biologics. Improved coding practices during the



**Figure 2: Incidence of autoimmune disorders by age**  
 Incidence rates were calculated per 1-year age band and divided into a colour-gradient of 20 quantiles to reflect incidence density by age. The definition of type 1 diabetes used in this study refers to childhood-onset type 1 diabetes (ie, individuals aged <20 years at the time of diagnosis).



**Figure 3: Incidence of autoimmune disorders by sex and over time**  
Age-standardised incidence rates by sex. Any autoimmune disorder refers to the primary incidence of the 19 autoimmune disorders investigated in this study. The definition of type 1 diabetes used in this study refers to childhood-onset type 1 diabetes. Denominator populations include all age groups. Yearly incidence estimates were smoothed using locally estimated scatterplot smoothing regression lines. IRRs are for women compared with men. IRR=incidence rate ratio.



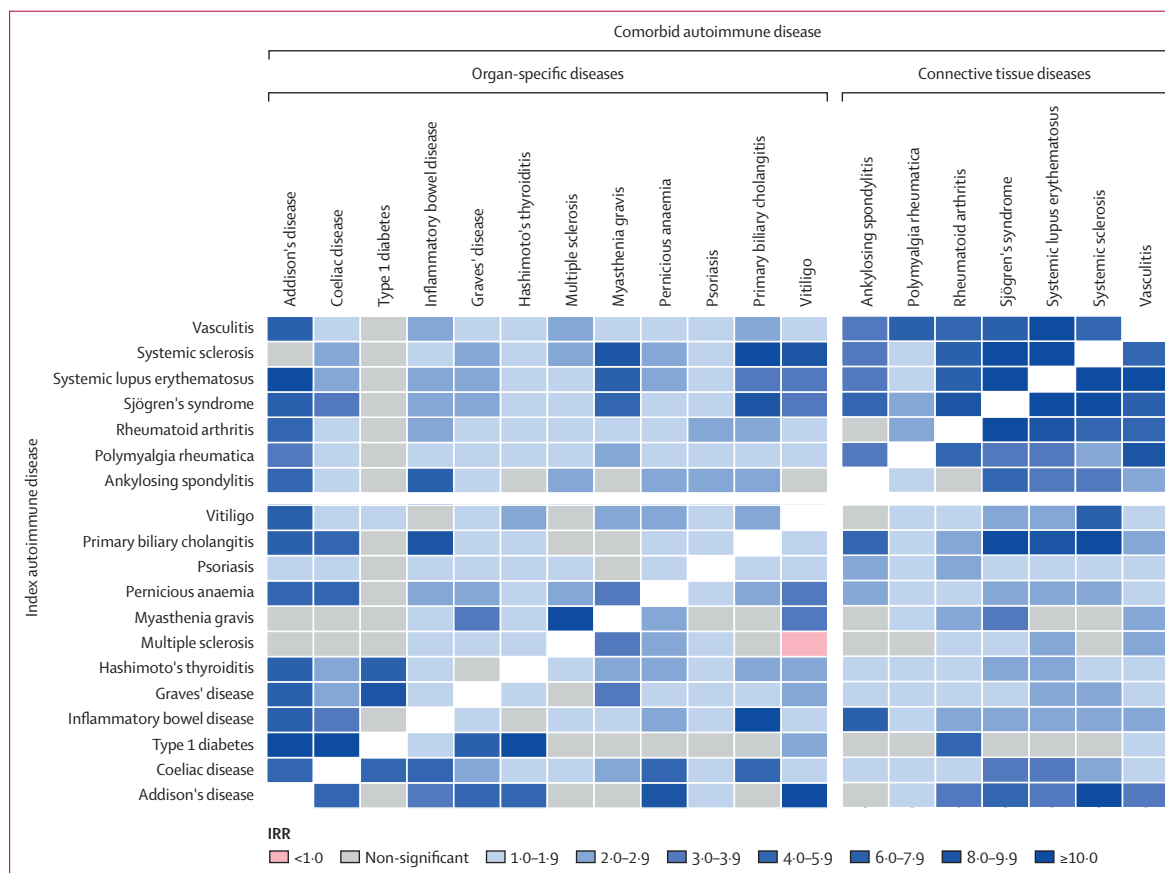
**Figure 4: Incidence of any and selected autoimmune disorders by socioeconomic quintile**

Age and sex standardised incidence rates by socioeconomic status quintile (Index of Multiple Deprivation 2015) for specific autoimmune disorders (specific examples chosen to reflect differences in socioeconomic status gradients among autoimmune disease incidence rates). Any autoimmune disorder refers to the primary incidence of the 19 autoimmune disorders investigated in this study. Yearly incidence estimates were smoothed using locally estimated scatterplot smoothing regression lines. IRRs are for the people in the most deprived socioeconomic quintile (five) compared with those in the least deprived (one) socioeconomic quintile. Individual plots for each of the diseases investigated are presented in the appendix (p 4). IRR=incidence rate ratio.

study period, the 2013 introduction of a quality audit in primary care (the so-called Quality and Outcomes Framework) rewarding general practitioners for maintaining a register and evaluating cardiovascular or fracture risks in patients with rheumatoid arthritis,<sup>30</sup> and the novel classification criteria for ankylosing spondylitis, are all likely to have contributed to the observed increase in incidence. The increase in incidence of axial spondyloarthritis in women starting around 2009 following the publication of classification criteria by the Assessment of Spondyloarthritis International Society<sup>31</sup>—which introduced the concept of non-radiographic axial spondyloarthritis—is consistent with other studies indicating that although ankylosing spondylitis is more

predominant in men than in women, non-radiographic axial spondyloarthritis is similarly common in women and men.<sup>32,33</sup>

Our stratified analyses by socioeconomic status, region (in England), and seasonal variations in disease incidence provide further insights into the possible role of environmental factors in the development of autoimmune diseases. Four diseases (ie, Graves' disease, pernicious anaemia, rheumatoid arthritis, and systemic lupus erythematosus) showed a clear socioeconomic gradient; individuals in the most deprived group were up to 70% more likely to develop the disease than the least deprived group. Such socioeconomic disparities could indicate that diet, smoking, obesity, air pollution, or other currently



**Figure 5:** IRRs for development of comorbid autoimmune disease among index populations with autoimmune disease compared with the general population. Co-occurrence of organ-specific diseases and connective tissue diseases. IRRs were calculated for development of a second (comorbid) autoimmune disease among populations with pre-existing autoimmune (index) disease compared with the general population using negative binomial regression models adjusted for age and sex. Type 1 diabetes refers to childhood-onset type 1 diabetes (ie, people aged <20 years at the time of diagnosis). IRR=incidence rate ratio.

unrecognised environmental exposures might play a role in the development of these diseases. Two conditions (ie, coeliac disease and polymyalgia rheumatica) presented an inverse socioeconomic gradient, a phenomenon rarely observed in public health research, which could be linked to increased awareness and testing for these diseases in more affluent populations or indeed lifestyle differences.

There were not many seasonal variations in the incidences of autoimmune diseases. Vitiligo was more commonly diagnosed in the summer months than in the winter months, perhaps due to increased visibility of depigmented skin areas in summer months. Furthermore, type 1 diabetes was more commonly diagnosed during the winter months and outside of London, a finding that is compatible with hypotheses of viral triggers, diet, higher bodyweight, or ethnicity playing a role in the disease's pathogenesis.<sup>34-36</sup> Other regional variations, such as coeliac disease being more common outside of London, remain unexplained for now. Although numerous reports have linked smoking to the incidence of some autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, or psoriasis,<sup>37</sup> we did not observe a decline in the incidence

of these diseases despite considerable reduction in smoking prevalence over the same time period (ie, 2000–02 vs 2017–19).<sup>38</sup> The absence of an observed decline in disease incidence corresponding with the reduction in smoking prevalence could be due to a parallel increase in other risk factors (eg, obesity) over the same period, or confounding via socioeconomic status, or it could be due to currently unknown reasons.

Furthermore, co-occurrences of autoimmune diseases provide valuable insights into possible common aetiology across some of these conditions. For example, we found high rates of co-occurrence among a range of connective tissue diseases, particularly Sjögren's syndrome, systemic lupus erythematosus, and systemic sclerosis, regardless of diagnostic sequence and after accounting for age and sex. Polymyalgia rheumatica did not have much association with other connective tissue disorders, except for vasculitis. Myasthenia gravis and multiple sclerosis also tended to co-occur. However, the association was weak, and given the nature of our data, which is based on routine clinical practice data, we cannot rule out the possibility of inaccurate diagnoses or coding.

Our study further provides robust evidence for an increased incidence of a range of autoimmune diseases, particularly coeliac disease and thyroid diseases, among individuals with childhood-onset type 1 diabetes. Such observations have been reported before and might suggest overlapping genetic or environmental risk factors, or be due to people with a first autoimmune disease being more likely to undergo screening for these conditions.<sup>39</sup> Although we did not observe associations between childhood-onset diabetes and diseases typically occurring in older age groups, our data were bounded by follow-up duration, so we cannot exclude that such associations might exist. Similarly, in our study, psoriasis presented little co-occurrence with autoimmune diseases, possibly because of the large proportion of mild cases typically observed among cohorts based on primary care data.<sup>40</sup>

Another consideration is whether treatment of an index autoimmune disease affects the risk of developing a comorbid autoimmune disease. Although non-specific immunosuppressive treatments could in theory decrease risk of a comorbid autoimmune disease, targeted therapies could have differential effects. For example, an intriguing finding was the high incidence of Addison's disease after almost every other autoimmune disorder, which could perhaps be related to glucocorticoid-induced adrenal insufficiency, which is typically recorded as Addison's disease in the UK.<sup>41</sup> Such a mechanism might also explain the higher rates of cardiovascular diseases observed in people with Addison's disease in this same cohort.<sup>42</sup> Nevertheless, given the relatively small number of people with Addison's disease, these results must be interpreted with caution. Overall, this research shows that some autoimmune diseases co-occur at a rate greater than expected by chance or surveillance bias alone, but it reveals that this phenomenon is not generalised across all autoimmune diseases.

A major strength of this study is the selection and use of a statistically powerful data source with over 130 million person-years of data to investigate the incidence, prevalence, and co-occurrence of autoimmune disorders. The very large size of our cohort allowed us to perform detailed stratified analyses, over a broad spectrum of conditions. Furthermore, we were able to examine the influence of age, sex, and socioeconomic status on autoimmune diseases, and observe trends of these diseases over 20 years. The use of routinely reported diagnoses also captures the burden of disease as experienced by physicians and health services, and probably increases the generalisability of findings. One of the key limitations of our study was the low diversity in ethnic backgrounds in our cohort. Unfortunately, there was also a marked scarcity of data or high amount of missing data on additional variables that are relevant to autoimmune disease pathogenesis such as smoking, BMI, and blood biomarkers (eg, vitamin D deficiency). The non-randomised design of our study further meant that we were unable to account for the effect of drug

therapy such as antirheumatic drugs, steroids, or biologics on the incidence of a second autoimmune disease. Research using electronic health records is also reliant on the accuracy of clinical coding performed during consultations and hospital admissions. The validity of diagnoses underlying our study has been carefully assessed and was considered appropriate in light of over 200 studies that have investigated the validity of diagnoses recorded in CPRD, and which reported an average positive predictive value of about 90% for a broad range of conditions.<sup>43</sup> Studies from 2011 and 2022 have examined several diseases included in our population-based study, and have shown that algorithms based on diagnostic codes perform well at identifying patients with these conditions in primary care records.<sup>33,40</sup> Generally, observed age distributions were consistent with previously published studies and add to the validity of our approach. Nevertheless, our results—particularly disease trends over time and co-occurrence of diseases—must be interpreted within the context and limitations of routinely collected health records data and the possibility that some amount of miscoding is present. Furthermore, a large quantity of tests and subgroup analyses within one study must also be interpreted with adequate caution.

Our findings present an important new piece in the puzzle of autoimmune disease aetiology, a group of conditions that are apparent in nearly 10% of the population, and that consume considerable health resources. The socioeconomic, seasonal, and regional disparities observed among several autoimmune disorders suggest the involvement of environmental factors in the pathogenesis of specific autoimmune diseases. The interrelations between many autoimmune diseases further suggest a shared pathogenesis, particularly among connective tissue diseases and between diabetes, coeliac disease, and thyroid diseases. Currently, the exact causes of many of the autoimmune diseases included in our study remain unknown and require further research.

#### Contributors

NC, GC, and JM conceived and designed the study. NC, GM, and GV designed the statistical analysis plan and NC performed the statistical analysis. All authors contributed to interpreting the results, drafting the manuscript, and the revisions. NC and GC had full access to the data in the study and had final responsibility for the decision to submit for publication. NC, GM, GV, and JYV had permission to access the data and NC and GM verified the data (CPRD requests that access to data is given only as absolutely necessary). All authors gave final approval of the version to be published, and accept responsibility to submit the manuscript for publication.

#### Declaration of interests

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Clyde Health Board; and stock or stock options with Evelo, Compugen, and Cabaletta. JJVM has received funding to his institution from Amgen and Cytokinetics for his participation in the Steering Committee for the ATOMIC-HF, COSMIC-HF, and GALACTIC-HF trials and meetings and other activities related to these trials; has received payments through Glasgow University from work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, Dal-Cor, GlaxoSmithKline, Ionis, KBP Biosciences, Novartis, Pfizer, and Theracos; and has received personal lecture fees from the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Alkem Metabolics, Eris Lifesciences, Lupin, ProAdWise Communications, Servier Director, and Global Clinical Trial Partners. NS declares consulting fees or speaker honoraria, or both, from Abbott Laboratories, Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi; and grant support paid to his university from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics. KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands and the NIHR Leicester Biomedical Research Centre. KK has also acted as a consultant, speaker, or received grants for investigator-initiated studies for AstraZeneca, Abbott, Amgen, Napp, Bayer, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, Oramed Pharmaceuticals, and Applied Therapeutics. PNT declares personal consulting fees from Immunovant and leadership roles in the Society for Endocrinology and British Thyroid Association. All other authors declare no competing interests. The views expressed are those of the authors and not necessarily those of the funder.

#### Data sharing

Access to CPRD data is conditional on a license agreement and protocol approval process that is overseen by CPRD's Independent Scientific Advisory Committee. A guide to access is provided on the CPRD website (<https://cprd.com/data-access>).

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