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DOI: 10.1186/s12916-023-03049-5

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Document Version Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Syed, U, Súbramanian, A, Wraith, D, Lord, J, McGee, K, Gokhale, K, Nirantharakumar, K & Haroon, S 2023, 'Incidence of immune-mediated inflammatory diseases following COVID-19: a matched cohort study in UK primary care', *BMC Medicine*, vol. 21, no. 1, 363. https://doi.org/10.1186/s12916-023-03049-5

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# **RESEARCH ARTICLE**



# Incidence of immune-mediated inflammatory diseases following COVID-19: a matched cohort study in UK primary care

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# Abstract

**Background** Some patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) go on to experience post-COVID-19 condition or long COVID. Preliminary findings have given rise to the theory that long COVID may be due in part to a deranged immune response. In this study, we assess whether there is an association between SARS-CoV-2 infection and the incidence of immune-mediated inflammatory diseases (IMIDs).

**Methods** Matched cohort study using primary care electronic health record data from the Clinical Practice Research Datalink Aurum database. The exposed cohort included 458,147 adults aged 18 years and older with a confirmed SARS-CoV-2 infection and no prior diagnosis of IMIDs. They were matched on age, sex, and general practice to 1,818,929 adults with no diagnosis of confirmed or suspected SARS-CoV-2 infection. The primary outcome was a composite of any of the following IMIDs: autoimmune thyroiditis, coeliac disease, inflammatory bowel disease (IBD), myasthenia gravis, pernicious anaemia, psoriasis, rheumatoid arthritis (RA), Sjogren's syndrome, systemic lupus erythematosus (SLE), type 1 diabetes mellitus (T1DM), and vitiligo. The secondary outcomes were each of these conditions separately. Cox proportional hazard models were used to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for the primary and secondary outcomes, adjusting for age, sex, ethnic group, smoking status, body mass index, relevant infections, and medications.

**Results** Six hundred and nighty six (0.15%) and 2230 (0.12%) patients in the exposed and unexposed cohort developed an IMID during the follow-up period over 0.29 person-years, giving a crude incidence rate of 4.59 and 3.65 per 1000 person-years, respectively. Patients in the exposed cohort had a 22% increased risk of developing an IMID, compared to the unexposed cohort (aHR 1.22, 95% CI 1.12 to 1.33). The incidence of three IMIDs was significantly associated with SARS-CoV-2 infection. These were T1DM (aHR 1.56, 1.09 to 2.23), IBD (aHR 1.36, 1.18 to 1.56), and psoriasis (1.23, 1.05 to 1.42).

**Conclusions** SARS-CoV-2 was associated with an increased incidence of IMIDs including T1DM, IBD and psoriasis. However, these findings could be potentially due to ascertainment bias. Further research is needed to replicate these findings in other populations and to measure autoantibody profiles in cohorts of individuals with COVID-19.

Keywords COVID-19, SARS-CoV-2, Cohort study, Immune-mediated inflammatory diseases

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#### Summary box

What is already known on this topic

- A subsection of the population infected with SARS-CoV-2 go on to experience post-COVID-19 condition or long COVID.
- Preliminary findings, such as case reports of post-COVID-19 immune-mediated inflammatory diseases, increased autoantibodies in COVID-19 patients, and molecular mimicry of the SARS-CoV-2 virus have given rise to the theory that long COVID may be due in part to a deranged immune response.

What this study adds

- SARS-CoV-2 infection was associated with a 22% relative increase in the risk of developing certain immune-mediated inflammatory diseases, including type 1 diabetes mellitus, inflammatory bowel disease, and psoriasis.
- These findings support the hypothesis that a subgroup of long COVID may be caused by immunemediated inflammatory mechanisms.

### Background

Emerging in late 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus causing the coronavirus disease-2019 (COVID-19) pandemic, as of March 2023, resulted in over 6 million deaths worldwide [1, 2]. The acute presentation can range from being completely asymptomatic to sepsis, organ failure and death [3]. The effects of COVID-19 are not limited solely to acute infection but have also manifested in a series of post-acute sequelae commonly referred to as long COVID or post-COVID-19 condition [4, 5].

The World Health Organisation define this as symptoms occurring in people with a history of probable or confirmed SARS-CoV-2 infection three months after the onset of COVID-19 that cannot be explained by an alternative diagnosis [5, 6]. With over a third of people with COVID-19 reporting persistent symptoms and over 1.7 million UK residents self-reporting the condition, long COVID is emerging as one of the major public health challenges of the modern era [7, 8]. Despite this, the pathogenesis behind the condition remains unclear [4, 9].

One theory is that SARS-CoV-2 infection causes an inappropriate immune response that leads to the varied symptoms of long COVID. This arose from evidence of a marked and persistent increase in autoantibodies in patients with COVID-19 compared to uninfected controls and high rates of patients hospitalised with

COVID-19 being transiently positive for anti-phospholipid (aPL) antibodies [10, 11].

Some of these autoantibodies were also deemed as potential risk factors for long COVID [12]. Several systematic reviews have collated case reports of patients with a history of COVID-19 who have experienced deranged immune manifestations. Tang et al. found 187 reports and Novelli et al. found 382 reports of autoimmune-like phenomena following COVID-19 [13, 14]. Among those with a history of COVID-19, one review reported thyroid dysfunction in up to 20% of patients, which is linked with B and T-cell autoimmunity [15].

Autoimmunity may be due to the degree of homology existing between some human self-proteins and components of SARS-CoV-2, a phenomenon termed molecular mimicry [16]. Molecular mimicry combined with the immune system dysregulation that occurs during SARS-CoV-2 infection may be the mechanism driving the development of immune-mediated inflammatory diseases. Alternatively, the reaction could arise from tissue damage and the release of autoantigens as a result of SARS-CoV-2 infection.

This preliminary evidence has been derived largely from case series, case reports, small cohort studies, or systematic reviews of these study types, which are weak study designs for ascertaining causal inference. Stronger study designs are needed that include appropriate control groups and large sample sizes. Furthermore, the data were drawn largely from patients with moderate or severe COVID-19, which underrepresents the mild or asymptomatic cases that make up most SARS-CoV-2 infections and that can also go on to develop long COVID [17]. To address these limitations, we conducted a retrospective matched cohort study using data from a large primary care database to assess the incidence of immune-mediated inflammatory diseases (IMIDs) in patients with SARS-CoV-2 infection compared to matched individuals with no record of SARS-CoV-2 infection.

### Methods

### Study design and data source

A retrospective cohort study was undertaken using data extracted from the Clinical Practice Research Datalink (CPRD) Aurum database between the 31st of January 2020 and the 30th of June 2021. The CPRD Aurum database consists of routinely collected, pseudo-anonymised data from general practices across England [18]. The data were extracted using the data extraction for epidemiological research (DExtER) tool, which facilitates extraction based on predefined parameters [19].

#### **Study population**

Patients were eligible to enter the study if they were at least 18 years old at the study start date, had no prior history of the IMIDs included in the primary outcome (see below), had an acceptable patient flag indicating provision of good quality data, and if they were registered with an eligible general practice for at least 12 months to allow sufficient time for recording baseline information.

# Exposure

All patients with a SNOMED-CT coded diagnosis of either a positive reverse transcriptase polymerase chain reaction (RT-PCR) or lateral flow antigen test for SARS-CoV-2 were included in the exposed cohort, and the date of coded diagnosis was assigned as the index date. Patients with a suspected COVID-19 diagnosis were not included to increase the specificity of the exposure definition. For each exposed patient, up to four patients were selected who did not have a coded record of a positive RT-PCR or lateral flow antigen test, or a diagnosis of suspected or confirmed diagnosis of COVID-19, and were matched on age, sex and registered general practice. This made up the unexposed cohort. The same index date of the exposed patients was assigned to the corresponding matched unexposed patients to avoid immortal time bias [20]. Data from the COVID-19 Second Generation Surveillance System was not used for this study as it comprised of data from swab testing in Public Health England (PHE) labs and NHS hospitals primarily for hospitalised patients and healthcare workers as opposed to data from the wider population which was required for this study.

# Outcomes

The primary outcome was a composite of the incidence of any of the following IMIDS: autoimmune thyroiditis, coeliac disease, inflammatory bowel disease (IBD), myasthenia gravis, pernicious anaemia, psoriasis, rheumatoid arthritis (RA), Sjogren's syndrome, systemic lupus erythematosus (SLE), type 1 diabetes mellitus (T1DM), and vitiligo. These conditions were selected as they cover a range of different systems and constitute many of the most prevalent IMIDs in the UK. The secondary outcomes were the individual diseases included in the primary outcome, to discern which of these IMIDs, if any, had the strongest association with SARS-CoV-2 infection. SNOMED-CT code lists used for the ascertainment of each IMID, as well as the exposure codes, are given at https://github.com/Umer-Syed/COVIDAutoimmune. In light of the CPRD policy on data governance, we have not reported outcomes that had below five events due to disclosure risk.

### Follow-up period

Participants were followed up from the index date to the end of the follow-up. The end of follow-up was defined as the earliest of any of the following: a coded diagnosis of an IMID, date of death, study end date (30 June 2021), date of practice de-registration, and date of the last practice contribution to the CPRD Aurum database.

#### Covariates

Age, sex, body mass index (BMI), smoking status, ethnicity, previous exposure to relevant viral infections (Epstein-Barr virus (EBV), human cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), human T lymphotropic virus type 1 (HTLV-1), hepatitis C virus (HCV), influenza A virus, and parvovirus B19), and previous prescriptions of selected medications (procainamide, hydralazine, quinidine, and isoniazid) were included as potential confounders. Previous studies found these variables to be associated with at least one of the outcome IMIDs and were thus adjusted for in the analysis [21–33].

Age was divided into the following bands: 18 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and  $\geq$  70 years. Ethnicity was identified through SNOMED CT codes and was classified into the following groups: white, South Asian, black, mixed ethnicity and other. BMI was divided in accordance with the WHO classification: underweight (body mass index (BMI) < 18.5 kg/m<sup>2</sup>), normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25–29.9 kg/m<sup>2</sup>) and obese ( $\geq$  30 kg/m<sup>2</sup>) [34]. Smoking status was categorised as current smoker, ex-smoker and never smoked. A separate 'data missing' category was used where data were missing for ethnicity, smoking status, and BMI.

#### Statistical analysis

Baseline characteristics of patients stratified by their exposure status were summarised using simple descriptive statistics. The number and percentage of each of the outcome events for the unexposed and exposed cohorts were reported and the crude incidence rates per 1000 person-years were calculated. Cox proportional hazards regression models were used to estimate the unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CI), for each of the outcomes among patients in the exposed and unexposed cohorts. P-values below 0.05 were considered statistically significant. In order to ensure our analysis was valid, a calculation to determine the Schoenfeld residual was undertaken. If this test yielded a value of < 0.05, then the data was not normally distributed and thus the proportional hazard assumption would not be met. All

analyses were conducted using Stata Version 17, the do-file for this is given at https://github.com/Umer-Syed/COVIDAutoimmune.

# Results

# Study population

We identified 458,147 patients with confirmed SARS-CoV-2 infection and matched them to 1,818,929 patients who lacked a confirmed or suspected diagnosis of COVID-19. Table 1 shows the baseline characteristics of patients in both cohorts. The mean age was 43.6 years (SD 17.1) in the exposed cohort and 42.8 (SD 18.0) in the unexposed cohort. Both groups had slightly more females than males (54.7% versus 45.3%, respectively). A slightly larger proportion of the exposed cohort were of white and South Asian ethnicity compared to the unexposed group (64.4% versus 59.4%, and 12.2% versus 10.6%, respectively). However, the unexposed cohort had a slightly higher amount of missing ethnicity data (21.6%) versus 16.2%, respectively). The mean BMI was similar between groups but there were slightly more current smokers in the unexposed cohort (26.5% versus 22.1%, respectively). Exposure to the selected infections and medications was similar between both groups.

# **Primary analysis**

Six hundred ninety-six (0.15%) patients in the exposed cohort developed the primary outcome compared to 2230 (0.12%) within the unexposed cohort. The median (interquartile range [IQR]) follow-up was 0.29 years (0.24-0.42) for both groups. The results of the primary analysis are reported in Table 2 and Fig. 1. The crude incidence rate (IR) per 1000 person-years was higher for the exposed cohort than the unexposed cohort (4.59 versus 3.65 per 1000 person-years, respectively). This yielded a crude hazard ratio of 1.26 (95% CI 1.16-1.37) for the composite primary outcome. When adjusted for pre-selected covariates, the HR slightly reduced to 1.22 (1.12–1.33) but remained statistically significant. The proportional hazard assumption was met based on Schoenfeld residuals for the composite outcome. Furthermore, a matched analysis yielded a hazard ratio of 1.25 (95% CI 1.15-1.36). Characteristics of patients stratified by their primary outcome status have been tabulated in Additional file 1: Supplementary Table 2.

# Secondary analysis

Table 3 and Fig. 1 report the results for each individual IMID as separate outcomes. Of the eleven conditions, SARS-CoV-2 infection was significantly associated with an increased incidence of T1DM, IBD and psoriasis. T1DM was 56% more likely to occur in the exposed cohort compared to the unexposed cohort (aHR 1.56,

95% CI 1.09 to 2.23). IBD was 36% more likely to occur in the exposed cohort compared to the unexposed cohort (aHR 1.36, 95% CI 1.18 to 1.56). This was the most common IMID to be diagnosed during the study period (39.6% of all IMIDs diagnosed in the exposed cohort and 36.6% in the unexposed cohort). Psoriasis was 23% more likely to occur in the exposed cohort compared to the unexposed cohort (1.23, 1.05 to 1.42) and was the second most diagnosed IMID, representing more than 30% of all new diagnoses of IMIDs in both cohorts.

# Discussion

# **Main findings**

Exposure to SARS-CoV-2 infection was associated with a 22% relative increase in the incidence of any of the eleven IMIDs considered in our study compared to a matched unexposed group during the same period. This was after adjustment for several important confounding factors and during a relatively short period of follow-up. We also found that this association was specific to an increased incidence of T1DM, inflammatory bowel disease, and psoriasis in the SARS-CoV-2 infected cohort.

#### Comparison with existing literature

The relatively high incidence of psoriasis in the SARS-CoV-2 infected cohort is supported by other reports from the literature which found increased cases of psoriasis, and flares of existing disease, following COVID-19 [13]. Evidence on the incidence of IBD following COVID-19 is scarcer, although ulcerative colitis has been reported to develop post-infection [13]. A systematic review on T1DM and COVID-19 noted that between 1.77 and 15.6% of newly diagnosed patients, depending on the study, had preceding COVID-19 [35].

SARS-CoV-2 may be associated with IMIDs due to several putative mechanisms that result in the release of autoantibodies following infection. All three conditions that were found to have a significantly increased incidence following SARS-CoV-2 infection in our study have at least a limited association with autoantibodies. T1DM is associated with islet cells and other autoantibodies, psoriasis is linked with anti-nuclear antibodies (ANAs) and inflammatory bowel disease has a limited association with pancreatic autoantibodies (PAB) [36–38]. The reason for the increased incidence of these conditions following SARS-CoV-2 infection is unclear as they are not typically the most strongly associated with the presence of autoantibodies. This requires further exploration in future mechanistic studies.

# Strengths and limitations

A large sample size was included, which provided sufficient statistical power to assess for differences in the

Characteristics	Exposed cohort ( <i>n</i> = 458,147)	Unexposed cohort ( <i>n</i> = 1,818.929)
		( 1,010,727)
Male	207.514 (45.3)	823,988 (45,3)
Female	250,633 (54.7)	994.941 (54.7)
Age (vears)		<i>y y y y y y y y y y</i>
Mean (SD)	43.6 (17.1)	42.8 (18.0)
Age categories, n (%)		
18–29	113,618 (24.8)	478,811 (26.3)
30–39	94,499 (20.6)	377,117 (20.7)
40–49	87,707 (19.1)	348,335 (19.2)
50–59	84,454 (18.4)	327,230 (18.0)
60–69	41.841 (9.1)	153,227 (8.4)
> 70	36,028 (7.9)	134,209 (7.4)
White	295,067 (64.4)	1,079,656 (59.4)
South Asian	55,792 (12.2)	192,600 (10.6)
Black	19,226 (4.2)	86,040 (4.7)
Mixed ethnicity	7066 (1.5)	34,134 (1.9)
Other	6614 (1.4)	33,873 (1.9)
Missing	74,382 (16.2)	392,626 (21.6)
BMI		
Mean (SD)	27.6 (6.3)	26.8 (6.1)
Median (IQR)	26.7 (23.3–30.9)	25.8 (22.5–29.8)
BMI categories, n (%)		
Underweight (< 18.5 kg/m <sup>2</sup> )	12,038 (2.6)	59,644 (3.3)
Normal weight (18.5–25 kg/m <sup>2</sup> )	136,480 (29.8)	594,657 (32.7)
Overweight (25–30 kg/m <sup>2</sup> )	131,076 (28.6)	473,031 (26.0)
Obese (> 30 kg/m <sup>2</sup> )	116,836 (25.5)	366,198 (20.1)
Missing	61,717 (13.5)	325,379 (17.9)
Smoking status, n (%)		
Neversmoked	168,415 (36.8)	657,775 (36.2)
Ex-smoker	167,507 (36.6)	548,695 (30.2)
Current smoker	101,351 (22.1)	482,322 (26.5)
Missing	20,874 (4.6)	130,137 (7.2)
Exposure to selected infection, <i>n</i> (%)		
All infections	2354 (0.5)	9098 (0.5)
EBV	153 (0.0)	579 (0.0)
CMV	123 (0.0)	327 (0.0)
HHV-6	0 (0.0)	4 (0.0)
HTLV-1	0 (0.0)	10 (0.0)
Hepatitis C virus	784 (0.2)	4161 (0.2)
Influenza A virus	968 (0.2)	2911 (0.2)
Parvovirus B19	282 (0.1)	947 (0.1)
Exposure to selected medication, <i>n</i> (%)		
All medications	821 (0.2)	2552 (0.1)
Procainamide	0 (0.00)	2 (0.0)
Hydralazine	218 (0.1)	753 (0.0)
Quinidine	26 (0.0)	92 (0.0)
Isoniazid	581 (0.1)	1724 (0.1)

 Table 1
 Baseline characteristics of the exposed and unexposed cohorts

**Table 2** Incidence rates and HRs for the composite outcome

Outcome	Exposed cohort (n=458,147)	Unexposed cohort (n = 1,818,929)
Outcome events, no. (%)	696 (0.15)	2230 (0.12)
Person-years of follow-up	151,569	611,211
Crude incidence rate per 1000 person-years	4.59	3.65
Median follow-up, years (IQR)	0.29 (0.24–0.42)	0.29 (0.24–0.42)
Crude HR (95% CI)	1.26 (1.16–1.37)	
Adjusted <sup>a</sup> HR (95% CI)	1.22 (1.12–1.33)	

Cl confidence interval, HR hazard ratio, IQR interquartile range

<sup>a</sup> Adjusted for age, sex, BMI, ethnicity, smoking status, selected viral infections, and selected medications

incidence of IMIDs between the exposed and unexposed cohorts over a relatively short follow-up period. This also allowed us to assess the relative incidence of eleven of the more common IMIDs across the two comparison groups. We included IMIDs in our outcome such as T1DM, that are likely to be well-recorded in primary care records. The use of primary care data meant that we were able to adjust for important demographic and clinical risk factors that are known to be associated with the incidence of IMIDs. The use of data from practices across a national database also improved the generalisability of our findings.

The study had several limitations. We had missing data for ethnicity (22% missing), BMI (18%), and smoking status (7%), which we accounted for in our analyses using a missing category variable. However, these missing data could lead to biased effect estimates. We also did not have access to data on socioeconomic status but partially accounted for this by matching patients in the unexposed and exposed cohorts on general practice, which would result in patients from both groups sharing their approximate residential geography, which is associated with socioeconomic status.

There is likely to be a degree of misclassification bias between the exposed and unexposed cohorts. There was little community testing for SARS-CoV-2 infection in the first wave of the pandemic, so some members of the unexposed cohort may have been infected but not diagnosed. IMIDs may also have been underdiagnosed during the study period due to the relative inaccessibility of healthcare services during the early phase of the pandemic. It is possible that only more severely affected patients with IMIDs presented to healthcare services during this period.

The study period was restricted as data availability only covered from 31 January 2020 to 30 June 2021. This encompassed three national lockdowns where reduced healthcare appointments led to a backlog of up to 300,000 patients waiting over a year for treatment [39, 40]. Beyond this period, there was reduced availability of community testing for SARS-CoV-2 infection in the UK at a time when an increasing proportion of the population had experienced at least one episode of COVID-19, thus diminishing future comparator populations.

The short follow-up period may have diluted the effect size and power of the study as IMIDs tend to have a

Outcomes		aHR (95% CI)
Composite Disease Outcome	•	1.22 (1.12, 1.33)
Autoimmune Thyroiditis —		0.63 (0.19, 2.15)
Celiac Disease	++	1.30 (0.90, 1.89)
IBD	+	1.36 (1.18, 1.56)
Myasthenia Gravis		0.92 (0.35, 2.45)
Pernicious Anaemia	++	1.34 (0.77, 2.32)
Psoriasis	<b>~</b>	1.23 (1.05, 1.42)
RA	_ <b>_</b>	1.06 (0.81, 1.40)
Sjogren's Syndrome		0.17 (0.02, 1.27)
SLE		1.02 (0.51, 2.05)
Type1DM		1.56 (1.09, 2.23)
Vilitigo	+	1.28 (0.77, 2.15)
01	1 2	5

Fig. 1 Forest plot of Adjusted HRs for IMIDs. \*aHR = Adjusted Hazard Ratio, CI = Confidence Interval, IBD = inflammatory bowel disease, RA = rheumatoid arthritis, SLE = systemic lupus erythematous, Type1DM = type 1 diabetes mellitus

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Autoimmune thyroiditis         N < 5	Outcome	Exposed cohort	Unexposed cohort
Outcome eventsN<518Crude incidence rate per 10000.0200.029Person-years0.63 (0.19–2.15)VCrude HR (95% CI)0.63 (0.19–2.15)VAdjusted HR (95% CI)0.63 (0.19–2.15)VCrude incidence rate per 10000.240.18person-years1.32 (0.91–1.92)JCrude HR (95% CI)1.32 (0.91–1.92)JAdjusted HR (95% CI)1.32 (0.91–1.92)JAdjusted HR (95% CI)1.32 (0.91–1.92)JAdjusted HR (95% CI)1.32 (0.91–1.92)JCrude incidence rate per 10000.180.13person-years1.37 (1.19–1.57)JCrude incidence rate per 10000.13 (1.18–1.56)Myasthenia gravis0.0330.034Outcome events521Crude incidence rate per 10000.0330.034person-years0.96 (0.36–2.55)JCrude HR (95% CI)0.96 (0.36–2.55)JAdjusted HR (95% CI)1.37 (0.79–2.38)JCrude HR (95% CI)1.37 (0.79–2.38)JAdjusted HR (95% CI)1.37 (0.79–2.38)JCrude HR (95% CI)1.32 (0.57–1.42)JAdjusted HR (95% CI)1.21 (1.04–1.41)JAdjusted HR (95% CI)1.08 (0.82–1.41)JAdjus	Autoimmune thyroiditis		
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Crude HR (95% CI)0.67(0.20-2.27)Adjusted HR (95% CI)0.63 (0.19-2.15)Corliac disease37113Cutdome events37113Crude Incidence rate per 10000.240.18person-years1.32 (0.91-1.92)Adjusted HR (95% CI)1.32 (0.91-1.92)Adjusted HR (95% CI)1.30 (0.90-1.89)Image and the second	Crude incidence rate per 1000 person-years	0.020	0.029
Adjusted HR (95% CI)0.63 (0.19–2.15)Colliac diseaseOutcome events37113Crude incidence rate per 10000.240.18person-years1.32 (0.91–1.92)Adjusted HR (95% CI)1.30 (0.90–1.89)Adjusted HR (95% CI)1.30 (0.90–1.89)Adjusted HR (95% CI)0.180.13Crude incidence rate per 10000.180.13person-years1.37 (1.19–1.57)Adjusted HR (95% CI)1.36 (1.18–1.56)Myasthenia gravis0.0330.034Crude HR (95% CI)0.0320.034person-years0.0330.034person-years0.00060.032Crude Incidence rate per 10000.0330.034person-years0.96 (0.36–2.55)Adjusted HR (95% CI)0.92 (0.35–2.45)Crude Incidence rate per 10000.96 (0.36–2.55)Adjusted HR (95% CI)0.011Qutcome events,1750Crude Incidence rate per 10000.92 (0.35–2.45)Adjusted HR (95% CI)Adjusted HR (95% CI)1.37 (0.79–2.38)IAdjusted HR (95% CI)1.37 (0.79–2.38)IAdjusted HR (95% CI)1.32 (1.05–1.42)Iperson-yearsI1.22 (ICrude Incidence rate per 10001.471.22 (Iperson-yearsI1.23 (I.05–1.42)person-yearsI1.23 (I.05–1.42)person-yearsII.23 (I.05–1.42)person-yearsII.23 (I.05–1.42)person-yearsII.36 (0.82–1.41) <td>Crude HR (95% CI)</td> <td>0.67(0.20-2.27)</td> <td></td>	Crude HR (95% CI)	0.67(0.20-2.27)	
Coeliac disease         37         113           Crude incidence rate per 1000         0.24         0.18           person-years         1.32 (0.91–1.92)         1.32 (0.91–1.92)           Crude HR (95% CI)         1.32 (0.91–1.92)         1.32 (0.91–1.92)           Adjusted HR (95% CI)         1.32 (0.91–1.92)         1.32 (0.91–1.92)           Crude Incidence rate per 1000         0.18         0.13           person-years         276         817           Crude Incidence rate per 1000         0.18         0.13           person-years         21         1.32 (0.11–8.1.56)           Maysthenia gravis         21         1.32 (0.11–8.1.56)           Mutcome events         5         21           Crude HR (95% CI)         0.033         0.034           person-years         21         1.32 (0.91–1.92)           Crude Incidence rate per 1000         0.96 (0.36–2.55)         1.40           person-years         21         1.32 (0.79–2.38)           Crude Incidence rate per 1000         0.11         0.82           person-years         1.37 (0.79–2.38)         1.22           Crude Incidence rate per 1000         1.47 (0.79–2.38)         1.22           Crude Incidence rate per 1000         1.47 (0.79–2.38)	Adjusted HR (95% CI)	0.63 (0.19–2.15)	
Outcome events37113Crude incidence rate per 1000 person-years0.240.18Crude HR (95% CI)1.32 (0.91–1.92)Adjusted HR (95% CI)1.30 (0.90–1.89)Inflammatory bowel disease276817Crude incidence rate per 1000 person-years0.180.13Crude HR (95% CI)1.37 (1.19–1.57)Adjusted HR (95% CI)1.36 (1.18–1.56)Myasthenia gravis0.0330.034Outcome events521Crude incidence rate per 1000 person-years0.0330.034Crude HR (95% CI)0.96 (0.36–2.55)Adjusted HR (95% CI)0.92 (0.35–2.45)Adjusted HR (95% CI)0.92 (0.35–2.45)Adjusted HR (95% CI)0.92 (0.35–2.45)Pernicious anaemiaOutcome events,1.37 (0.79–2.38)Crude incidence rate per 1000 person-years1.37 (0.79–2.38)Crude HR (95% CI)1.31 (0.77–2.32)Peroirais223743Crude incidence rate per 1000 person-years1.471.22Crude Incidence rate per 1000 person-years1.471.22Person-yearsCrude Incidence rate per 1000 person-years1.471.22Crude Incidence rate per 1000 person-yearsCrude Incidence rate per 1000 person-yearsCrude Incidence rate per 1000 person-years <td>Coeliac disease</td> <td></td> <td></td>	Coeliac disease		
Crude incidence rate per 1000         0.24         0.18           person-years         1.32 (0.91–1.92)         1.33 (0.90–1.89)           Crude HR (95% CI)         1.30 (0.90–1.89)         1.33 (0.90–1.89)           Inflammatory bowel disease         0.18         0.13           Outcome events         0.18         0.13           Crude Incidence rate per 1000         0.18         0.13           person-years         1.37 (1.19–1.57)         4djusted HR (95% CI)         1.36 (1.18–1.56)           Myasthenia gravis         0.033         0.034           Crude IR (95% CI)         0.96 (0.36–2.55)         0.034           person-years         0.96 (0.36–2.55)         Adjusted HR (95% CI)         0.92 (0.35–2.45)           Crude IR (95% CI)         0.92 (0.35–2.45)         50           Crude HR (95% CI)         0.11         0.082           person-years         1.31 (0.79–2.38)         1.31 (0.79–2.38)           Crude IR (95% CI)         1.31 (0.79–2.38)         1.34 (0.77–2.32)           Adjusted HR (95% CI)         1.32 (1.05–1.42)         1.22           person-years         1.47         1.22           Crude IR (95% CI)         1.21 (1.04–1.41)         1.22           person-years         1.21 (1.04–1.41)         1.22     <	Outcome events	37	113
Crude HR (95% CI)         1.32 (0.91–1.92)           Adjusted HR (95% CI)         1.30 (0.90–1.89)           Inflarmatory bowel disease         276         817           Outcome events         276         817           Crude incidence rate per 1000         0.18         0.13           person-years         1.37 (1.19–1.57)	Crude incidence rate per 1000 person-years	0.24	0.18
Adjusted HR (95% CI)         1.30 (0.90–1.89)           Inflammatory bowel disease         276         817           Outcome events         276         817           Crude incidence rate per 1000         0.18         0.13           person-years         1.37 (1.19–1.57)         Adjusted HR (95% CI)         1.37 (1.19–1.57)           Myasthenia gravis         1.36 (1.18–1.56)         Image: Second	Crude HR (95% CI)	1.32 (0.91–1.92)	
Inflammatory bowel disease Outcome events Outcome events Crude incidence rate per 1000 Person-years Crude HR (95% Cl) Adjusted HR (95% Cl) Adjusted HR (95% Cl) Outcome events Outcome events Crude incidence rate per 1000 Person-years Crude HR (95% Cl) Outcome events Outcome events Outcome events Crude HR (95% Cl) Outcome events Outcome events Crude Incidence rate per 1000 Outcome events Outcome events Crude HR (95% Cl) Outcome events Outcome events Outcome events Crude Incidence rate per 1000 Outcome events Crude HR (95% Cl) Outcome events Outcome events Outcome events Outcome events Crude Incidence rate per 1000 Person-years Crude Incidence rate per 1000 Person-	Adjusted HR (95% CI)	1.30 (0.90–1.89)	
Outcome events         276         817           Crude incidence rate per 1000         0.18         0.13           person-years         1.37 (1.19–1.57)         Adjusted HR (95% CI)         1.36 (1.18–1.56)           Myasthenia gravis         5         21           Outcome events         5         0.033         0.034           person-years         0.96 (0.36–2.55)         Adjusted HR (95% CI)         0.11         0.082           Perricious anaemia         17         50         0.082         Perricious anaemia         I           Outcome events, Ciude incidence rate per 1000         1.31 (0.77–2.32)         Adjusted HR (95% CI)         1.21 (1.04–1.41)         I.22           Permatoid arthritis         I.21 (1.04–1.41)         I.22         IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	Inflammatory bowel disease		
Crude incidence rate per 1000         0.18         0.13           person-years         1.37 (1.19–1.57)         Adjusted HR (95% CI)         1.36 (1.18–1.56)           Myasthenia gravis         0.033         0.034           Outcome events         5         21           Crude HR (95% CI)         0.033         0.034           person-years         0.96 (0.36–2.55)         Adjusted HR (95% CI)         0.92 (0.35–2.45)           Crude HR (95% CI)         0.92 (0.35–2.45)         Termicious anaemia         0.033           Outcome events,         17         50           Crude IR (95% CI)         0.11         0.082           person-years         1.37 (0.79–2.38)         Adjusted HR (95% CI)           Adjusted HR (95% CI)         1.37 (0.79–2.38)         Adjusted HR (95% CI)           Adjusted HR (95% CI)         1.37 (0.79–2.38)         Adjusted HR (95% CI)           Adjusted HR (95% CI)         1.37 (0.79–2.38)         I.21 (1.04–1.41)           Adjusted HR (95% CI)         1.21 (1.04–1.41)         I.22           person-years         Crude HR (95% CI)         1.21 (1.04–1.41)         I.21 (1.04–1.41)           Adjusted HR (95% CI)         1.21 (1.04–1.41)         I.22         I.21 (1.04–1.41)         I.21 (1.04–1.41)         I.21 (1.04–1.41)         I.21 (1.04	Outcome events	276	817
Crude HR (95% Cl)         1.37 (1.19–1.57)           Adjusted HR (95% Cl)         1.36 (1.18–1.56)           Myatthenia gravis         21           Outcome events         5         21           Crude incidence rate per 1000         0.033         0.034           person-years         0.96 (0.36–2.55)         Adjusted HR (95% Cl)         0.92 (0.35–2.45)           Adjusted HR (95% Cl)         0.92 (0.35–2.45)         Son           Pernicious anaemia         0.011         0.082           Outcome events,         17         50           Crude HR (95% Cl)         0.11         0.082           person-years         27         Crude HR (95% Cl)         1.37 (0.79–2.38)           Adjusted HR (95% Cl)         1.34 (0.77–2.32)         Adjusted HR (95% Cl)           Adjusted HR (95% Cl)         1.47         1.22           person-years         211 (1.04–1.41)         Jadjusted HR (95% Cl)         Jat (1.04–1.41)           Adjusted HR (95% Cl)         1.21 (1.04–1.41)         Jadjusted HR (95% Cl)         Jat (1.04–1.41)           Adjusted HR (95% Cl)         0.44         0.41         Jat (1.04–1.41)           Adjusted HR (95% Cl)         1.08 (0.82–1.41)         Jat (1.04–1.41)         Jat (1.04–1.41)         Jat (1.04–1.41)         Jat (1.04–1.41) <td>Crude incidence rate per 1000 person-years</td> <td>0.18</td> <td>0.13</td>	Crude incidence rate per 1000 person-years	0.18	0.13
Adjusted HR (95% CI)       1.36 (1.18–1.56)         Myasthenia gravis       21         Outcome events       5       21         Crude incidence rate per 1000       0.033       0.034         person-years       0.02 (0.35–2.45)       1         Crude HR (95% CI)       0.92 (0.35–2.45)       1         Adjusted HR (95% CI)       0.92 (0.35–2.45)       1         Outcome events,       17       50         Crude incidence rate per 1000       0.11       0.082         person-years       1.37 (0.79–2.38)       1         Crude HR (95% CI)       1.37 (0.79–2.38)       1         Adjusted HR (95% CI)       1.37 (0.79–2.38)       1         Adjusted HR (95% CI)       1.34 (0.77–2.32)       1         Adjusted HR (95% CI)       1.47       1.22         Outcome events       223       743         Grude incidence rate per 1000       1.47       1.22         person-years       1.21 (1.04–1.41)       1.22         Crude HR (95% CI)       1.21 (1.04–1.41)       1.22         Adjusted HR (95% CI)       0.44       0.41         person-years       1.08 (0.82–1.41)       1.41         crude Incidence rate per 1000       0.00066       0.038	Crude HR (95% CI)	1.37 (1.19–1.57)	
Myasthenia gravis         5         21           Outcome events         5         0.034           Crude incidence rate per 1000         0.033         0.034           person-years         0.96 (0.36–2.55)         Adjusted HR (95% CI)         0.92 (0.35–2.45)           Adjusted HR (95% CI)         0.92 (0.35–2.45)         Termicious anaemia           Outcome events,         17         50           Crude incidence rate per 1000         0.11         0.082           person-years         1.37 (0.79–2.38)         Termicious           Crude HR (95% CI)         1.37 (0.79–2.38)         Termicious           Adjusted HR (95% CI)         1.34 (0.77–2.32)         Termicious           Person-years         223         743           Crude HR (95% CI)         1.21 (1.04–1.41)         1.22           person-years         Termicious anthritis         Termicious anthritis           Quitcome events         66         248           Crude HR (95% CI)         1.08 (0.82–1.41)         Termicious           person-years         Termicious         Termicious           Crude HR (95% CI)         1.08 (0.82–1.41)         Termicious           person-years         Termicious         Termicious           Crude HR (95% CI) <t< td=""><td>Adjusted HR (95% CI)</td><td>1.36 (1.18–1.56)</td><td></td></t<>	Adjusted HR (95% CI)	1.36 (1.18–1.56)	
Outcome events         5         21           Crude incidence rate per 1000         0.033         0.034           person-years         0.034         0.034           Crude HR (95% CI)         0.90 (0.36–2.55)         1           Adjusted HR (95% CI)         0.92 (0.35–2.45)         1           Pernicious anaemia         0         0.082           Outcome events,         17         50           Crude incidence rate per 1000         0.11         0.082           person-years         1.37 (0.79–2.38)         1.34 (0.77–2.32)           Crude HR (95% CI)         1.34 (0.77–2.32)         1.22           Portaisis         223         743           Crude nicidence rate per 1000         1.21 (1.04–1.41)         1.22           person-years         21         1.05–1.42)         1.22           Crude HR (95% CI)         1.21 (1.04–1.41)         1.22           Adjusted HR (95% CI)         1.21 (1.04–1.41)         1.22           Adjusted HR (95% CI)         0.44         0.41           person-years         1.08 (0.82–1.41)         1.22           Crude HR (95% CI)         1.08 (0.82–1.41)         1.21           Adjusted HR (95% CI)         0.00066         0.038           person-ye	Myasthenia gravis		
Crude incidence rate per 1000         0.033         0.034           person-years         0.96 (0.36–2.55)	Outcome events	5	21
Crude HR (95% CI)       0.96 (0.36–2.55)         Adjusted HR (95% CI)       0.92 (0.35–2.45)         Pernicious anaemia       17       50         Outcome events,       17       50         Crude incidence rate per 1000       0.11       0.082         person-years       1.37 (0.79–2.38)       1.34 (0.77–2.32)         Crude HR (95% CI)       1.34 (0.77–2.32)       1.44         Adjusted HR (95% CI)       1.47       1.22         Potrome events       223       743         Crude Incidence rate per 1000       1.47       1.22         person-years       1.21 (1.04–1.41)       1.22         Crude HR (95% CI)       1.21 (1.04–1.41)       1.22         Adjusted HR (95% CI)       1.23 (1.05–1.42)       1.41         Adjusted HR (95% CI)       1.23 (1.05–1.42)       1.41         Adjusted HR (95% CI)       1.04       0.41         person-years       1.04       0.41         Crude Incidence rate per 1000       0.44       0.41         person-years       1.06 (0.81–1.40)       1.41         Adjusted HR (95% CI)       1.06 (0.81–1.40)       1.41         Adjusted HR (95% CI)       0.108 (0.82–1.41)       1.41         Adjusted HR (95% CI)       0.0066 <td>Crude incidence rate per 1000 person-years</td> <td>0.033</td> <td>0.034</td>	Crude incidence rate per 1000 person-years	0.033	0.034
Adjusted HR (95% Cl)       0.92 (0.35–2.45)         Pernicious anaemia       17       50         Outcome events,       17       50         Crude incidence rate per 1000       0.11       0.082         person-years       1.37 (0.79–2.38)       1.34 (0.77–2.32)         Adjusted HR (95% Cl)       1.34 (0.77–2.32)       1.34 (0.77–2.32)         Psoriasis       223       743         Outcome events       223       743         Crude incidence rate per 1000       1.47       1.22         person-years       1.23 (1.05–1.42)       1.22         Crude HR (95% Cl)       1.21 (1.04–1.41)       1.22         Adjusted HR (95% Cl)       1.21 (1.04–1.41)       1.22         Adjusted HR (95% Cl)       1.23 (1.05–1.42)       1.24         Matiguted HR (95% Cl)       1.23 (1.05–1.42)       1.24         Matiguted HR (95% Cl)       0.44       0.41         person-years       1.06 (0.81–1.40)       1.24         Crude Incidence rate per 1000       0.44       0.41         person-years       1.06 (0.81–1.40)       1.24         Gutcome events       N<5	Crude HR (95% CI)	0.96 (0.36–2.55)	
Pernicious anaemia         I7         50           Outcome events,         0.11         0.082           person-years         1.37 (0.79–2.38)         1.34 (0.77–2.32)           Crude HR (95% Cl)         1.34 (0.77–2.32)         1.34 (0.77–2.32)           Pointais           Outcome events         223         743           Crude incidence rate per 1000         1.47         1.22           Person-years         1.21 (1.04–1.41)         1.22           Crude HR (95% Cl)         1.21 (1.04–1.41)         1.21           Adjusted HR (95% Cl)         1.21 (1.04–1.41)         1.22           Person-years         1.23 (1.05–1.42)         1.22           Crude HR (95% Cl)         0.21 (1.04–1.41)         1.22           Adjusted HR (95% Cl)         0.21 (1.04–1.41)         1.22           Adjusted HR (95% Cl)         0.44         0.41           Person-years         1.06 (0.82–1.41)         1.21           Crude IR (95% Cl)         1.08 (0.82–1.41)         1.22           Adjusted HR (95% Cl)         0.00066         0.038           Person-years         Crude IR (95% Cl)         0.00066         0.038           Crude IR (95% Cl)         0.18 (0.02–1.31)         1.21           Adjusted HR (	Adjusted HR (95% CI)	0.92 (0.35–2.45)	
Outcome events,         17         50           Crude incidence rate per 1000         0.11         0.082           person-years         1.37 (0.79–2.38)         1.34 (0.77–2.32)           Crude HR (95% Cl)         1.34 (0.77–2.32)         1.34 (0.77–2.32)           Pointais           Outcome events         223         743           Crude incidence rate per 1000         1.47         1.22           person-years         1.21 (1.04–1.41)         1.22           Crude HR (95% Cl)         1.21 (1.04–1.41)         1.21           Adjusted HR (95% Cl)         1.21 (1.04–1.41)         1.22           Adjusted HR (95% Cl)         1.23 (1.05–1.42)         1.24           Adjusted HR (95% Cl)         0.44         0.41           person-years         1.06 (0.81–1.40)         1.41           person-years         1.06 (0.82–1.41)         1.41           person-years         1.06 (0.81–1.40)         1.41           person-years         1.000066	Pernicious anaemia		
Crude incidence rate per 1000       0.11       0.082         person-years       1.37 (0.79–2.38)       1.34 (0.77–2.32)         Adjusted HR (95% CI)       1.34 (0.77–2.32)       743         Psoriasis         Outcome events       223       743         Crude Incidence rate per 1000       1.47       1.22         person-years       1.21 (1.04–1.41)       1.22         Crude HR (95% CI)       1.21 (1.04–1.41)       1.21         Adjusted HR (95% CI)       1.23 (1.05–1.42)       1.21         Adjusted HR (95% CI)       1.23 (1.05–1.42)       1.21         Matter Person-years       66       248         Crude incidence rate per 1000       0.44       0.41         person-years       1.06 (0.81–1.40)       1.21         Crude HR (95% CI)       1.08 (0.82–1.41)       1.21         person-years       1.06 (0.81–1.40)       1.21         Crude HR (95% CI)       1.06 (0.81–1.40)       1.21         Adjusted HR (95% CI)       0.00066       0.038         person-years       23       1.22         Crude HR (95% CI)       0.18 (0.02–1.31)       1.21         Adjusted HR (95% CI)       0.17 (0.02–1.27)       1.21         Crude HR (95% CI)	Outcome events,	17	50
Crude HR (95% Cl)       1.37 (0.79–2.38)         Adjusted HR (95% Cl)       1.34 (0.77–2.32)         Psoriasis       223       743         Outcome events       223       743         Crude incidence rate per 1000       1.47       1.22         person-years       1.21 (1.04–1.41)       1.21         Crude HR (95% Cl)       1.21 (1.04–1.41)       1.21         Adjusted HR (95% Cl)       1.23 (1.05–1.42)       1.21         Adjusted HR (95% Cl)       0.23 (1.05–1.42)       1.21         Outcome events       66       248         Crude incidence rate per 1000       0.44       0.41         person-years       1.06 (0.81–1.40)       1.21         Crude HR (95% Cl)       1.08 (0.82–1.41)       1.21         Adjusted HR (95% Cl)       1.06 (0.81–1.40)       1.21         Adjusted HR (95% Cl)       0.00066       0.038         Crude HR (95% Cl)       0.100066       0.038         Outcome events       N<5	Crude incidence rate per 1000 person-years	0.11	0.082
Adjusted HR (95% Cl)       1.34 (0.77–2.32)         Psoriasis       223       743         Outcome events       223       743         Crude incidence rate per 1000       1.47       1.22         person-years       1.21 (1.04–1.41)       1.22         Crude HR (95% Cl)       1.23 (1.05–1.42)       1.21         Adjusted HR (95% Cl)       1.23 (1.05–1.42)       1.21         Boutcome events       66       248         Crude incidence rate per 1000       0.44       0.41         person-years       1.06 (0.81–1.40)       1.21         Crude HR (95% Cl)       1.08 (0.82–1.41)       1.21         Adjusted HR (95% Cl)       1.08 (0.82–1.41)       1.21         Adjusted HR (95% Cl)       0.000 (0.01–1.40)       1.21         Sjogren's syndrome       0.00066       0.038         Quitcome events       N<5	Crude HR (95% CI)	1.37 (0.79–2.38)	
Psoriasis         223         743           Outcome events         223         743           Crude incidence rate per 1000         1.47         1.22           person-years         1.21 (1.04–1.41)         1.21           Adjusted HR (95% CI)         1.23 (1.05–1.42)         1.21           Adjusted HR (95% CI)         1.23 (1.05–1.42)         1.21           Boutcome events         66         248           Crude incidence rate per 1000         0.44         0.41           person-years         1.06 (0.81–1.40)         1.21           Crude HR (95% CI)         1.08 (0.82–1.41)         1.21           Adjusted HR (95% CI)         1.06 (0.81–1.40)         1.21           Stoppers's syndrome         1.000066         0.038           Crude incidence rate per 1000         0.00066         0.038           Crude incidence rate per 1000         0.00066         0.038           person-years         Crude incidence rate per 1000         0.00066         0.038           person-years         Crude IR (95% CI)         0.18 (0.02–1.31)         1.21           Adjusted HR (95% CI)         0.17 (0.02–1.27)         1.21         1.21           Systemic lupus erythematosus         Joutcome events, no.(M <sup>3</sup> )         10         39	Adjusted HR (95% CI)	1.34 (0.77–2.32)	
Outcome events       223       743         Crude incidence rate per 1000       1.47       1.22         person-years       1.21 (1.04–1.41)       1.23         Crude HR (95% Cl)       1.23 (1.05–1.42)       1.24         Adjusted HR (95% Cl)       1.23 (1.05–1.42)       1.24         Rheumatoid arthritis         Outcome events       66       248         Crude incidence rate per 1000       0.44       0.41         person-years       1.06 (0.81–1.40)       1.21         Crude HR (95% Cl)       1.08 (0.82–1.41)       1.21         Adjusted HR (95% Cl)       1.06 (0.81–1.40)       1.21         Sjogren's syndrome       23       23         Outcome events       N < 5	Psoriasis		
Crude incidence rate per 1000       1.47       1.22         person-years       1.21 (1.04–1.41)       1.23 (1.05–1.42)         Adjusted HR (95% Cl)       1.23 (1.05–1.42)       1.24         Adjusted HR (95% Cl)       1.23 (1.05–1.42)       1.24         Rheumatoid arthritis       66       248         Outcome events       66       0.41         person-years       1.08 (0.82–1.41)       1.24         Crude HR (95% Cl)       1.06 (0.81–1.40)       1.24         Adjusted HR (95% Cl)       1.06 (0.81–1.40)       1.24         Sjogren's syndrome       23       1.24         Outcome events       N < 5	Outcome events	223	743
Crude HR (95% Cl)       1.21 (1.04–1.41)         Adjusted HR (95% Cl)       1.23 (1.05–1.42)         Rheumatoid arthritis       66       248         Outcome events       66       0.41         person-years       7.000 (0.82–1.41)       0.41         Crude HR (95% Cl)       1.08 (0.82–1.41)       1.01         Adjusted HR (95% Cl)       1.06 (0.81–1.40)       1.01         Sjogren's syndrome       0.00066       0.038         Outcome events       N < 5	Crude incidence rate per 1000 person-years	1.47	1.22
Adjusted HR (95% Cl)       1.23 (1.05–1.42)         Rheumatoid arthritis       66       248         Outcome events       66       0.41         person-years       0.44       0.41         Crude incidence rate per 1000       0.44       0.41         person-years       1.08 (0.82–1.41)       1.41         Adjusted HR (95% Cl)       1.06 (0.81–1.40)       1.41         Adjusted HR (95% Cl)       0.0006.081–1.40)       1.41         Sjogren's syndrome       0.00066       0.038         Outcome events       N<5	Crude HR (95% CI)	1.21 (1.04–1.41)	
Bleumatoid arthritis         66         248           Out come events         66         0.41           person-years         0.44         0.41           Crude incidence rate per 1000         0.42         0.41           person-years         1.08 (0.82–1.41)         1.41           Adjusted HR (95% Cl)         1.06 (0.81–1.40)         1.41           Sjogren's syndrome         0.00066         0.038           Out come events         N < 5	Adjusted HR (95% CI)	1.23 (1.05–1.42)	
Outcome events         66         248           Crude incidence rate per 1000         0.44         0.41           person-years         1.08 (0.82–1.41)         1.44           Adjusted HR (95% Cl)         1.06 (0.81–1.40)         1.06 (0.81–1.40)           Sjogren's syndrome         1.06 (0.81–1.40)         1.06 (0.81–1.40)           Outcome events         N < 5	Rheumatoid arthritis		
Crude incidence rate per 1000       0.44       0.41         person-years       1.08 (0.82–1.41)       1.04         Adjusted HR (95% Cl)       1.06 (0.81–1.40)       1.05         Sjogren's syndrome       1.06 (0.81–1.40)       1.05         Outcome events       N < 5	Outcome events	66	248
Crude HR (95% Cl)       1.08 (0.82–1.41)         Adjusted HR (95% Cl)       1.06 (0.81–1.40)         Sjogren's syndrome       0         Outcome events       N < 5	Crude incidence rate per 1000 person-years	0.44	0.41
Adjusted HR (95% Cl)       1.06 (0.81–1.40)         Sjøgren's syndrome       23         Outcome events       0.00066       0.038         Crude incidence rate per 1000       0.00066       0.038         person-years       0.18 (0.02–1.31)       10         Kajusted HR (95% Cl)       0.17 (0.02–1.27)       10         Systemic lupus erythematosus       10       39	Crude HR (95% CI)	1.08 (0.82–1.41)	
Sjogren's syndrome         N < 5         23           Outcome events         0.00066         0.038           person-years         0.18 (0.02–1.31)         1           Crude HR (95% CI)         0.17 (0.02–1.27)         1           Adjusted HR (95% CI)         0.17 (0.02–1.27)         1           Systemic lupus erythematosus         10         39	Adjusted HR (95% CI)	1.06 (0.81-1.40)	
Outcome events         N < 5         23           Crude incidence rate per 1000         0.00066         0.038           person-years         0.18 (0.02–1.31)         -           Crude HR (95% Cl)         0.17 (0.02–1.27)         -           Adjusted HR (95% Cl)         0.17 (0.02–1.27)         -           Systemic lupus erythematosus         -         -           Outcome events, no. (% <sup>a</sup> )         10         39	Sjogren's syndrome		
Crude incidence rate per 1000         0.00066         0.038           person-years         0.18 (0.02–1.31)         -           Crude HR (95% Cl)         0.17 (0.02–1.27)         -           Adjusted HR (95% Cl)         0.17 (0.02–1.27)         -           Systemic lupus erythematosus         -         -           Outcome events, no. (% <sup>a</sup> )         10         39	Outcome events	N<5	23
Crude HR (95% Cl)     0.18 (0.02–1.31)       Adjusted HR (95% Cl)     0.17 (0.02–1.27)       Systemic lupus erythematosus     0utcome events, no. (% <sup>a</sup> )     10     39	Crude incidence rate per 1000 person-years	0.00066	0.038
Adjusted HR (95% Cl)     0.17 (0.02–1.27)       Systemic lupus erythematosus     0utcome events, no. (% <sup>a</sup> )       10     39	Crude HR (95% CI)	0.18 (0.02–1.31)	
Systemic lupus erythematosusOutcome events, no. (%ª)1039	Adjusted HR (95% CI)	0.17 (0.02–1.27)	
Outcome events, no. (% <sup>a</sup> ) 10 39	Systemic lupus erythematosus		
	Outcome events, no. (% <sup>a</sup> )	10	39

# Table 3 (continued)

Outcome	Exposed cohort	Unexposed cohort
Crude incidence rate per 1000 person-years	0.066	0.064
Crude HR (95% CI)	1.03 (0.51–2.06)	
Adjusted HR (95% CI)	1.02 (0.51–2.05)	
Type 1 diabetes mellitus		
Outcome events	42	106
Crude incidence rate per 1000	0.28	0.17
	1 (0 (1 12 2 20)	
	1.60 (1.12-2.29)	
Adjusted HR (95% CI)	1.56 (1.09–2.23)	
Vitiligo		
Outcome events	19	60
Crude incidence rate per 1000 person-years	0.13	0.098
Crude HR (95% CI)	1.28 (0.76–2.14)	
Adjusted HR (95% CI)	1.28 (0.77–2.15)	

Cl confidence interval, HR hazard ratio

<sup>a</sup> Total outcome events

clinical latency period and thus the full scope of the potential impact of SARS-CoV-2 infections is likely to have been underrepresented [41]. It also cannot be confirmed whether the true onset of these conditions preceded SARS-CoV-2 infection or the matched index dates. However, we would expect these issues to equally bias our estimates of disease incidence in both the exposed and unexposed cohorts and would therefore not anticipate it affecting the hazard ratios. There also exists the possibility that patients experiencing COVID-19 may have accessed healthcare services more than those with no prior infection and thus had more opportunities to be diagnosed with IMIDs. Likewise, patients with underlying IMIDs may have had their symptoms exacerbated by COVID-19 which resulted in seeking healthcare services and subsequent diagnosis.

# Implications for practice, policy, and research

Our findings provide epidemiological evidence that SARS-CoV-2 infection is associated with an increased risk of a range of IMIDs, including T1DM, IBD, and psoriasis. This provides evidence that autoimmunity may be a potential mechanism that accounts for some of the longer-term symptoms and health impacts of a subgroup of those with long COVID. This is particularly of interest given the finding that women are generally at increased risk of both IMIDs as well as Long COVID, that symptoms of long COVID are diverse and often overlap with those of IMIDs, and that the symptoms of both IMIDs and long COVID characteristically follow a relapsing–remitting pattern over time [42].

Further epidemiological studies with a longer followup period are needed to confirm our findings and to test for relevant autoantibodies in the serum of participants to correlate with symptoms and clinical findings. These studies could also include other rarer IMIDs potentially associated with COVID-19 such as Guillain-Barré syndrome [14]. Evidence suggests that those who have been vaccinated against COVID-19 are approximately half as likely to develop symptoms lasting over 28 days than unvaccinated individuals [43]. It would be valuable to know if these differences in long COVID incidence rates are also associated with differences in the incidence of IMIDs.

# Conclusions

SARS-CoV-2 infection was associated with an increased incidence of several IMIDs, including type 1 diabetes mellitus, inflammatory bowel disease, and psoriasis. This lends support to the hypothesis that the long-term effects of COVID-19 or long COVID may in part be related to autoimmune mechanisms. Further research is needed to replicate these findings in other populations, over a longer time period and to sample autoantibody profiles in people with long COVID and matched control groups.

### Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-023-03049-5.

Additional file 1: Supplementary Table 1. Adjusted hazard ratios for other risk factors included in the Cox proportional hazards model. Supplementary Table 2. Population characteristics by outcome cohort. The RECORD statement: A checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

#### Acknowledgements

Not applicable.

#### Declarations

The lead author (SH) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

#### Authors' contributions

SH and AS conceptualised the research question. US conducted the study under the supervision of AS and SH. DW, JL, and KM provided expert input on immunology and autoimmunity. KN and KG provided expertise on data science and data management. All authors reviewed and approved the submitted form of the manuscript.

#### Funding

This study was not externally funded.

#### Availability of data and materials

Access to anonymized patient data from CPRD is subject to a data-sharing agreement containing detailed terms and conditions of use following

protocol approval from the MHRA Independent Scientific Advisory Committee. The dataset for this study is not publicly available but may be requested from the corresponding author at a.subramanian@bham.ac.uk if in accordance with data governance approvals. Details about Independent Scientific Advisory Committee applications and data costs are available on the CPRD website (cprd.com).

# Declarations

#### Ethics approval and consent to participate

This study consists of secondary data analysis of pseudo-anonymised data from the CPRD Aurum database and thus approval was only required to access the database. The project was reviewed and approved by the CPRD Independent Scientific Advisory Committee (study #21\_000712) on the 24th of February 2022.

#### **Consent for publication**

Not applicable.

#### **Competing interests**

SH reports receiving funding from NIHR and UKRI. US report no competing interests. AS has no declarations during the study period; after the study was completed, she has taken a post in AstraZeneca. JL receives grant funding from NIHR, UKRI, Versus Arthritis, The Scar Free Foundation, FOREUM, and Bayer Healthcare for which also she acts as a consultant.

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#### Received: 19 January 2023 Accepted: 24 August 2023 Published online: 21 September 2023

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