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Supplementary appendix

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Supplementary Material for 'Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune modifying therapies: a nationwide cohort study in the OpenSAFELY platform'

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Text S1. High-cost drugs dataset

To achieve a comprehensive national medicines dataset, we arranged for the unique collation of a single national hospital medication dataset for "high-cost drugs". High-cost drugs are typically newer and more expensive medications (e.g., adalimumab) that are supplied by hospitals in England for ongoing disease management. High-cost drugs are paid for by commissioners (in England, National Health Service Clinical Commission Groups commission most secondary care services and play a part in the commissioning of GP services) and as part of this process, unique patient identifiers are supplied by hospitals, the responsible commissioner (there are approximately 200 commissioners). The North East Commissioning Support Unit collected high-cost drug data from commissioners and compiled it into a single national dataset (including medication name, date of medication supply and a unique patient identifier – NHS number – allowing linkage with other healthcare data). To our knowledge this is the first time in England that a comprehensive national medicines dataset including high-cost drug data has been available at individual patient level. More information is available in our accompanying short data report.[link will be provided in published paper]

Drug exposure was defined by at least one prescription, or delivery of medication to an individual before March 1st, 2020 (date chosen as some medications were either specifically used, or stopped, due to the pandemic). For each individual, we defined drug exposure based on the closest drug recorded prior to the study start (March 1st 2020) allowing for a maximum of 6 months before the start of the study for all agents apart from rituximab, where we permitted a 12-month exposure window (to allow for the frequency of treatment and the longer duration of response of rituximab, including known prolonged effects on vaccine responses).[1,2] We could not evaluate medication switching or adherence during the follow-up period, as data was only available up to March 2020.

Text S2. Covariates

All analytical code for all covariates definitions are openly available online for inspection and re-use. Some brief descriptions are provided below.

Age

Age was defined by the age reached by the 1st March 2020 (study start date). We categorised age groups as: 18–39, 40–49, 50–59, 60–69, 70–79 and 80+ years.

Smoking and body mass index

We categorised smoking status as current-, former- or never-smokers, based on primary care morbidity coding recorded prior to March 1st, 2020. People with missing smoking status were categorised as never smokers.

Body mass index (BMI) was calculated from height and weight measures recorded in primary care, based on weight measurements within the last 10 years (before March 1st, 2020), and restricted to records from after age 16 years. BMI was categorised according to World Health Organisation (WHO) BMI classification: no evidence of obesity (BMI < 30); obese class I (BMI 30–34·9); obese class II (BMI 35–39·9); and obese class III (BMI 40+). Individuals with missing BMI data were categorised as having no evidence of obesity (i.e., BMI < 30).

We undertook a sensitivity analysis without re-categorising missing BMI and smoking status data (i.e., complete-case analysis of only those with complete smoking and BMI data). Our approach reflects an awareness that BMI and smoking data are likely to be not missing at random, and has precedent in previous OpenSAFELY analyses.[3,4]

Current glucocorticoid use

We defined current glucocorticoid use based on a primary care prescription of oral prednisolone at any dose in the three months before study start.

Diabetes mellitus

We defined diabetes mellitus based on the most recent glycosylated haemoglobin (Hba1c) measurement recorded in primary care at any time before study start (March 1st 2020): controlled diabetes Hba1c<58mmol/mol; uncontrolled diabetes Hba1c≥58mmol/mol; or diabetes (based on morbidity coded diabetes) with no recorded Hba1c measure.

End stage renal failure

We defined end stage renal failure based on estimated glomerular filtration rate calculated from the most recent serum creatinine result recorded 15 months before study start (March 1st, 2020) in primary care data. We only adjusted for end stage renal failure in sensitivity analyses.

Ethnicity

We defined ethnicity based on coding in primary care. We classified ethnicity as: White, Black, South Asian, and mixed or other. We only adjusted for ethnicity in sensitivity analyses due to the large proportion of missing data (**Tables 1 and 2**).

Other chronic comorbidities

We defined cardiovascular disease (chronic heart failure, ischaemic heart disease, and severe valve or congenital heart disease likely to require lifelong follow-up), cancer (excluding non-melanoma skin cancer), and stroke based on any morbidity coding in primary care recorded prior to March 1st, 2020 (study start date). We also adjusted for chronic respiratory disease (chronic obstructive pulmonary disease, fibrosing lung disease, bronchiectasis or cystic fibrosis) and chronic liver disease in a sensitivity analysis, again defined based on any morbidity coding in primary care recorded prior to study start.

Text S3. Quantitative bias analysis

Methods

We considered severity of immune-mediated inflammatory disease and degree of shielding to be potential confounders which are not available in the data. As such we conducted quantitative bias analysis using E-values to assess how strongly associated these unmeasured confounders would need to be with exposure and outcome to potentially fully explain observed non-null associations (i.e., the association adjusted for both measured covariates and the unmeasured confounder would be null).[5] In order to apply these methods to the hazard ratio, rather than the risk ratio, we make the assumption that the outcomes are rare.

Results

A non-null association was observed between rituximab and COVID-19 death, critical care admission/death, and hospitalisation. For an unmeasured confounder to potentially fully explain the point estimate for the observed confounder-adjusted association the unmeasured confounder would need to be associated with one of exposure or outcome, conditional on measured covariates, by at least risk ratios 2·75, 3·25 and 2·56 for COVID-19 death, critical care admission/death, and hospitalisation respectively (1·46, 1·95, and 1·59 to potentially explain the lower bound of the 95% CI) (**Figures S6-S8, Tables S14-S17**).

Furthermore, to potentially fully explain the point estimate the unmeasured confounder would need to be associated with both exposure and outcome, conditional on measured covariates, by at least risk ratio 1·68, 1·92 and 1·59 for COVID-19 death, critical care admission/death and hospitalisation (1·11, 1·31, and 1·16 to potentially explain the lower bound of the 95% CI).

Additionally, a non-null association was observed between JAK-inhibitors and COVID-19 hospitalisation. To potentially fully explain the confounder-adjusted point estimate (lower bound of 95% CI) the unmeasured confounder would need to be associated with one of exposure or outcome, conditional on measured covariates, by at least risk ratio 3·02 (1·40) and both of exposure and outcome by 1·81 (1·09) (**Figure S9, Table S17.).**

Discussion

An unmeasured confounder moderately associated with both exposure and outcome could potentially explain the associations of rituximab and JAK inhibitors with COVID-19 outcomes. However, whether this is the case in this study and the extent of true residual confounding depends on both the prevalence of and strength of associations with exposure and outcome of the unmeasured confounders, shielding and severity of IMID, which are not known.

Table S1. Sensitivity analyses

Sensitivity analysis	Justification
Comparing risk of COVID-19-related death in: 1) people with **IMIDs to general population**; and 2) people with IMIDs on **targeted compared to standard systemic** immune modifying therapies.	
Additionally adjusting our confounder-adjusted models for **ethnicity**	We did not adjust for ethnicity in our main analysis due to a large proportion of missing ethnicity data. In this sensitivity analysis, we therefore additionally adjusted confounder adjusted models for ethnicity and restricted our analysis to people with known ethnicity (i.e., complete case analysis). This was done for both of the main study objectives (IMIDs and severe COVID-19 outcomes; and immunosuppressants and severe COVID-19 outcomes).
Additionally adjusting our confounder-adjusted model for **chronic respiratory disease, end stage renal failure and chronic liver disease**	We additionally adjusted for further potential confounders (chronic respiratory disease, end stage renal failure and chronic liver disease) to explore: how robust our effect estimates were; and the assumptions underlying the causal diagrams informing our main analyses (i.e., we additionally adjusted for wider sets of confounders, identified in causal diagrams drawn under less restrictive assumptions regarding potential confounding factors).This was done for the objective concerning IMIDs and severe COVID-19 outcomes only, as the confounder adjusted model for the objective concerning immunosuppressants and severe COVID-19 outcomes already included the comorbidities in question.
Repeating the main analysis and adjusting for **smoking/BMI without missing data reclassification**	In our main analyses, individuals with missing BMI measures were categorised as having 'no evidence of obesity (BMI < 30)', and those with missing smoking status were categorised as or never-smokers. We therefore undertook a sensitivity analysis restricting to those with known BMI and smoking status (complete case analysis).This was done for both of the main study objectives (IMIDs and severe COVID-19 outcomes; and immunosuppressants and severe COVID-19 outcomes).
Excluding people with records of **haematological malignancy or organ transplants**	While only a small number are likely to have haematological malignancy or organ transplant, there is an established very high risk of COVID-19-reated death and adverse outcomes.[6,7]
Adjusting for **age** using a four-knot cubic **spline**	In our main analyses we included age as a categorical variable. In a sensitivity analysis, we used four-knot cubic splines to adjust for age in our age and sex adjusted models, and confounder adjusted models, in order to more granularly account for the effect of age.
Comparing risk of COVID-19-related critical care admission in people with IMIDs to general population	
Alternative end point of **COVID-19-related critical care admission**	For our main analysis we combined COVID-19-related critical admission and death as one outcome, as not all individuals with severe COVID-19 are admitted to critical care. Combining the outcomes allowed us to capture all individuals with severe COVID-19. However, we explored COVID-19-related critical care admission only as a sensitivity analysis.
Analyses of specific targeted drugs only (compared to standard systemics)	
Reduced exposure window for **TNF inhibition** prior to study start compared standard systemic	In our main analyses we assessed exposure to standard and targeted immune modifying drugs within six months of the study start (March 1st, 2020). In a sensitivity analysis for TNF inhibition only, as the most frequently used targeted therapy, we restricted this period to within three months before March 1st, 2020.
TNFi exposure as **TNFi monotherapy**, compared	In our main analysis, we defined TNFi exposure to include TNFi monotherapy and TNFi combination therapy with standard systemic agents. In a sensitivity

to TNFi combination therapy with standard systemic	analysis we compared the risk of COVID-19-related death in individuals prescribed TNFi monotherapy against TNFi combination therapy, as differences in infection outcomes have been described in individuals prescribed TNFi monotherapy compared to combination therapy.[8]
TNFi exposure defined as **infliximab** only	In our main analysis, we defined TNFi exposure including all TNF inhibitor medications. However, with the TNFi class, individuals prescribed infliximab might be systematically different in terms of disease severity (a confounder that is difficult to capture); it was also more likely that they were treated in hospital; and we hypothesised that exposure may be associated with an increased risk of severe COVID-19 outcomes. Therefore, we repeated our main analysis including those on infliximab only.
Rituximab and JAK inhibitor quantitative bias analysis	We considered severity of immune-mediated inflammatory disease and degree of shielding to be potential confounders that are not available in the data. We therefore conducted quantitative bias analysis using E-values to assess how strongly associated these unmeasured confounders would need to be with exposure and outcome to potentially fully explain observed non-null associations (i.e., the association adjusted for both measured covariates and the unmeasured confounder would be null). In order to apply these methods to the hazard ratio to rather than the risk ratio, we made the assumption that the outcomes were rare.

Table S2. Main analysis: Hazard Ratios (HRs) and 95% confidence intervals (CI) for COVID-19-related death, death/critical care admission or hospitalisation, in people with IMIDs compared to the general population

	Events	Person-years	Rate per 1000 PY (95%CI)	Crude HR (95%CI)	Age and sex adjusted HR (95%CI)	Confounder adjusted HR (95%CI)	Mediator adjusted HR (95% CI)
COVID-19 death							
General population	40,453	8,293,798	4·88 (4·83, 4·93)	REF	REF	REF	REF
All IMID	4,824	583,617	8·27 (8·03, 8·50)	1·70 (1·65, 1·75)	1·27 (1·23, 1·31)	1·23 (1·20, 1·27)	1·15 (1·11, 1·18)
Inflammatory joint disease	1,856	136,333	13·61 (13·00, 14·25)	2·75 (2·62, 2·88)	1·51 (1·44, 1·58)	1·47 (1·40, 1·54)	1·30 (1·24, 1·37)
Inflammatory skin disease	2,608	386,455	6·75 (6·49, 7·01)	1·34 (1·29, 1·40)	1·16 (1·11, 1·20)	1·12 (1·08, 1·17)	1·07 (1·02, 1·11)
Inflammatory bowel disease	721	99,875	7·22 (6·70, 7·77)	1·42 (1·32, 1·53)	1·15 (1·07, 1·24)	1·12 (1·04, 1·21)	1·07 (0·99, 1·15)
COVID-19 critical care admission or death							
General population	43,972	8,311,564	5·29 (5·24, 5·34)	REF	REF	REF	REF
All IMID	5,208	585,538	8·89 (8·65, 9·14)	1·68 (1·63, 1·73)	1·28 (1·24, 1·31)	1·24 (1·21, 1·28)	1·16 (1·12, 1·19)
Inflammatory joint disease	1,950	137,026	14·23 (13·61, 14·88)	2·64 (2·52, 2·76)	1·50 (1·43, 1·57)	1·46 (1·39, 1·52)	1·30 (1·24, 1·36)
Inflammatory skin disease	2,867	387,508	7·40 (7·13, 7·67)	1·36 (1·31, 1·41)	1·18 (1·13, 1·22)	1·15 (1·10, 1·19)	1·08 (1·04, 1·13)
Inflammatory bowel disease	784	100,186	7·83 (7·29, 8·39)	1·42 (1·33, 1·53)	1·16 (1·08, 1·24)	1·13 (1·06, 1·22)	1·08 (1·01, 1·16)
COVID-19 hospitalisation							
General population	72,862	8,309,954	8·77 (8·70, 8·83)	REF	REF	REF	REF
All IMID	8,376	585,324	14·31 (14·01, 14·62)	1·63 (1·60, 1·67)	1·34 (1·31, 1·37)	1·32 (1·29, 1·35)	1·20 (1·17, 1·23)
Inflammatory joint disease	2,869	136,962	20·95 (20·19, 14·62)	2·34 (2·26, 2·43)	1·57 (1·51, 1·63)	1·53 (1·47, 1·59)	1·32 (1·27, 1·37)
Inflammatory skin disease	4,752	387,377	12·27 (11·92, 12·62)	1·36 (1·33, 1·41)	1·22 (1·19, 1·26)	1·21 (1·17, 1·24)	1·10 (1·07, 1·14)
Inflammatory bowel disease	1,426	100,146	14·24 (13·51, 15·00)	1·57 (1·49, 1·65)	1·35 (1·28, 1·42)	1·31 (1·24, 1·38)	1·25 (1·19, 1·31)

Planned comparisons were made between people with IMIDs, and IMID types (joint, bowel, skin), using the general population as the reference group.
Confounder adjusted: age, sex, deprivation,and smoking status
Mediator adjusted: age, sex, deprivation, smoking status, BMI, cardiovascular disease, diabetes mellitus and current glucocorticoid use
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; BMI, body mass index.

Table S3. Sensitivity analyses: COVID-19-related death in IMIDs compared to the general population.

		Confounder-adjusted models Total n events: 45,065 Total n analysis: 17,527,579	Additionally adjusting our confounder -adjusted models for **ethnicity** Total n events: 45,065 Total n analysis: 17,527,579	Additionally adjusting our confounder -adjusted model for **chronic respiratory disease, end stage renal failure and chronic liver disease** Total n events: 45,065, Total n analysis: 17,527,579	Repeating the main analysis and adjusting for **smoking/BMI without missing data reclassification** Total n events: 33,829, Total n analysis: 13,235,476	Confounder-adjusted models excluding people with records of **haematological malignancy or organ transplants** Total n events: 43,292, Total n analysis: 17,395,123	
	Events	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**Events**	**HR (95% CI)**
General population	40,453	REF	REF	REF	REF	38,841	REF
All IMID	4,824	1·23 (1·20, 1·27)	1·22 (1·17, 1·26)	1·17 (1·14, 1·21)	1·23 (1·19, 1·27)	4,652	1·24 (1·20, 1·28)
Inflammatory joint disease	1,856	1·47 (1·40, 1·54)	1·43 (1·36, 1·51)	1·37 (1·31, 1·44)	1·46 (1·40, 1·53)	1971	1·48 (1·41, 1·55)
Inflammatory skin disease	2,608	1·12 (1·08, 1·17)	1·12 (1·07, 1·17)	1·08 (1·04, 1·12)	1·12 (1·08, 1·16)	2515	1·13 (1·08, 1·18)
Inflammatory bowel disease	721	1·12 (1·04, 1·21)	1·11 (1·02, 1·20)	1·06 (0·98, 1·14)	1·12 (1·04, 1·21)	690	1·12 (1·04, 1·21)

Planned comparisons were made between people with IMIDs, and IMID subcategories (joint, bowel, skin), using the general population as the reference group.
Confounder adjsuted: age, sex, deprivation, smoking status.**Abbreviations**: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; BMI, body mass index.
* Events counts are different for these analyses due to exclusion of those with missing data on the additionally included variables (complete case analysis).

Table S4. Sensitivity analyses: COVID-19-related critical care admission/death in IMIDs compared to the general population.

	COVID-19 death or critical care admission Confounder adjusted analysis		**COVID-19 critical care admission alternative outcome Confounder adjusted analysis**	
	Events	**Confounder Adjusted HR (95%CI)**	**Events**	**Confounder adjusted HR (95%CI)**
General population	43,972	REF	6070	REF
All IMID	5,208	1·24 (1·21, 1·28)	679	1·36 (1·25, 1·47)
Inflammatory joint disease	1,950	1·46 (1·39, 1·52)	213	1·59 (1·38, 1·82)
Inflammatory skin disease	2,867	1·15 (1·10, 1·19)	431	1·33 (1·21, 1·47)
Inflammatory bowel disease	784	1·13 (1·06, 1·22)	96	1·05 (0·86, 1·29)

Planned comparisons were made between people with IMIDs, and IMID type (joint, bowel, skin), using the general population as the reference group.
Confounder adjusted: age, sex, deprivation,and smoking status
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; BMI, body mass index.

Table S5. Number of individuals with each IMID type receiving standard systemic or any targeted immune modifying therapy

	Total	**Standard systemics**	**Any targeted immune modifying therapy**
	N=200,813	181,694 (90·5%)	19,119 (9·5%)
Joint disease	**111,759**	**98,830 (88·4%)**	**12,929 (11·6%)**
Psoriatic arthritis	19,698	17,162 (87·1%)	2,536 (12·9%)
Rheumatoid arthritis	87,581	79,154 (90·4%)	8,427 (9·6%)
Ankylosing spondylitis	4,801	2,794 (58·2%)	2,007 (41·8%)
Skin disease	**36,967**	**31695 (85·7%)**	**5,272 (14·3%)**
Psoriasis	34,894	30,113 (86·3%)	4,781 (13·7%)
Hidradenitis suppurativa	2,079	1,588 (76·4%)	4,91 (23·6%)
Bowel disease	**84,333**	**79239 (94·0%)**	**5,094 (6·0%)**
Ulcerative Colitis	47,784	46,435 (97·2%)	1,349 (2·8%)
Crohn's	26,179	22,994 (87·8%)	3,185 (12·2%)
Undifferentiated IBD	12,241	11,544 (94·3%)	697 (5·7%)

Table S6. Main analysis: Hazard Ratios (HRs) and 95% confidence intervals (CI) for COVID-19-related death, death/critical care admission or hospitalisation, in people with IMIDs on targeted immune modifying therapies compared to those with IMIDs on standard systemic immune modifying therapies.

	Events	Person-years	Rate per 1000 PY (95%CI)	Crude HR (95%CI)	Age/sex adjusted HR (95%CI)	Confounder adjusted HR (95%CI)	Mediator adjusted HR (95%CI)
COVID-19 death							
Standard therapy	987	91,113	10·83 (10·17, 11·53)	REF	REF	REF	REF
Targeted therapy	66	9,604	6·87 (5·31, 8·74)	0·63 (0·49, 0·81)	1·11 (0·87, 1·43)	1·03 (0·80, 1·33)	1·01 (0·78, 1·30)
TNF inhibitor	32	6,800	Redacted††	0·43 (0·31, 0·62)	0·85 (0·60, 1·21)	0·84 (0·58, 1·20)	0·84 (0·59, 1·20)
IL-12/23 inhibitor	Redacted†	692	Redacted†	0·53 (0·20, 1·42)	1·47 (0·55, 3·95)	1·61 (0·60, 4·30)	1·59 (0·60, 4·23)
IL-17 inhibitor	Redacted†	522	Redacted†	0·18 (0·02, 1·25)	0·46 (0·06, 3·26)	0·45 (0·06, 3·21)	0·46 (0·06, 3·28)
IL-6 inhibitor	Redacted†	380	Redacted†	0·49 (0·12, 1·94)	0·63 (0·16, 2·52)	0·54 (0·14, 2·09)	0·48 (0·12, 1·89)
JAK inhibitor	Redacted†	437	Redacted†	1·06 (0·44, 2·54)	1·51 (0·63, 3·63)	1·35 (0·56, 3·21)	1·22 (0·51, 2·92)
Rituximab	Redacted††	998	Redacted††	2·23 (1·49, 3·34)	2·11 (1·41, 3·16)	1·68 (1·11, 2·56)	1·59 (1·05, 2·42)
COVID-19 critical care admission or death							
Standard therapy	1070	91,411	11·71 (11·01, 12·43)	REF	REF	REF	REF
Targeted therapy	76	9,622	7·90 (6·52, 10·3)	0·67 (0·53, 0·85)	1·11 (0·88, 1·40)	1·04 (0·82, 1·32)	1·02 (0·80, 1·29)
TNF inhibitor	Redacted††	6,809	5·43 (3·83, 7·49)	0·46 (0·33, 0·64)	0·84 (0·61, 1·17)	0·83 (0·59, 1·16)	0·83 (0·60, 1·16)
IL-12/23 inhibitor	Redacted†	694	Redacted†	0·49 (0·18, 1·31)	1·17 (0·44, 3·15)	1·25 (0·47, 3·33)	1·23 (0·46, 3·27)
IL-17 inhibitor	Redacted†	522	Redacted†	0·16 (0·02, 1·16)	0·37 (0·05, 2·62)	0·35 (0·05, 2·53)	0·36 (0·05, 2·58)

IL-6 inhibitor	Redacted†	382	Redacted†	0·67 (0·22, 2·08)	0·86 (0·28, 2·66)	0·75 (0·25, 2·27)	0·67 (0·22, 2·05)
JAK inhibitor	Redacted†	438	Redacted†	0·97 (0·41, 2·34)	1·33 (0·55, 3·20)	1·19 (0·50, 2·83)	1·09 (0·46, 2·60)
Rituximab	Redacted††	1,002	28·94 (19·38, 41·56)	2·48 (1·71, 3·58)	2·36 (1·63, 3·41)	1·92 (1·31, 2·81)	1·81 (1·24, 2·64)
COVID-19 hospitalisation							
Standard therapy	1787	91,360	19·56 (18·66, 20·49)	REF	REF	REF	REF
Targeted therapy	150	9,619	15·59 (13·20, 18·30)	0·80 (0·68, 0·94)	1·05 (0·89, 1·24)	0·99 (0·84, 1·17)	0·98 (0·82, 1·16)
TNF inhibitor	77	6,808	11·31 (8·93,14·14)	0·58 (0·46, 0·73)	0·80 (0·64, 1·01)	0·79 (0·63, 1·00)	0·80 (0·63, 1·00)
IL-12/23 inhibitor	11	694	15·85 (7·91, 28·36)	0·81 (0·45, 1·46)	1·29 (0·71, 2·32)	1·21 (0·67, 2·20)	1·70 (1·02, 2·82)
IL-17 inhibitor	8	521	15·35 (6·63, 30·24)	0·78 (0·39, 1·57)	1·18 (0·59, 2·37)	0·98 (0·49, 1·97)	0·99 (0·49, 2·00)
IL-6 inhibitor	6	381	15·76 (5·78, 34·30)	0·81 (0·36, 1·80)	0·91 (0·41, 2·03)	0·80 (0·36, 1·79)	0·74 (0·33, 1·65)
JAK inhibitor	15	437	34·31 (19·20, 56·59)	1·76 (1·06, 2·91)	2·04 (1·23, 3·39)	1·81 (1·09, 3·01)	1·70 (1·02, 2·82)
Rituximab	40	1,002	39·91 (28·51, 54·35)	2·04 (1·49, 2·79)	1·93 (1·41, 2·64)	1·59 (1·16, 2·18)	1·51 (1·10, 2·07)

Planned comparisons were made between people with IMIDs on any targeted immune modifying therapy (and for each group on specific targeted therapies) compared to people with IMIDs on standard systemic therapy as the reference group**.**

†Cells with counts less than 5 are redacted to protect anonymity.

††Cells which introduce a potential secondary statistical disclosure have been redacted to protect anonymity

Confounder adjusted: age, sex, deprivation, smoking status, BMI, specific IMID (inflammatory joint, bowel and skin disease), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end stage renal failure, chronic liver disease, chronic respiratory disease and diabetes mellitus.

Mediator adjusted: age, sex, deprivation, smoking status, BMI, specific IMID (inflammatory joint, bowel and skin disease), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end stage renal failure, chronic liver disease, chronic respiratory disease, diabetes mellitus and current glucocorticoid use.

Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; BMI, body mass index.

Table S7. Sensitivity analyses: for COVID-19-related death in people with IMIDs on targeted immune modifying therapies compared to those with IMIDs on standard systemic immune modifying therapies.

		Confounder-adjusted models Total n events: 1,046 Total n analysis: 199,248	Additionally adjusting our confounder -adjusted models for **ethnicity** Total n events: 1,046 Total n analysis: 199,248	Repeating the main analysis and adjusting for **smoking/BMI without missing data reclassification** Total n events: 994 Total n analysis: 184,272	Confounder-adjusted models excluding people with records of **haematological malignancy or organ transplants** Total n events: 1,001 Total n analysis: 196,404		**TNF inhibition limited to individuals with a prescription within the 3 months prior to study start compared to standard systemic therapy (prescribed within 3 months of study start).** Confounder-adjusted models Total n events: 901 Total n analysis: 162,949	
	Events	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**
Standard therapy	987	REF	REF	REF	951	REF	885	REF
Targeted therapy	66	1·03 (0·80, 1·33)	1·14 (0·86, 1·52)	0·98 (0·75, 1·28)	57	0·95 (0·72, 1·25)	N/A	N/A
TNF inhibitor	32	0·84 (0·58, 1·20)	0·93 (0·62, 1·39)	0·77 (0·52, 1·13)	Redacted††	0·83 (0·58, 1·20)	22	0·62 (0·40, 0·96)
IL-12/23 inhibitor	Redacted†	1·61 (0·60, 4·30)	2·22 (0·83, 5·93)	1·24 (0·40, 3·82)	Redacted†	1·69 (0·63, 4·51)	N/A	N/A
IL-17 inhibitor	Redacted†	0·45 (0·06, 3·21)	0·58 (0·08, 4·15)	0·47 (0·07, 3·36)	Redacted†	0·48 (0·07, 3·42)	N/A	N/A
IL-6 inhibitor	Redacted†	0·54 (0·14, 2·09)	0·68 (0·18, 2·58)	0·57 (0·15, 2·20)	Redacted†	0·29 (0·04, 2·06)	N/A	N/A
JAK inhibitor	Redacted†	1·35 (0·56, 3·21)	1·81 (0·76, 4·30)	1·41 (0·59, 3·36)	Redacted†	1·12 (0·42, 2·97)	N/A	N/A
Rituximab	24	1·68 (1·11, 2·56)	1·72 (1·06, 2·79)	1·68 (1·09, 2·57)	18	1·54 (0·95, 2·49)	N/A	N/A

Planned comparisons were made between people with IMIDs on any targeted immune modifying therapy (and for each group on specific targeted therapies) compared to people with IMIDs on standard systemic therapy as the reference group.
† Cells with counts less than 5 are redacted to protect anonymity.
††Cells which introduce a potential secondary statistical disclosure have been redacted to protect anonymity
Confounder adjusted: age, sex, deprivation, smoking status, BMI, specific IMID (inflammatory joint, bowel and skin disease), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end stage renal failure, chronic liver disease, chronic respiratory disease and diabetes mellitus.
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; BMI, body mass index.
* Events counts are different for these analyses due to exclusion of those with missing data on the additionally included variables (complete case analysis).

Table S8. Sensitivity analyses: COVID-19-related critical care admission/death in people with IMIDs on targeted immune modifying therapies compared to those with IMIDs on standard systemic immune modifying therapies

	COVID-19 death or critical care admission Confounder adjusted		**COVID-19 critical care admission alternative outcome Confounder adjusted**	
	Events	**Adjusted HR (95%CI)**	**Events**	**Adjusted HR (95%CI)**
Standard therapy	1070	REF	172	REF
Targeted therapy	76	1·04 (0·82, 1·32)	17	0·90 (0·54, 1·49)
TNF inhibitor	Redacted††	0·83 (0·59, 1·16)	8	0·63 (0·31, 1·30)
IL-12/23 inhibitor	Redacted†	1·25 (0·47, 3·33)	Redacted†	0·91 (0·12, 6·61)
IL-17 inhibitor	Redacted†	0·35 (0·05, 2·53)	Redacted†	0·83 (0·11, 6·03)
IL-6 inhibitor	Redacted†	0·75 (0·25, 2·27)	Redacted†	2·44 (0·60, 10·02)
JAK inhibitor	Redacted†	1·19 (0·50, 2·83)	0	0
Rituximab	Redacted††	1·92 (1·31, 2·81)	7	2·69 (1·24, 5·85)

Planned comparisons were made between people with IMIDs on any targeted immune modifying therapy (and for each group on specific targeted therapies) compared to people with IMIDs on standard systemic therapy as the reference group.
† Cells with counts less than 5 are redacted to protect anonymity.
††Cells which introduce a potential secondary statistical disclosure have been redacted to protect anonymity
Confounder adjusted: age, sex, deprivation, smoking status, BMI, specific IMID (inflammatory joint, bowel and skin disease), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end stage renal failure, chronic liver disease, chronic respiratory disease and diabetes mellitus.
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; BMI, body mass index.

Table S9. Sensitivity analysis: Hazard Ratios (95% CI) for COVID-19-related death with TNF inhibition monotherapy compared to those receiving combination TNF inhibition and standard systemic therapy.

	Events	**Confounder adjusted HR (95%CI)**
TNF and standard systemic combination therapy	21	REF
TNF inhibitor monotherapy	11	0·58 (0·26, 1·34)

Confounder adjusted: age, sex, deprivation, smoking status, BMI, specific IMID (inflammatory joint, bowel and skin disease), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end stage renal failure, chronic liver disease, chronic respiratory disease and diabetes mellitus
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; BMI, body mass index.

Table S10. Descriptive characteristics of population on targeted immunosuppression with infliximab

	Standard	**TNFi**	**Infliximab**
	N=181,694	N=13,524	N=2,112
Age			
18-39	24,898 (13·7%)	3,467 (25·6%)	915 (43·3%)
40-49	23,140 (12·7%)	2,456 (18·2%)	365 (17·3%)
50-59	36,588 (20·1%)	3,068 (22·7%)	372 (17·6%)
60-69	40,134 (22·1%)	2,523 (18·7%)	255 (12·1%)
70-79	38,842 (21·4%)	1,603 (11·9%)	165 (7·8%)
80+	18,092 (10·0%)	407 (3·0%)	40 (1·9%)
Sex			
Male	76,134 (41·9%)	6,259 (46·3%)	1,052 (49·8%)
BMI			
Underweight (<18·5)	3,752 (2·1%)	342 (2·5%)	93 (4·4%)
Normal (18·5-24·9)	52,050 (28·6%)	3,761 (27·8%)	694 (32·9%)
Overweight (25-29·9)	59,223 (32·5%)	3,989 (29·5%)	568 (26·9%)
Obese I (30-34·9)	32,671 (18·0%)	2,334 (17·3%)	310 (14·7%)
Obese II (35-39·9)	13,370 (7·4%)	1,071 (7·9%)	123 (5·8%)
Obese III (40+)	7,836 (4·3%)	650 (4·8%)	68 (3·2%)
Missing	12,792 (7·0%)	1,377 (10·2)	256 (12·1%)
Index of multiple deprivation			
1 (least deprived)	39,830 (21·9%)	3,104 (23·0%)	479 (22·7%)
2	38,618 (21·3%)	2,904 (21·5%)	431 (20·4%)
3	37,626 (20·7%)	2,724 (20·1%)	400 (18·9%)
4	34,698 (19·1%)	2,473 (18·3%)	423 (20·0%)
5 (most deprived)	29,508 (16·2%)	2,209 (16·3%)	354 (16·8%)
Missing	1,414 (0·8%)	110 (0·8%)	25 (1·2%)
Smoking			
Never	68,915 (37·9%)	5,214 (38·6%)	895 (42·4%)
Former	89,418 (49·2%)	5,769 (42·7%)	794 (37·6%)
Current	22,338 (12·3%)	2,352 (17·4%)	338 (16·0%)
Missing	1,023 (0·6%)	189 (1·4%)	85 (4·0)

	Standard	**TNFi**	**Infliximab**
	N=181,694	N=13,524	N=2,112
Comorbidities			
Diabetes mellitus			
With HbA1c<58mmol/mol	19,572 (10·8%)	1,007 (7·4%)	121 (5·7%)
With HbA1c≥58mmol/mol	7,863 (4·3%)	516 (3·8%)	60 (2·8%)
With unknown HbA1c	3,343 (1·8%)	245 (1·8%)	39 (1·8%)
Cardiovascular disease	24,056 (13·2%)	1,074 (7·9%)	105 (5·0%)
Stroke	7,204 (4·0%)	273 (2·0%)	26 (1·2%)
Cancer	16,721 (9·2%)	487 (3·6%)	75 (3·6%)
Glucocorticoids			
1 or more prescriptions in last 3 months*	20,254 (11·1%)	1,292 (9·6%)	204 (9·7%)
Ethnicity			
White	130,217 (71·7%)	9,481 (70·1%)	1,383 (65·5%)
Asian/Asian British	8,451 (4·7%)	671 (5·0%)	135 (6·4%)
Black	1,361 (0·7%)	123 (0·9%)	20 (0·9%)
Mixed/other	2,183 (1·2%)	201 (1·5%)	35 (1·7%)
Missing	39,482 (21·7%)	3,048 (22·5%)	539 (25·5%)

All figures are n (%) unless otherwise specified.
Individuals treated with systemic therapy and targeted therapy were included in the targeted therapy cohort.
*Glucocorticoid use refers to individuals with 1 or more primary care prescriptions for any dose of oral glucocorticoid in the last 3 months prior to the study start date (1st March 2020).
Abbreviations: TNFi, TNF inhibitors; BMI, Body mass index; Hba1c: glycosylated haemoglobin.

Table S11. Sensitivity analysis: Hazard Ratios (95% CI) for COVID-19-related death in people with an IMID on infliximab therapy compared to those on standard systemic therapy

	Events	**Confounder adjusted HR (95%CI)**
Main analysis		
Standard therapy	987	REF
TNF inhibitor	32	0·84 (0·58, 1·20)
Sensitivity analysis with TNFi exposure defined as infliximab only		
Standard therapy	987	REF
Infliximab	Redacted [#]	1·44 (0·60, 3·48)

Confounder adjusted: age, sex, deprivation, smoking status, BMI, specific IMID (inflammatory joint, bowel and skin disease), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end stage renal failure, chronic liver disease, chronic respiratory disease and diabetes mellitus
Abbreviations: HR, hazard ratio; CI, confidence interval.

Table S12. Analysis adjusting for age using a four-knot cubic spline: Hazard Ratios (HRs) and 95% confidence intervals (CI) for COVID-19-related death, death/critical care admission or hospitalisation, in people with IMIDs compared to the general population

	Main analysis: Age and sex adjusted HR (95%CI)	**Main analysis: Confounder adjusted HR (95%CI)**	**Age and sex adjusted with spline HR (95%CI)**	**Confounder adjusted HR with spline (95%CI)**
COVID-19 death				
General population	REF	REF	REF	REF
All IMID	1·27 (1·23, 1·31)	1·23 (1·20, 1·27)	1·32 (1·28, 1·35)	1·28 (1·24, 1·32)
Inflammatory joint disease	1·51 (1·44, 1·58)	1·47 (1·40, 1·54)	1·58 (1·51, 1·66)	1·54 (1·47, 1·61)
Inflammatory skin disease	1·16 (1·11, 1·20)	1·12 (1·08, 1·17)	1·19 (1·14, 1·24)	1·16 (1·11, 1·20)
Inflammatory bowel disease	1·15 (1·07, 1·24)	1·12 (1·04, 1·21)	1·19 (1·10, 1·28)	1·16 (1·08, 1·25)
COVID-19 critical care admission or death				
General population	REF	REF	REF	REF
All IMID	1·28 (1·24, 1·31)	1·24 (1·21, 1·28)	1·31 (1·28, 1·35)	1·28 (1·24, 1·32)
Inflammatory joint disease	1·50 (1·43, 1·57)	1·46 (1·39, 1·52)	1·56 (1·49, 1·63)	1·51 (1·45, 1·58)
Inflammatory skin disease	1·18 (1·13, 1·22)	1·15 (1·10, 1·19)	1·21 (1·16, 1·25)	1·18 (1·13, 1·22)
Inflammatory bowel disease	1·16 (1·08, 1·24)	1·13 (1·06, 1·22)	1·19 (1·11, 1·28)	1·17 (1·09, 1·25)
COVID-19 hospitalisation				
General population	REF	REF	REF	REF
All IMID	1·34 (1·31, 1·37)	1·32 (1·29, 1·35)	1·34 (1·31, 1·37)	1·33 (1·30, 1·36)
Inflammatory joint disease	1·57 (1·51, 1·63)	1·53 (1·47, 1·59)	1·57 (1·51, 1·63)	1·53 (1·48, 1·59)
Inflammatory skin disease	1·22 (1·19, 1·26)	1·21 (1·17, 1·24)	1·22 (1·19, 1·26)	1·21 (1·18, 1·25)
Inflammatory bowel disease	1·35 (1·28, 1·42)	1·31 (1·24, 1·38)	1·35 (1·28, 1·42)	1·31 (1·25, 1·38)

Planned comparisons were made between people with IMIDs, and IMID types (joint, bowel, skin), using the general population as the reference group.
Confounder adjusted: age, sex, deprivation,and smoking status
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; deprivation, index of multiple deprivation.

Table S13. Analysis adjusting for age using a four-knot cubic spline: Hazard Ratios (HRs) and 95% confidence intervals (CI) for COVID-19-related death, death/critical care admission or hospitalisation, in people with IMIDs on targeted immune modifying therapies compared to those with IMIDs on standard systemic immune modifying therapies.

	Main analysis: Age and sex adjusted HR (95%CI)	**Main analysis: Confounder adjusted HR (95%CI)**	**Using age spline: Age and sex adjusted HR (95%CI)**	**Using age spline: Confounder adjusted HR (95%CI)**
COVID-19 death				
Standard therapy	REF	REF	REF	REF
Targeted therapy	1·11 (0·87, 1·43)	1·03 (0·80, 1·33)	1·18 (0·92, 1·52)	1·16 (0·90, 1·50)
TNF inhibitor	0·85 (0·60, 1·21)	0·84 (0·58, 1·20)	0·49 (0·07, 3·48)	0·90 (0·63, 1·29)
IL-12/23 inhibitor	1·47 (0·55, 3·95)	1·61 (0·60, 4·30)	1·56 (0·58, 4·18)	1·57 (0·59, 4·22)
IL-17 inhibitor	0·46 (0·06, 3·26)	0·45 (0·06, 3·21)	0·68 (0·17, 2·72)	0·50 (0·07, 3·57)
IL-6 inhibitor	0·63 (0·16, 2·52)	0·54 (0·14, 2·09)	1·34 (0·55, 3·23)	0·68 (0·17, 2·68)
JAK inhibitor	1·51 (0·63, 3·63)	1·35 (0·56, 3·21)	1·54 (0·64, 3·70)	1·56 (0·65, 3·74)
Rituximab	2·11 (1·41, 3·16)	1·68 (1·11, 2·56)	2·24 (1·50, 3·36)	2·16 (1·42, 3·26)
COVID-19 critical care admission or death				
Standard therapy	REF	REF	REF	REF
Targeted therapy	1·11 (0·88, 1·40)	1·04 (0·82, 1·32)	1·17 (0·93, 1·48)	1·16 (0·91, 1·47)
TNF inhibitor	0·84 (0·61, 1·17)	0·83 (0·59, 1·16)	0·89 (0·64, 1·24)	0·88 (0·63, 1·23)
IL-12/23 inhibitor	1·17 (0·44, 3·15)	1·25 (0·47, 3·33)	1·23 (0·46, 3·30)	1·24 (0·46, 3·33)
IL-17 inhibitor	0·37 (0·05, 2·62)	0·35 (0·05, 2·53)	0·39 (0·05, 2·75)	0·39 (0·06, 2·80)
IL-6 inhibitor	0·86 (0·28, 2·66)	0·75 (0·25, 2·27)	0·92 (0·30, 2·84)	0·92 (0·30, 2·81)
JAK inhibitor	1·33 (0·55, 3·20)	1·19 (0·50, 2·83)	1·36 (0·57, 3·27)	1·38 (0·58, 3·31)
Rituximab	2·36 (1·63, 3·41)	1·92 (1·31, 2·81)	2·48 (1·72, 3·59)	2·40 (1·65, 3·50)
COVID-19 hospitalisation				
Standard therapy	REF	REF	REF	REF
Targeted therapy	1·05 (0·89, 1·24)	0·99 (0·84, 1·17)	1·07 (0·90, 1·26)	1·08 (0·92, 1·28)
TNF inhibitor	0·80 (0·64, 1·01)	0·79 (0·63, 1·00)	0·82 (0·65, 1·03)	0·83 (0·66, 1·05)
IL-12/23 inhibitor	1·29 (0·71, 2·32)	1·21 (0·67, 2·20)	1·31 (0·73, 2·37)	1·35 (0·75, 2·43)
IL-17 inhibitor	1·18 (0·59, 2·37)	0·98 (0·49, 1·97)	1·20 (0·60, 2·39)	1·23 (0·62, 2·46)
IL-6 inhibitor	0·91 (0·41, 2·03)	0·80 (0·36, 1·79)	0·93 (0·42, 2·08)	0·94 (0·42, 2·08)
JAK inhibitor	2·04 (1·23, 3·39)	1·81 (1·09, 3·01)	2·05 (1·23, 3·40)	2·07 (1·25, 3·44)
Rituximab	1·93 (1·41, 2·64)	1·59 (1·16, 2·18)	1·94 (1·42, 2·65)	1·93 (1·41, 2·64)

Planned comparisons were made between people with IMIDs on any targeted immune modifying therapy (and for each group on specific targeted therapies) compared to people with IMIDs on standard systemic therapy as the reference group**.**

†Cells with counts less than 5 are redacted to protect anonymity.

Confounder adjusted: age, sex, deprivation, smoking status, BMI, specific IMID (inflammatory joint, bowel and skin disease), cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, end stage renal failure, chronic liver disease, chronic respiratory disease and diabetes mellitus.age, sex, deprivation, smoking status, BMI, specific IMID, chronic cardiovascular disease, cancer (excluding non-melanoma skin cancer), stroke, and diabetes mellitus.

Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; BMI, body mass index.

Table S14. Minimum possible bias-adjusted association between rituximab and COVID-19 death

Risk ratio between exposure and unmeasured confounder	Risk ratio between unmeasured confounder and outcome				
	1·2	**1·5**	**2**	**3**	**5**
1·2	1·63 (1·08-2·49)	1·59 (1·05-2·42)	1·54 (1·02-2·35)	1·49 (0·99-2·28)	1·46 (0·96-2·22)
1·5	1·59 (1·05-2·42)	1·49 (0·99-2·28)	1·40 (0·93-2·13)	1·31 (0·86-1·99)	1·23 (0·81-1·88)
2	1·54 (1·02-2·35)	1·40 (0·93-2·13)	1·26 (0·83-1·92)	1·12 (0·74-1·71)	1·01 (0·67-1·54)
3	1·49 (0·99-2·28)	1·31 (0·86-1·99)	1·12 (0·74-1·71)	0·93 (0·62-1·42)	0·78 (0·52-1·19)
5	1·46 (0·96-2·22)	1·23 (0·81-1·88)	1·01 (0·67-1·54)	0·78 (0·52-1·19)	0·60 (0·40-0·92)

Table S15. Minimum possible bias-adjusted association between rituximab and COVID-19 critical care admission/death

Risk ratio between exposure and unmeasured confounder	Risk ratio between unmeasured confounder and outcome				
	1·2	**1·5**	**2**	**3**	**5**
1·2	1·87 (1·27-2·73)	1·81 (1·24-2·65)	1·76 (1·20-2·58)	1·71 (1·16-2·50)	1·66 (1·14-2·44)
1·5	1·81 (1·24-2·65)	1·71 (1·16-2·50)	1·60 (1·09-2·34)	1·49 (1·02-2·19)	1·41 (0·96-2·06)
2	1·76 (1·20-2·58)	1·60 (1·09-2·34)	1·44 (0·98-2·11)	1·28 (0·87-1·87)	1·15 (0·79-1·69)
3	1·71 (1·16-2·50)	1·49 (1·02-2·19)	1·28 (0·87-1·87)	1·07 (0·73-1·56)	0·90 (0·61-1·31)
5	1·66 (1·14-2·44)	1·41 (0·96-2·06)	1·15 (0·79-1·69)	0·90 (0·61-1·31)	0·69 (0·47-1·01)

Table S16. Minimum possible bias-adjusted association between rituximab and COVID-19 hospitalisation

Risk ratio between exposure and unmeasured confounder	Risk ratio between unmeasured confounder and outcome				
	1·2	**1·5**	**2**	**3**	**5**
1·2	1·55 (1·13-2·12)	1·50 (1·10-2·06)	1·46 (1·06-2·00)	1·41 (1·03-1·94)	1·38 (1·01-1·89)
1·5	1·50 (1·10-2·06)	1·41 (1·03-1·94)	1·32 (0·97-1·82)	1·24 (0·90-1·70)	1·17 (0·85-1·60)
2	1·46 (1·06-2·00)	1·32 (0·97-1·82)	1·19 (0·87-1·64)	1·06 (0·77-1·45)	0·95 (0·70-1·31)
3	1·41 (1·03-1·94)	1·24 (0·90-1·70)	1·06 (0·77-1·45)	0·88 (0·64-1·21)	0·74 (0·54-1·02)
5	1·38 (1·01-1·89)	1·17 (0·85-1·60)	0·95 (0·70-1·31)	0·74 (0·54-1·02)	0·57 (0·42-0·78)

Table S17. Minimum possible bias-adjusted association between JAK inhibitors and COVID-19 hospitalisation

Risk ratio between exposure and unmeasured confounder	Risk ratio between unmeasured confounder and outcome				
	1·2	**1·5**	**2**	**3**	**5**
1·2	1·76 (1·06-2·93)	1·71 (1·03-2·84)	1·66 (1·00-2·76)	1·61 (0·97-2·68)	1·57 (0·94-2·61)
1·5	1·71 (1·03-2·84)	1·61 (0·97-2·68)	1·51 (0·91-2·51)	1·41 (0·85-2·34)	1·33 (0·80-2·21)
2	1·66 (1·00-2·76)	1·51 (0·91-2·51)	1·36 (0·82-2·26)	1·21 (0·73-2·01)	1·09 (0·65-1·81)
3	1·61 (0·97-2·68)	1·41 (0·85-2·34)	1·21 (0·73-2·01)	1·01 (0·61-1·67)	0·84 (0·51-1·40)
5	1·57 (0·94-2·61)	1·33 (0·80-2·21)	1·09 (0·65-1·81)	0·84 (0·51-1·40)	0·65 (0·39-1·08)

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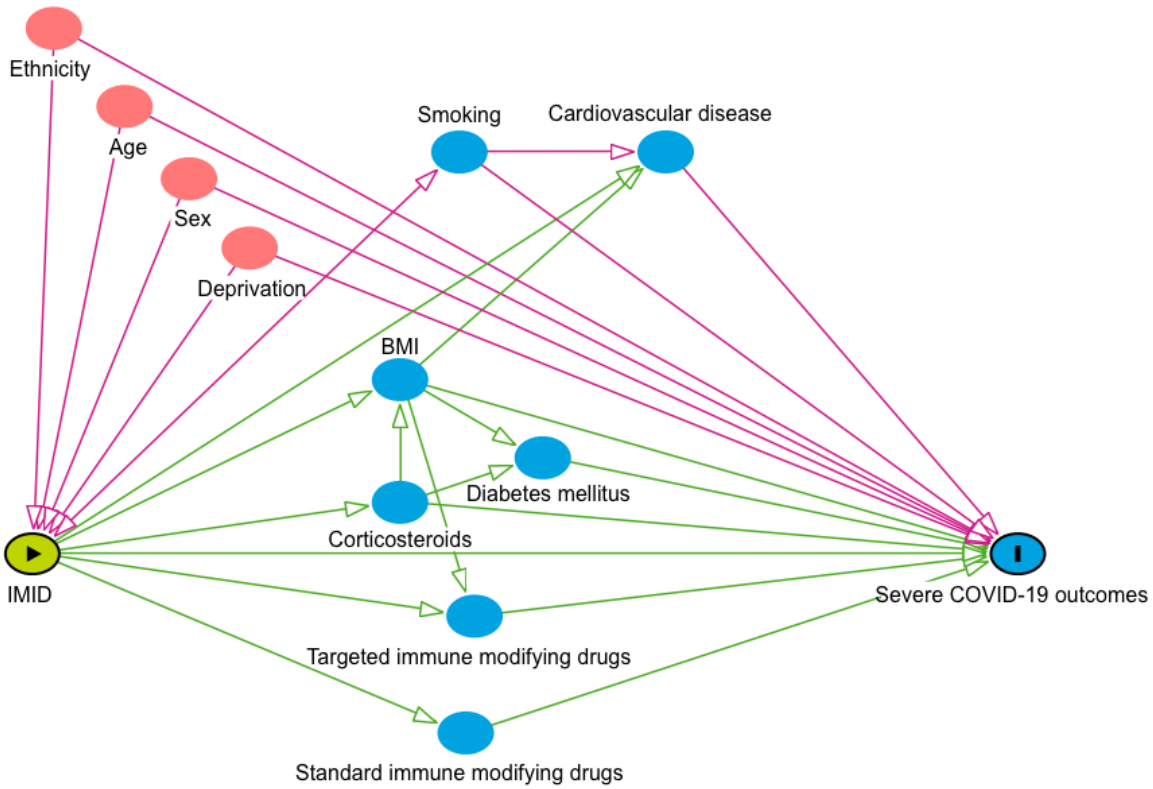
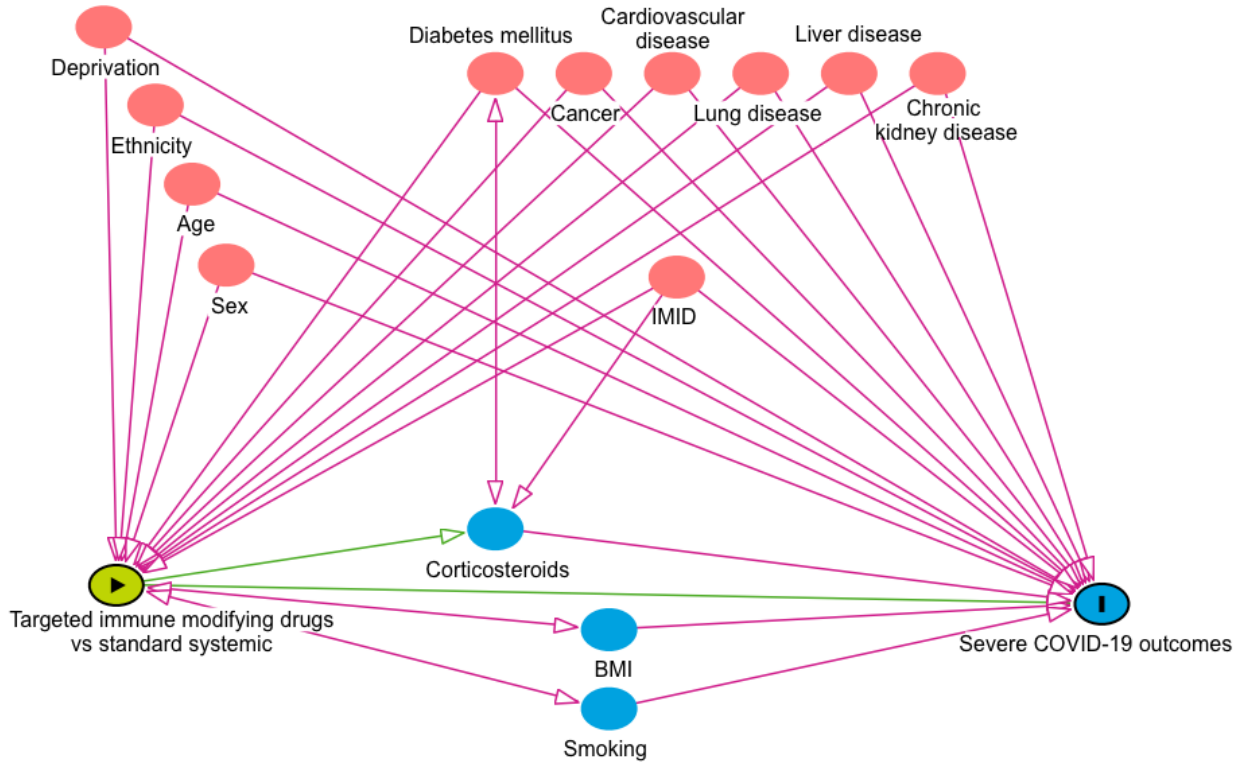
Figure S1. Conceptual framework: risk of COVID-19-related death in people with IMIDs compared to the general population



The conceptual framework represents the assumed associations between covariates and primary exposure and outcome. Pink circles represent ancestors of the exposure and outcome, blue circles represent ancestors of the outcome, pink lines represent biasing paths (i.e. confounding) and green lines represent causal paths.. The minimally sufficient adjustment set (i.e. the covariates adjusted for in confounder adjusted models) represents covariates such that the adjustment for this set of variables will minimize confounding bias when estimating the association between the exposure and the outcome.

Figure S2. Conceptual framework: risk of COVID-19-related death in people with IMIDS taking targeted immunosuppressive drugs compared to those prescribed standard systemic drugs.



The conceptual framework A directed acyclic graph represents the assumed associations between covariates and primary exposure and outcome. Pink circles represent ancestors of the exposure and outcome, blue circles represent ancestors of the outcome, pink lines represent biasing paths (i.e. confounding) and green lines represent causal paths. The minimally sufficient adjustment set (i.e. the covariates adjusted for in confounder adjusted models) represents covariates such that the adjustment for this set of variables will minimize confounding bias when estimating the association between the exposure and the outcome.

Figure S3. Age and sex distribution by ethnic group among people with an immune-mediate inflammatory disease within the OpenSafely cohort

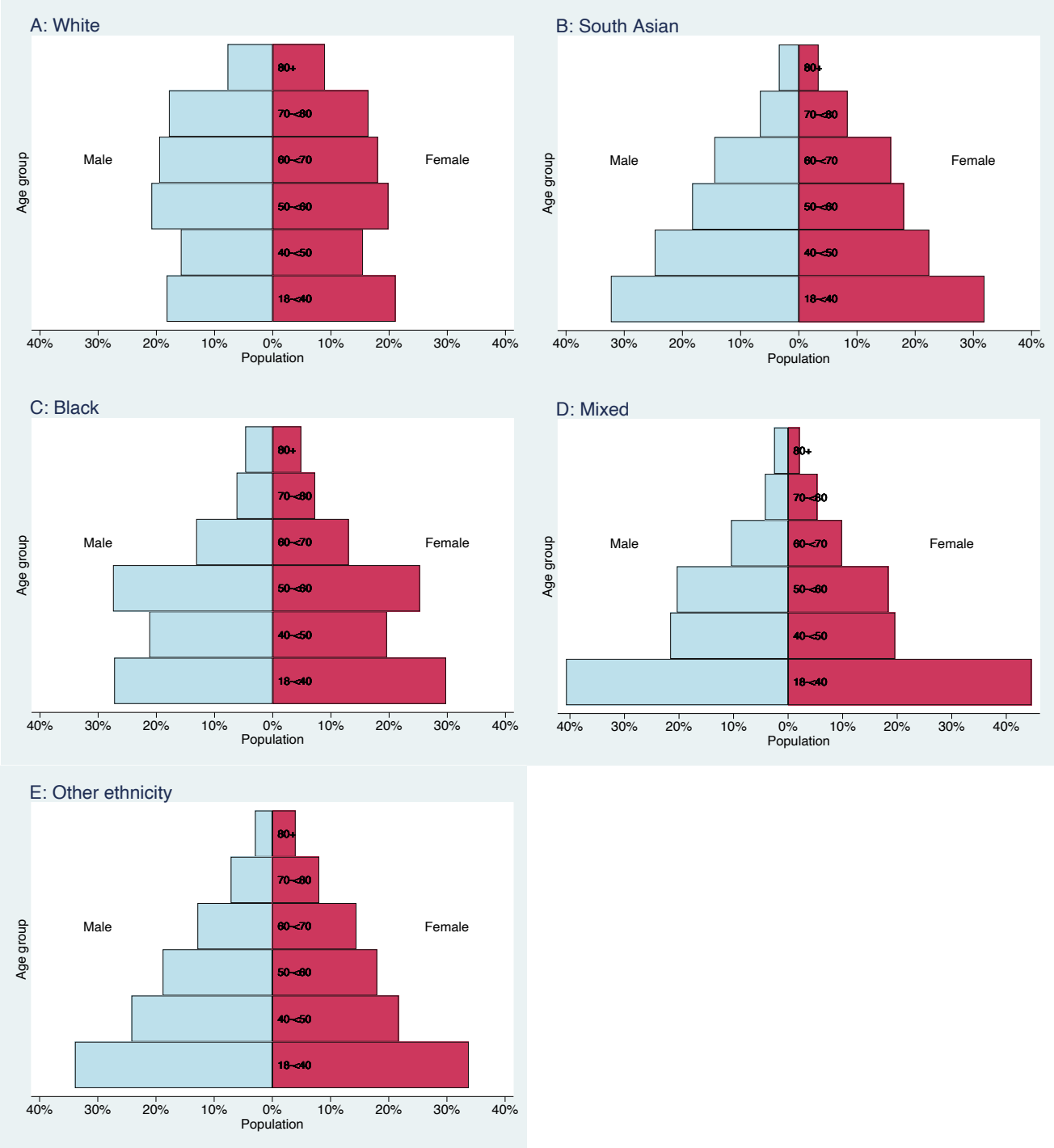


Figure S4. Outcomes in people with IMIDs compared to the general population by ethnic group

Comparisons were made within each ethnic group between people with IMIDs, and IMID types (joint, bowel, skin), using the general population as the reference group.
* Cells with counts less than or equal to 5 are redacted to protect anonymity. Cells which would potentially lead to a secondary risk of statistical disclosure are marked with an asterisk.
Minimally adjusted: age and sex
Confounder adjusted (IMID): age, sex, deprivation, smoking status
Mediator adjusted (IMID): age, sex, deprivation, smoking status, BMI, cardiovascular disease, diabetes, current glucocorticoid use
Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person years; IMID, immune mediated inflammatory disease; BMI, body mass index; ICU: intensive care unit (critical care admission).
NB: There was a small variation in the event counts for the IMID subtype analyses (inflammatory joint, bowel and skin disease). The general population event counts shown in this figure are for the all-IMID compared to general population analyses.

Figure S4a. Death from COVID-19

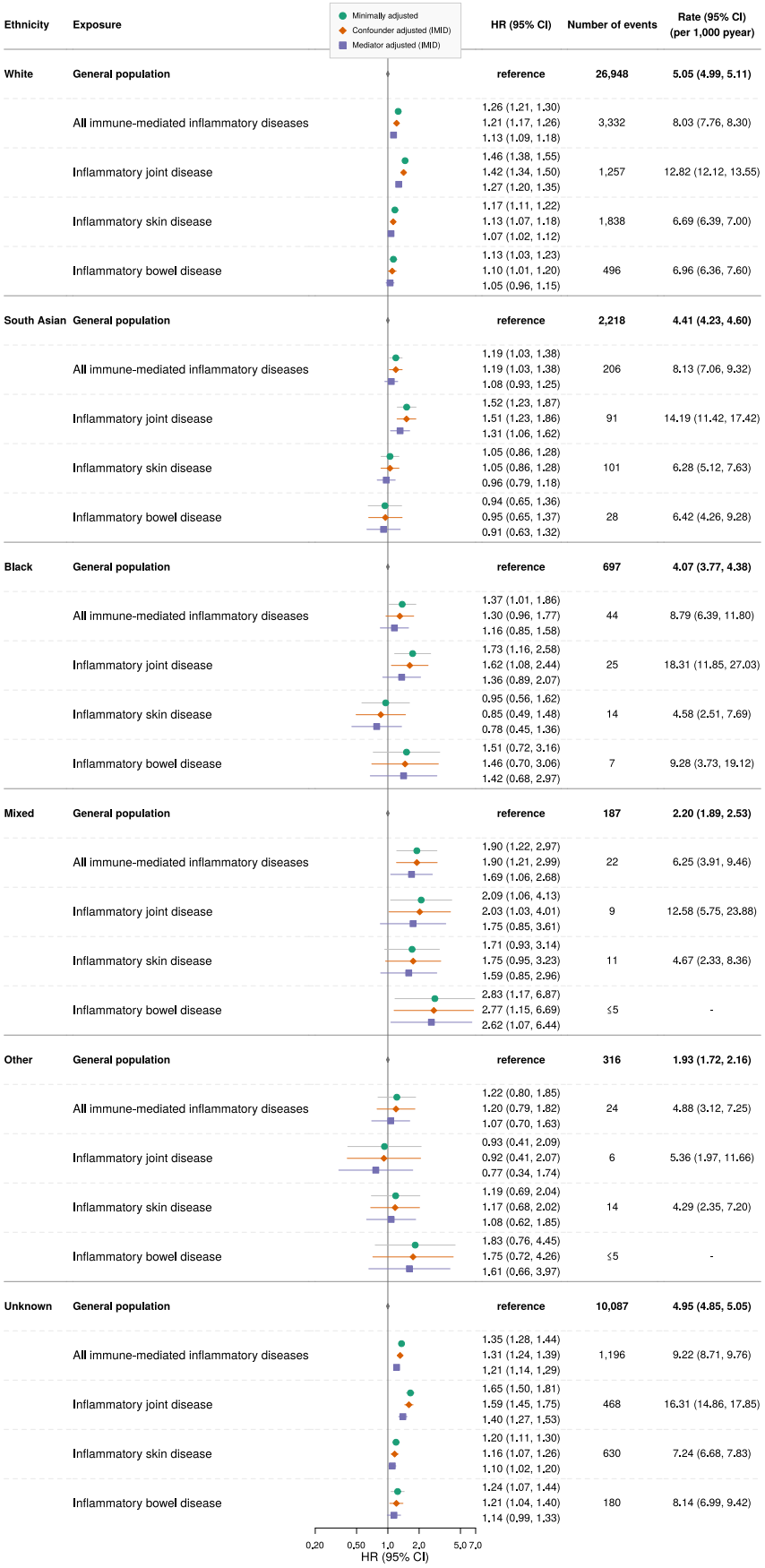


Figure S4b. Critical care admission or death related to COVID-19

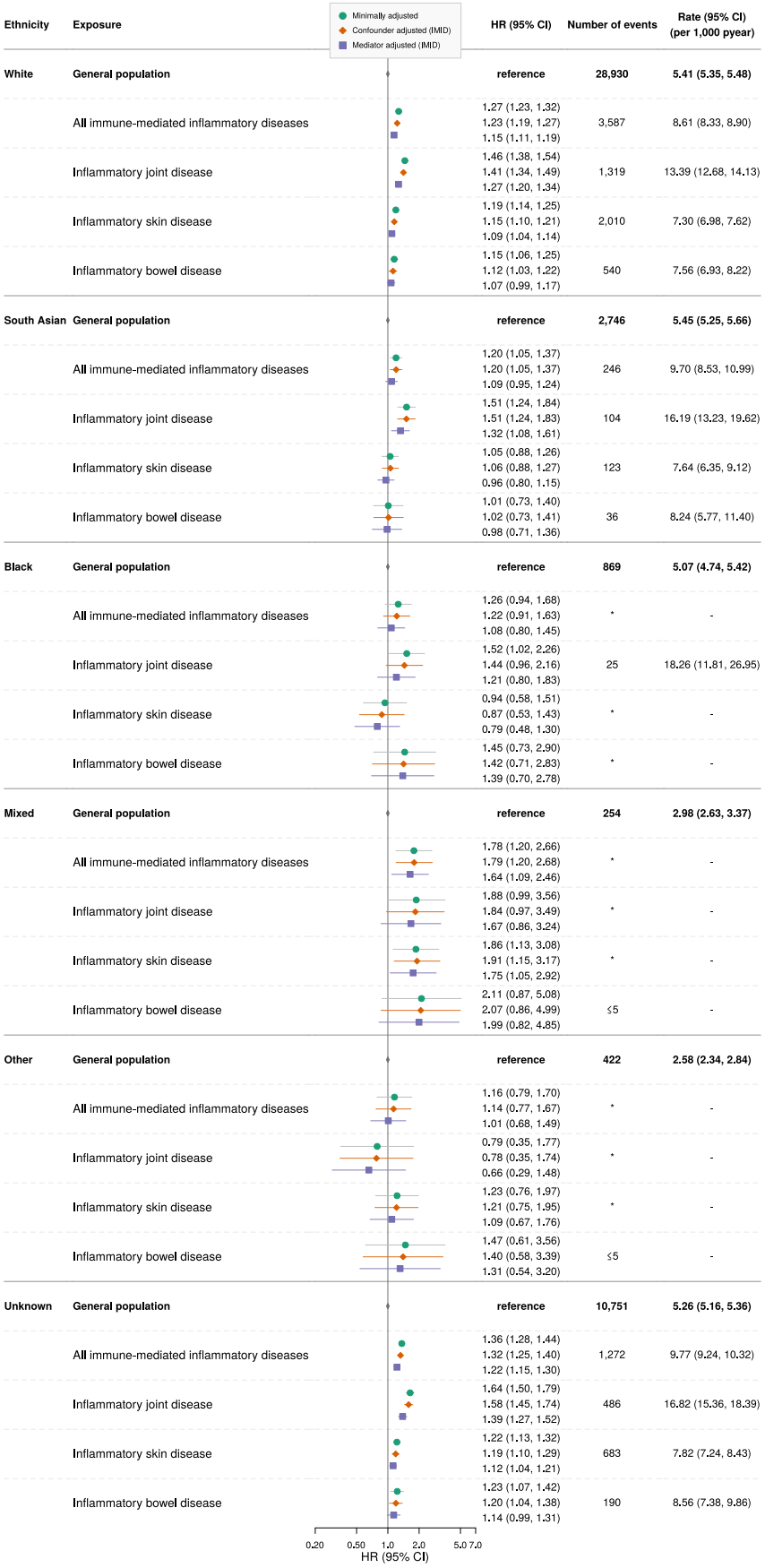


Figure S4c. Hospitalisation for COVID-19

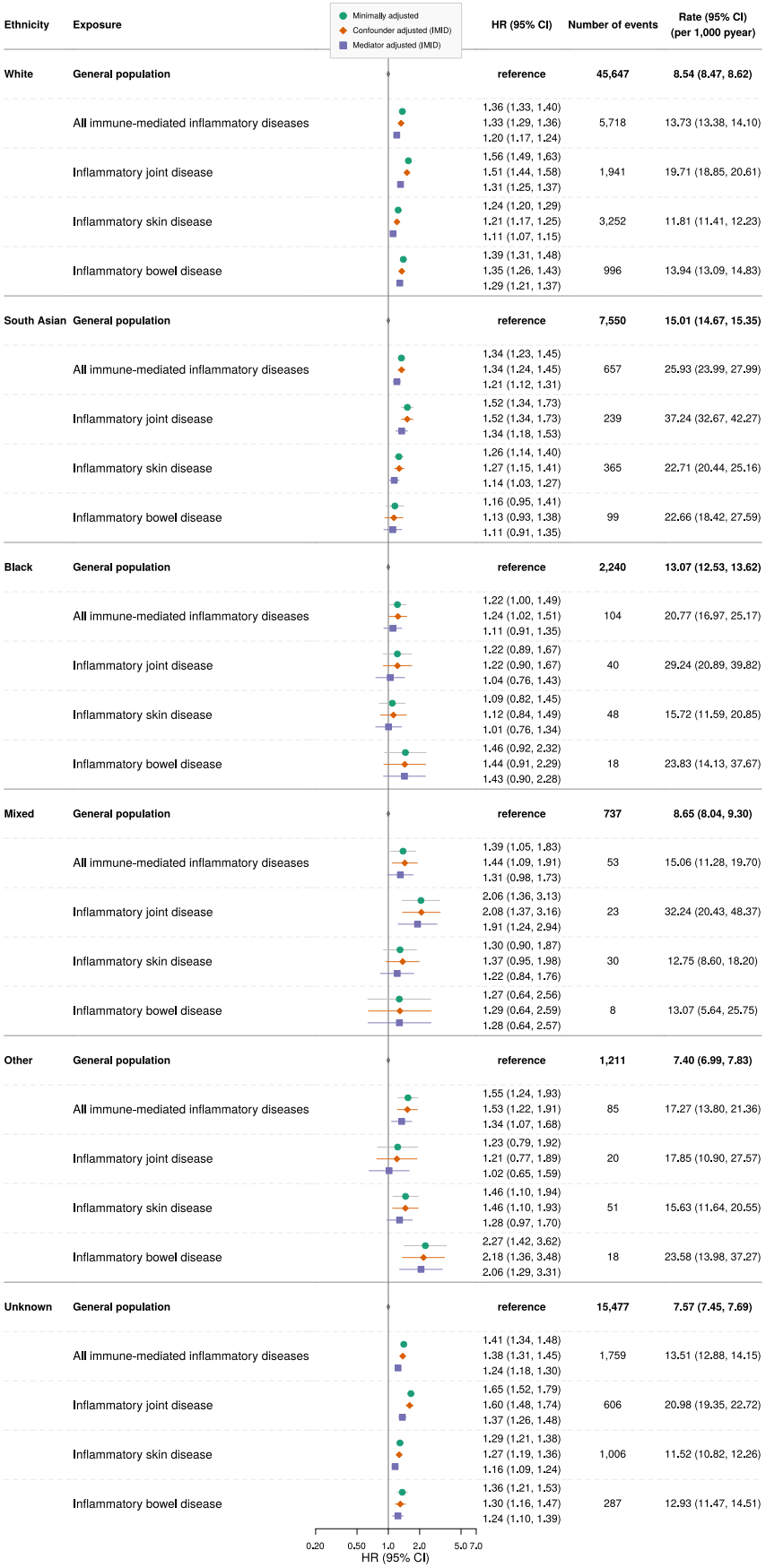


Figure S5. Minimum associations with unmeasured confounder required to potentially explain observed confounder-adjusted association between rituximab and COVID-19 death

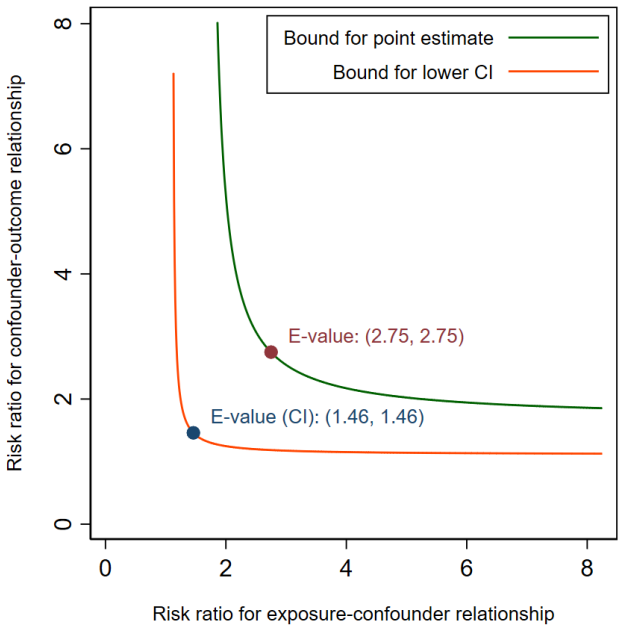


Figure S6. Minimum associations with unmeasured confounder required to potentially explain observed confounder-adjusted association between rituximab and COVID-19 critical care admission/death

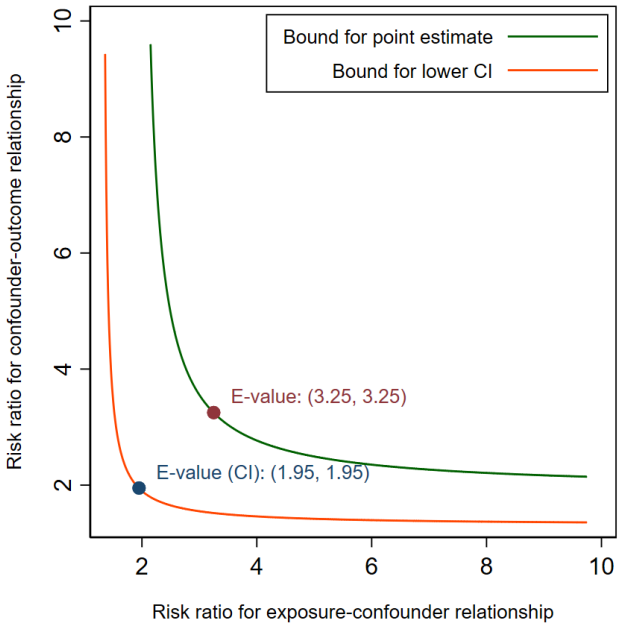


Figure S7. Minimum associations with unmeasured confounder required to potentially explain observed confounder-adjusted association between rituximab and COVID-19 hospitalisation

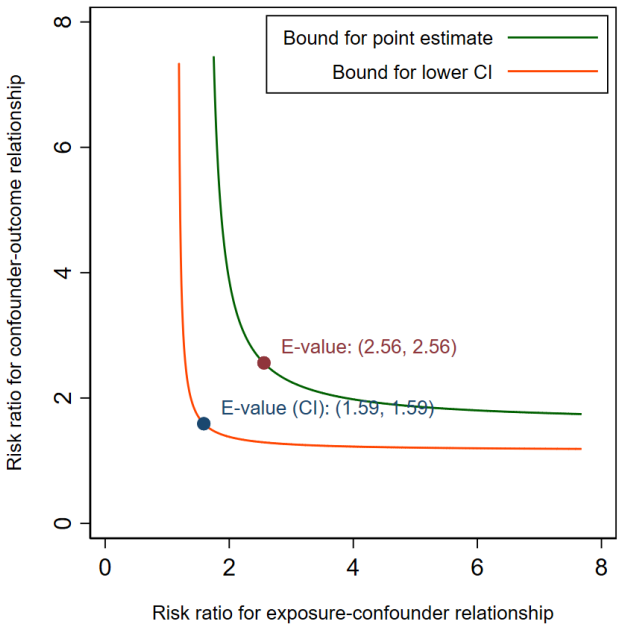


Figure S8. Minimum associations with unmeasured confounder required to potentially explain observed confounder-adjusted association between JAK inhibitors and COVID-19 hospitalisation