ACR Open Rheumatology
Vol. 3, No. 5, May 2021, pp 333–340
DOI 10.1002/acr2.11252

American College of Rheumatology
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Gout, Rheumatoid Arthritis, and the Risk of Death Related to Coronavirus Disease 2019: An Analysis of the UK Biobank

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Objectives. The objectives for this study were to assess whether gout and/or rheumatoid arthritis (RA) are risk factors for coronavirus disease 2019 (COVID-19) diagnosis and to assess whether gout and/or RA are risk factors for death from COVID-19.

Methods. We used data from the UK Biobank. Multivariable-adjusted logistic regression was employed in the following analyses: analysis A, to test for association between gout and/or RA and COVID-19 diagnosis (n = 473,139); analysis B, to test for association between gout and/or RA and death from COVID-19 in a case-control cohort of people who died of or survived COVID-19 (n = 2059); analysis C, to test for association between gout and/or RA and death from COVID-19 in the entire UK Biobank cohort (n = 473,139).

Results. RA, but not gout, was associated with COVID-19 diagnosis in analysis A. Neither RA nor gout was associated with risk of death in the group diagnosed with COVID-19 in analysis B. However, RA was associated with risk of death related to COVID-19 by using the UK Biobank cohort in analysis C, independent of comorbidities and other measured risk factors (odds ratio [OR] 1.9; 95% confidence interval CI 1.2–3.0). Gout was not associated with death related to COVID-19 in the same UK Biobank analysis (OR 1.2; 95% CI 0.8–1.7).

Conclusion. RA is a risk factor for death from COVID-19 by using the UK Biobank cohort. These findings require replication in larger data sets that also allow for inclusion of a wider range of factors.

INTRODUCTION

Data on coronavirus disease 2019 (COVID-19) outcomes for people with the two most common inflammatory arthropathies, gout and rheumatoid arthritis (RA), are scarce. An international registry study of 600 people with rheumatic diseases did not report any data on association of gout with hospitalization, owing to the small number of people with gout included (1). In the same study, people with RA did not have a different risk of hospitalization compared with people with other rheumatic diseases (1). In the OpenSAFELY study (2), which compared risk factors for 10,926 people who died of COVID-19 versus the general population in the United Kingdom, RA was pooled with systemic lupus erythematosus and psoriasis; this combined group had a hazard ratio of 1.2 (95% confidence interval [CI] 1.1–1.3) for death. However, gout was not examined in the OpenSAFELY study. A population-based study in Denmark reported a hazard ratio of 1.4 (95% CI 0.8–2.5) for an outcome of mechanical ventilation or severe respiratory disease or death from COVID-19 in people with RA (3). In a US study comparing people with COVID-19 with systemic autoimmune rheumatic diseases(of whom 45% had RA) with people with COVID-19 without these diseases, there was increased risk of hospitalization and admission to intensive care but not increased risk of death (4). A Spanish study reported no evidence for association of chronic inflammatory arthritis (48% with RA) with poor outcome in people with COVID-19 (5).

Gout is caused by an exuberant autoinflammatory interleukin 1β–driven innate immune system response to monosodium urate crystals (6). Theoretically, this has the potential to lead to an increased immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Poorer COVID-19 outcomes have been associated with high serum levels of interleukin 6 (IL-6),

The study was funded by the Health Research Council of New Zealand (grant 19/206).

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No potential conflicts of interest relevant to this article were reported.

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Submitted for publication December 28, 2020; accepted in revised form February 26, 2021.

SIGNIFICANCE & INNOVATIONS

- Information on the risk of death from coronavirus disease 2019 (COVID-19) for people with gout and rheumatoid arthritis is scarce.
- In an analysis of the UK Biobank, there is an increased risk of death related to COVID-19 for people with rheumatoid arthritis, independent of included comorbidities, but not gout.
- The findings need to be replicated in other data sets in which the influence of therapies for rheumatoid arthritis can be tested.

interleukin 8, and tumor necrosis factor α (TNF-α) (7), raising the possibility that people with gout might be at risk of a poor outcome because they also have higher circulating levels of these factors (8). Gout is also strongly associated with cardiometabolic comorbidities, such as type 2 diabetes, kidney disease, and heart disease (9), all established risk factors for COVID-19-related mortality (2). Gout medications may also influence outcomes following the development of COVID-19: two randomized controlled trials of colchicine, which is widely used as prophylaxis and treatment for gout flare (10), reported better clinical outcomes, including a shorter hospital length of stay and shorter supplemental oxygen duration, in people hospitalized with COVID-19 in those randomly assigned to receive colchicine (11,12). There is also nonrandomized evidence of the efficacy of colchicine in COVID-19 in a small case-control study (13).

RA is a T-cell and B-cell–mediated autoimmune disease that primarily affects the joints but also includes systemic manifestations. Like gout, RA is an independent risk factor for cardiovascular disease (14). The profile of RA includes increased levels of the proinflammatory cytokines TNF-α and IL-6 (15), a similar profile to COVID-19 (16), with the potential to lead to an increased immune response to infection by SARS-CoV-2.

The aim of this study was to determine whether gout and RA are risk factors for COVID-19 diagnosis or death from COVID-19.

PATIENTS AND METHODS

Data Availability Statement. This research was conducted by using the UK Biobank resource (approval No. 12611). The UK Biobank is a large resource of nearly 500,000 volunteers 49 to 86 years of age at recruitment. Recruitment began in 2006, with follow-up for at least 30 years (17). SARS-CoV-2 test information, *International Classification of Diseases, 10th Revision* (ICD-10) hospital codes, death records, and general practice prescription information were obtained via the UK Biobank data portal on September 16, 2020. This information covered hospital diagnoses between 1991 and June 30, 2020, SARS-CoV-2 tests between March 16 and August 24, 2020, and death records up until August 14, 2020.

Gout, RA, and COVID-19 definitions and case-control data sets. The criteria for COVID-19 diagnosis was defined as participants with 1) a positive SARS-CoV-2 test result and/or 2) an ICD-10 code for confirmed COVID-19 (U07.1) or probable COVID-19 (U07.2) in hospital records or death records (Figure 1). This definition resulted in identification of 2118 individuals, who were further divided into those who died (n = 457), based on death records, and those who were known to survive (n = 1602). Fifty-nine participants who were diagnosed after July 26, 2020 (28 days before the last recorded death), were removed from the cohort used in analysis B (below) given the unknown outcome in these individuals. Gout was ascertained by a previously validated gout definition (18,19) using the following criteria: self-reported gout (visits 0-2), or allopurinol or sulphinpyrazone therapy either by self-report or from linked general practice prescriptions (excluding those who also had hospital-diagnosed lymphoma or leukemia [ICD-10 codes C81-C96]), or hospital-diagnosed gout (ICD-10 code M10) (18). The gout case-control cohort (n = 473,139) consisted of 13,105 case patients (with gout) and 460,034 controls (without gout). RA affection was ascertained by using a combination of self-reported RA at more than one study visit, hospital-recorded RA (ICD-10 codes M05-M06) on more than one occasion, or self-reported RA at recruitment and at least one hospital record of RA. The RA cohort (n = 473,139) consisted of 5409 people with RA and 467,730 people without RA (Table 1).

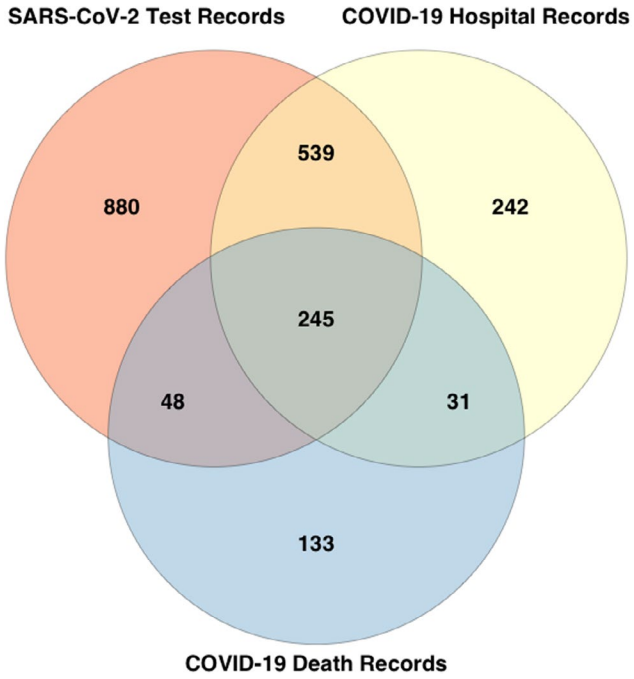

Figure 1. Data sources of individuals diagnosed with coronavirus disease 2019 (COVID-19)-. Of the 2118 individuals diagnosed with COVID-19, 1712 were identified from positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test results (880 unique to this group), 1057 were identified from hospital records (242 unique to this group), and 457 were identified from death records (133 unique to this group).

Table 1. Characteristics of participants with and without gout and RA

	With Gout	Without Gout	With RA	Without RA
n	13,105	460,034	5409	467,730
Age, n (%)				
<60 years	1110 (8.5)	88,499 (19.2)	465 (8.6)	89,144 (19.1)
60-69 years	3285 (25.1)	147,857 (32.1)	1466 (27.1)	149,676 (32.0)
70-74 years	3457 (26.4)	106,705 (23.2)	1470 (27.2)	108,692 (23.2)
>74 years	5253 (40.1)	116,973 (25.4)	2008 (37.1)	120,218 (25.7)
Sex, n (%)				
Male	11,253 (85.9)	200,374 (43.6)	1537 (28.4)	210,090 (44.9)
Female	1852 (14.1)	259,660 (56.4)	3872 (71.6)	257,640 (55.1)
BMI, mean (SD)	30.4 (5.0)	27.3 (4.7)	28.5 (5.6)	27.4 (4.8)
Townsend deprivation index score, mean (SD)	−1.07 (3.2)	−1.34 (3.1)	−0.86 (3.3)	−1.34 (3.1)
Ethnicity, n (%)				
White British	12,321 (94.2)	432,226 (94.1)	5042 (93.5)	439,505 (94.1)
Black British	368 (2.8)	11,458 (2.5)	161 (3.0)	11,665 (2.5)
Asian British	189 (1.5)	8599 (1.9)	114 (2.1)	8674 (1.9)
Other	196 (1.5)	6940 (1.5)	77 (1.4)	7059 (1.5)
Smoking status, n (%)				
Never smoker	5612 (43.2)	256,879 (56.2)	2495 (46.6)	259,996 (55.9)
Current smoker	6202 (47.7)	154,574 (33.8)	2210 (41.3)	158,566 (34.1)
Ex-smoker	1190 (9.2)	46,005 (10.1)	650 (12.1)	46,545 (10.0)
Asthma, n (%)	1562 (11.9)	39,336 (8.6)	1073 (19.8)	39,825 (8.5)
Cancer, n (%)	2653 (20.2)	64,197 (14.0)	1135 (21.0)	65,715 (14.1)
Cerebrovascular diseases, n (%)	939 (7.2)	13,154 (2.9)	410 (7.6)	13,683 (2.9)
Chronic kidney disease, n (%)	1844 (14.1)	11,489 (2.5)	570 (10.5)	12,763 (2.7)
Chronic obstructive pulmonary diseases, n (%)	932 (7.1)	13,724 (3.0)	650 (12.0)	14,006 (3.0)
Dementia, n (%)	140 (1.1)	2208 (0.5)	88 (1.6)	2260 (0.5)
Diabetes mellitus, n (%)	2,552 (19.5)	30,595 (6.7)	812 (15.0)	32,335 (6.9)
Gout, n (%)	-	-	258 (4.8)	12,847 (2.8)
Heart failure, n (%)	1247 (9.5)	8712 (1.9)	370 (6.8)	9589 (2.1)
Hypertensive diseases, n (%)	7807 (59.6)	118,291 (25.7)	2890 (53.4)	123,208 (26.3)
Immunodeficiencies, n (%)	102 (0.8)	1664 (0.4)	91 (1.7)	1675 (0.4)
Ischemic heart diseases, n (%)	3301 (25.2)	42,250 (9.2)	1189 (22.0)	44,362 (9.5)
Lipoprotein disorders, n (%)	4163 (31.8)	58,824 (12.8)	1482 (27.4)	61,505 (13.2)
Osteoarthritis, n (%)	4018 (30.7)	75,353 (16.4)	2825 (52.2)	76,546 (16.4)
Pulmonary heart disease, n (%)	463 (3.5)	6002 (1.3)	227 (4.2)	6238 (1.3)
RA, n (%)	258 (2.0)	5151 (1.1)	-	-

Abbreviations: BMI, body mass index; RA, rheumatoid arthritis.

For the RA and gout cohorts, we developed three case-control data sets to test for association with the following outcomes:

1. Data set A (analysis A) to test for association with COVID-19 diagnosis in a population-based cohort. There were 2118 case patients and 471,021 controls
2. Data set B (analysis B) to test for association with death from COVID-19 in people with COVID-19. There were 457 people diagnosed with COVID-19 who died and 1602 people diagnosed with COVID-19 who survived
3. Data set C (analysis C) to test for association with death related to COVID-19 in a population-based cohort. There were 457 people diagnosed with COVID-19 who died and 472,682 others, including 1616 people diagnosed with COVID-19 not known to have died

Ethnicity, age, and comorbidity data. Self-reported ethnicity was grouped into White British (British, Irish, White, or any other White background), Black British (African, White and Black African, Black or Black British, Caribbean, White and Black Caribbean, or any other Black background), Asian British (Asian or Asian British, Chinese, Indian, Pakistani, Bangladeshi, White and Asian, or any other Asian background), and other (other ethnic group, mixed, any other mixed background, do not know, or prefer not to answer). Age was calculated for 2020 from year of birth. The ICD-10 hospital codes used to determine additional comorbidity status were the following: C00 to C96 (cancer), D80 to D89 (immunodeficiencies), E08 to E13 (diabetes mellitus), E78 (disorders of lipoprotein metabolism and other lipidemia disorders), F01 to F03 (dementia), I10 to I15 (hypertensive diseases), I60 to I69 (cerebrovascular diseases), I20 to I25 (ischemic heart diseases), I26 to I28 (pulmonary heart disease), I50 (heart failure), J44 (chronic obstructive pulmonary diseases), J45 (asthma), M19.9 (osteoarthritis), and N18 (chronic kidney disease).

Statistical analysis. All association analyses were done by using R version 4.0.2 in RStudio 1.2.5019 (R Foundation for Statistical Computing). Age groups used in the analysis were <60 years (n = 89,607), 60 to 69 years (n = 151,139), 70 to 74 years (n = 110,159), and >74 years (n = 122,222). Two models were used: adjustment with age group, sex, ethnicity, Townsend deprivation index, body mass

Table 2. Logistic regression association analyses adjusted for current age, sex, ethnicity, Townsend deprivation index, BMI, and smoking status (model 1)

	COVID-19 diagnosis (analysis A)			Death in group diagnosed with COVID-19 (analysis B)			Death from COVID-19 in entire cohort (analysis C)		
	Yes/No	OR (95% CI)	*P*	Died/surviving	OR (95% CI)	*P*	Died/remaining cohort	OR (95% CI)	*P*
N	2118/471,021	-	-	457/1602	-	-	457/472,682	-	-
Gout	117/12,988	1.50 (1.24–1.82)	3.6×10^{-5}	42/73	1.29 (0.84–1.98)	0.24	42/13,063	1.71 (1.23–2.38)	1.4×10^{-3}
Men only	97/11,156	1.36 (1.10–1.69)	4.7×10^{-3}	33/62	1.18 (0.73–1.92)	0.49	33/11,220	1.52 (1.05–2.20)	0.027
Women only	20/1832	2.05 (1.30–3.22)	1.9×10^{-3}	9/11	2.38 (0.91–6.22)	0.076	9/1843	3.19 (1.60–6.37)	1.0×10^{-3}
RA	61/5348	2.22 (1.70–2.90)	4.2×10^{-9}	23/38	1.68 (0.93–3.03)	0.085	23/5386	3.23 (2.07–5.04)	2.2×10^{-7}
Men only	20/1517	1.76 (1.09–2.86)	0.022	10/10	2.14 (0.78–5.86)	0.14	10/1527	2.90 (1.48–5.66)	1.9×10^{-3}
Women only	41/3831	2.56 (1.86–3.53)	8.8×10^{-9}	13/28	1.46 (0.69–3.07)	0.32	13/3859	3.51 (1.94–6.36)	3.4×10^{-5}
Dementia	203/2145	18.23 (15.52–21.43)	2.8×10^{-272}	76/122	1.36 (0.97–1.90)	0.075	76/2272	19.22 (14.76–25.01)	4.2×10^{-107}
Cerebrovascular diseases	313/13,780	4.70 (4.14–5.34)	1.3×10^{-125}	95/210	0.98 (0.73–1.31)	0.90	95/13,998	4.62 (3.65–5.85)	3.3×10^{-37}
Heart failure	223/9736	4.02 (3.47–4.67)	1.1×10^{-74}	83/139	1.34 (0.97–1.86)	0.08	83/9876	4.53 (3.51–5.85)	4.6×10^{-31}
Chronic kidney disease	260/13,073	3.74 (3.25–4.29)	2.7×10^{-77}	89/167	1.35 (0.99–1.83)	0.057	89/13,244	4.04 (3.16–5.16)	6.8×10^{-29}
Pulmonary heart disease	116/6349	3.40 (2.80–4.13)	3.1×10^{-35}	32/82	0.98 (0.62–1.54)	0.93	32/6433	3.30 (2.29–4.76)	1.4×10^{-10}
Immunodeficiencies	28/1738	3.25 (2.23–4.74)	10.0×10^{-10}	14/14	3.41 (1.49–7.78)	3.57×10^{-3}	14/1752	7.26 (4.23–12.47)	6.2×10^{-13}
Chronic obstructive pulmonary diseases	241/14,415	3.09 (2.67–3.57)	2.1×10^{-51}	81/157	1.16 (0.84–1.62)	0.37	81/14,575	3.20 (2.46–4.15)	2.7×10^{-18}
Hypertensive diseases	1076/125,022	2.44 (2.22–2.69)	1.7×10^{-74}	299/757	1.10 (0.85–1.41)	0.48	299/125,799	2.60 (2.11–3.21)	2.2×10^{-19}
Diabetes mellitus	430/32,717	2.38 (2.11–2.68)	7.1×10^{-47}	132/285	1.29 (0.98–1.71)	0.07	132/33,015	2.67 (2.13–3.34)	2.1×10^{-17}
Lipoprotein disorders	610/62,377	2.12 (1.92–2.35)	3.2×10^{-47}	170/428	0.99 (0.78–1.26)	0.93	170/62,817	1.96 (1.60–2.40)	5.2×10^{-11}
Ischemic heart diseases	438/45,113	1.95 (1.74–2.18)	6.0×10^{-31}	131/295	1.05 (0.81–1.37)	0.72	131/45,420	1.88 (1.52–2.33)	8.6×10^{-9}
Cancer	476/66,374	1.73 (1.55–1.92)	9.9×10^{-24}	127/343	0.97 (0.75–1.25)	0.80	127/66,723	1.59 (1.29–1.97)	1.6×10^{-5}
Asthma	306/40,592	1.59 (1.40–1.80)	2.7×10^{-13}	67/226	1.11 (0.80–1.53)	0.54	67/40,831	1.60 (1.23–2.08)	4.6×10^{-4}
Osteoarthritis	558/78,813	1.54 (1.39–1.71)	3.6×10^{-16}	144/404	0.84 (0.65–1.08)	0.18	144/79,227	1.40 (1.14–1.72)	1.6×10^{-3}

Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio; RA, rheumatoid arthritis.

index (BMI), and smoking status (model 1) and model 1 plus adjustment by the 15 other comorbidities evaluated (model 2). A threshold of $P < 0.05$ indicated nominal evidence for association.

Ethical approval. The UK Biobank resource was conducted under ethical approval from the North West Multi-centre Research Ethics Committee of the United Kingdom. The study complies with the Declaration of Helsinki, and informed consent was obtained from all participants.

RESULTS

Association with diagnosis of COVID-19. Results from the analyses of associations of gout and RA with COVID-19 diagnosis (analysis A) using model 1 (adjustment for current age, sex, Townsend deprivation index, ethnicity groups, BMI, and smoking status) are presented in Table 2. Gout and RA were associated with a 1.5-fold (95% CI 1.2–1.8) and 2.2-fold (95% CI 1.7–2.9) increased risk of COVID-19 diagnosis, respectively. We also included in our study other diseases known to be risk factors for poor COVID-19 outcome (2) both for comparison of effect sizes and for inclusion in models as potential confounders. In comparison, data for other diseases were as follows: cerebrovascular diseases, odds ratio (OR) 4.7 (95% CI 4.1–5.3); heart failure, OR 4.0 (95% CI 3.5–4.7); chronic kidney disease, OR 3.7 (95% CI 3.3–4.3); pulmonary heart disease, OR 3.4 (95% CI 2.8–4.1); immunodeficiencies, OR 3.3 (95% CI 2.2–4.7); and chronic obstructive pulmonary disorders, OR 3.1 (95% CI 2.7–3.6). Twofold to threefold increases in risk were estimated for hypertensive diseases (OR 2.4; 95% CI 2.2–2.7), diabetes mellitus (OR 2.4; 95% CI 2.1–2.7), and lipoprotein disorders (OR 2.1; 95% CI 1.9–2.4). Onefold to twofold increases in risk were estimated for ischemic heart diseases (OR 2.0; 95% CI 1.7–2.2), cancer (OR 1.7; 95% CI 1.6–1.9), asthma (OR 1.6; 95% CI 1.4–1.8), osteoarthritis (OR 1.5; 95% CI 1.4–1.7), and dementia (OR 18.2; 95% CI 15.5–21.4), which were all strongly associated with COVID-19. After adjustment for model 1 variables and the additional 15 comorbidities evaluated (model 2), gout was no longer associated with COVID-19 diagnosis, nor was ischemic heart disease, asthma, and osteoarthritis (Table 3). RA maintained nominal association (OR 1.3; 95% CI 1.0–1.8). Increased age was associated with decreased risk of COVID-19 diagnosis (OR 0.54 [95% CI 0.47–0.61] for 60-69 years, OR 0.45 [95% CI 0.39–0.53] for 70-74 years, and OR 0.60 [95% CI 0.52–0.69] for >74 years when compared with <60 years; Table 3). This decreased risk may reflect a number of factors that influence exposure to SARS-CoV-2 in these age groups, including public health messaging around limiting exposure for older people.

Associations with death after diagnosis of COVID-19. When testing for association with death related to COVID-19 within the cohort with COVID-19 diagnosis (analysis B), there was no evidence for association with gout or RA in either model 1 or 2 (Tables 2 and 3). For other diseases, there was association with immunodeficiencies (model 1: OR 3.4 [95% CI 1.5–7.8]; model 2: OR 3.6 [95% CI 1.6–8.4]). Established risk factors for death from COVID-19, namely male sex and older age, were associated with death (OR 1.4 [95% CI 1.1–1.9] for men; OR 3.6 [95% CI 2.0–6.6] for 60-69 years, OR 9.4 [95% CI 5.2–17.0] for 70-74 years, and OR 16.3 [95% CI 9.2–28.9] for >74 years, compared with <60 years) (Table 3).

We then tested for association with death related to COVID-19, comparing to the entire UK Biobank cohort (analysis C). Gout was associated with a 1.7-fold increase (95% CI 1.2–2.4) in COVID-19-related death under model 1 but not model 2 (OR 1.2; 95% CI 0.8–1.7). In contrast, RA was associated with increased risk of death from COVID-19 in both models (model 1: OR 3.2 [95% CI 2.1–5.0]; model 2: OR 1.9 [95% CI 1.2–3.0]). Given the association of sex with prevalence of comorbidity in gout and RA (20-23), sex-specific analyses were performed. In RA, the data were OR 2.9 (95% CI 1.5–5.7) for men and OR 3.5 (95% CI 1.9–6.4) for women in model 1 and OR 1.5 (95% CI 0.7–3.1) for men and OR 2.0 (95% CI 1.0–3.7) for women in model 2. In gout, the data were OR 1.5 (95% CI 1.1–2.2) for men and OR 3.2 (95% CI 1.6–6.4) for women in model 1 and OR 1.2 (95% CI 0.8–1.7) for men and OR 1.7 (95% CI 0.9–3.5) for women in model 2.

In analysis C, we also assessed the 14 additional diseases for association with death from COVID-19, comparing to the entire UK Biobank cohort. Dementia, immunodeficiencies, chronic obstructive pulmonary diseases, cerebrovascular diseases, heart failure, pulmonary heart disease, chronic kidney disease, hypertensive diseases, diabetes mellitus, and cancer were all associated with additional risk of death in model 2 (Table 3), with dementia and immunodeficiencies having the strongest effects (OR 10.2 [95% CI 7.6–13.6] and OR 4.6 [95% CI 2.6–8.0], respectively). In model 2, people of Black British ancestry had the highest risk of death (OR 2.7; 95% CI 1.7–4.3), compared with people of White British ancestry, and there was a positive association of death with BMI (OR 1.03 [95% CI 1.01–1.05] per unit increase in BMI) and with an increased Townsend deprivation index score (OR 1.07; 95% CI 1.04–1.10), consistent with a higher prevalence of seroprevalence of SARS-CoV-2 infection in people living in more deprived areas in the United Kingdom (24). Ex-smokers were at an increased risk of death from COVID-19 in model 2 (OR 1.7; 95% CI 1.3–2.3) compared with never smokers, consistent with the OpenSAFELY data from the United Kingdom (2), although directionality of association was different from the OpenSAFELY data for current smokers (OR 1.3; 95% CI 1.0–1.6). Age group was also associated with death (OR 2.0 [95% CI 1.1–3.5] for 60-69 years, OR 3.7 [95% CI 2.1–6.5] for 70-74 years, and OR 7.3 [95% CI 4.3–12.5] for >74 years when compared with <60 years).

DISCUSSION

We identified RA as a risk factor for death related to COVID-19 in a multivariable-adjusted analysis of the UK Biobank

Table 3. Logistic regression association analyses adjusted for all other exposures (model 2)

	COVID-19 diagnosis (analysis A)		Death in group diagnosed with COVID-19 (analysis B)		COVID-19-related death in entire cohort (analysis C)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	1.18 (1.08–1.30)	2.71×10^{-4}	1.44 (1.12–1.85)	4.00×10^{-3}	1.69 (1.38–2.07)	6.00×10^{-7}
Age						
60-69 years[a]	0.54 (0.47–0.61)	6.96×10^{-21}	3.61 (1.99–6.57)	2.49×10^{-5}	1.97 (1.11–3.49)	0.021
70-74 years[a]	0.45 (0.39–0.53)	2.50×10^{-26}	9.37 (5.18–16.95)	1.41×10^{-13}	3.70 (2.12–6.46)	4.09×10^{-6}
>74 years[a]	0.60 (0.52–0.69)	1.33×10^{-13}	16.31 (9.20–28.91)	1.21×10^{-21}	7.30 (4.25–12.53)	5.60×10^{-13}
Ethnicity						
Asian British[b]	1.83 (1.48–2.26)	2.77×10^{-8}	0.65 (0.32–1.33)	0.24	1.10 (0.58–2.09)	0.77
Black British[b]	2.08 (1.68–2.56)	1.17×10^{-11}	1.56 (0.88–2.76)	0.13	2.72 (1.73–4.28)	1.50×10^{-5}
Other[b]	1.54 (1.16–2.04)	3.10×10^{-3}	0.51 (0.19–1.40)	0.19	0.83 (0.34–2.02)	0.68
Townsend deprivation index	1.05 (1.04–1.06)	7.74×10^{-12}	1.04 (1.00–1.07)	0.044	1.07 (1.04–1.10)	7.44×10^{-6}
BMI (per unit increase)	1.02 (1.01–1.03)	1.27×10^{-5}	1.02 (1.00–1.05)	0.073	1.03 (1.01–1.05)	1.33×10^{-3}
Smoking status						
Current smoker[c]	1.17 (1.06–1.29)	1.51×10^{-3}	1.05 (0.81–1.37)	0.70	1.27 (1.03–1.58)	0.027
Ex-smoker[c]	1.10 (0.95–1.27)	0.20	1.52 (1.04–2.21)	0.029	1.70 (1.25–2.31)	6.46×10^{-4}
Gout	1.01 (0.83–1.24)	0.91	1.26 (0.81–1.95)	0.31	1.18 (0.84–1.65)	0.35
Men only	1.01 (0.81–1.26)	0.91	1.20 (0.73–1.99)	0.47	1.15 (0.78–1.69)	0.47
Women only	0.96 (0.60–1.54)	0.86	2.16 (0.80–5.86)	0.13	1.71 (0.85–3.46)	0.13
RA	1.34 (1.02–1.77)	0.038	1.63 (0.89–2.96)	0.11	1.89 (1.19–3.02)	7.24×10^{-3}
Men only	1.00 (0.60–1.66)	0.99	2.33 (0.84–6.52)	0.11	1.50 (0.73–3.07)	0.27
Women only	1.58 (1.13–2.21)	7.60×10^{-3}	1.41 (0.64–3.09)	0.39	1.96 (1.04–3.67)	0.037
Dementia	9.39 (7.89–11.18)	9.14×10^{-140}	1.33 (0.95–1.88)	0.10	10.18 (7.64–13.58)	2.67×10^{-56}
Cerebrovascular diseases	2.30 (2.00–2.65)	1.48×10^{-30}	0.93 (0.69–1.26)	0.64	2.08 (1.60–2.71)	5.04×10^{-8}
Heart failure	1.75 (1.47–2.08)	2.14×10^{-10}	1.27 (0.88–1.84)	0.20	2.05 (1.52–2.76)	2.57×10^{-6}
Chronic kidney disease	1.68 (1.44–1.96)	5.07×10^{-11}	1.23 (0.87–1.72)	0.24	1.69 (1.28–2.23)	1.83×10^{-4}
Pulmonary heart disease	1.93 (1.57–2.37)	4.12×10^{-10}	0.90 (0.56–1.44)	0.66	1.80 (1.22–2.64)	2.84×10^{-3}
Immunodeficiencies	1.99 (1.35–2.93)	5.31×10^{-4}	3.63 (1.58–8.36)	2.45×10^{-3}	4.58 (2.62–8.01)	9.77×10^{-8}
Chronic obstructive pulmonary diseases	1.64 (1.39–1.93)	3.09×10^{-9}	1.08 (0.76–1.54)	0.66	1.67 (1.25–2.24)	5.47×10^{-4}
Hypertensive diseases	1.57 (1.40–1.75)	4.07×10^{-15}	1.04 (0.78–1.37)	0.81	1.56 (1.23–1.99)	3.09×10^{-4}
Diabetes mellitus	1.36 (1.19–1.54)	3.37×10^{-6}	1.25 (0.93–1.69)	0.14	1.52 (1.19–1.94)	7.24×10^{-4}
Lipoprotein disorders	1.17 (1.03–1.31)	0.013	0.88 (0.67–1.16)	0.37	1.03 (0.82–1.30)	0.80
Ischemic heart diseases	0.92 (0.81–1.05)	0.23	0.92 (0.68–1.24)	0.57	0.85 (0.66–1.10)	0.21
Cancer	1.44 (1.29–1.61)	5.86×10^{-11}	1.00 (0.77–1.30)	0.98	1.29 (1.04–1.61)	0.020
Asthma	1.07 (0.93–1.22)	0.35	1.10 (0.78–1.54)	0.59	1.01 (0.76–1.34)	0.97
Osteoarthritis	1.08 (0.97–1.21)	0.16	0.78 (0.60–1.01)	0.059	0.93 (0.75–1.16)	0.54

Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio; RA, rheumatoid arthritis.
[a] Reference group was <60 years of age.
[b] Reference group was White British.
[c] Reference group was never smokers.

cohort. Of clinical relevance, given implication of the type 1 interferon response in biologic therapy in RA (25), is involvement of a type 1 interferon–mediated immune response in people who die of COVID-19 (26), including in people with mutations in regulatory genes (27). It is important that the findings presented here are replicated in larger administrative data sets (eg, the US-based National COVID Cohort Collaborative [www.ncats.nih.gov/n3c] and the UK OpenSAFELY cohort) (2). These data sets would allow for more stratification and use of additional models to fully explore factors, including medications that might influence the observed association with RA. For example, the OpenSAFELY study included 962 individuals who died of COVID-19 who also had RA or systemic lupus erythematosus or psoriasis (2); the number of people with RA in this group is likely to be at least 10-fold greater than in the UK Biobank data set used here. If the association we report here were replicated, investigation of the reasons for the relationship between RA and death from COVID-19 would improve understanding and potentially improve clinical management of COVID-19.

There are limitations to our analyses. Firstly, these analyses pertain to the population from which the UK Biobank was derived, predominantly the middle-aged White European ethnic group of the United Kingdom, and are not necessarily generalizable to other ethnic groups or other White European ethnic groups. There is also no available information on recovery status, so there is the possibility of additional unidentified deaths in the group diagnosed with COVID-19 in analysis B. In addition, COVID-19 outcomes would have been influenced over the time period of this study (March to August 2020) as clinical treatments evolved. General practice prescriptions were only available up until August 2019

and could not reliably be used to determine current medication usage. Thus, the effect of antirheumatic treatments, particularly biologic disease-modifying antirheumatic drugs, could not be assessed in this study. Nor could the potential effect of disease activity in RA be assessed. Limited testing outside of the hospital settings means that the full extent of SARS-CoV-2 infection is not known in this population. Thus, it is not possible to accurately compare those with asymptomatic or mild COVID-19 with those with more severe disease. The UK Biobank data set is also limited to those aged 49 to 86 years as of 2020, a demographic with a higher infection fatality ratio (28). This would have contributed to the inflated infection fatality ratio in the UK Biobank cohort of 22% (which is well above general population estimates of 0.5% to 1.5%; ref. 29). In addition, a greater proportion of cases ascertained earlier in the pandemic by hospitalization aligned with insufficient testing capability to detect community and mild cases (30,31). Therefore, our findings cannot be generalized to those younger than 50 years of age. There is the potential in analysis B for index event (collider) bias, resulting from conditioning the sample set on COVID-19 diagnosis, which would serve to bias toward the null (32). With respect to the lack of association of established risk factors for adverse COVID-19 outcomes (eg, dementia) with death, the increased ascertainment of cases through hospitalization earlier in the pandemic would also have contributed to bias toward the null in analysis B. However, these limitations were addressed by using the entire cohort-based approach in analysis C. We did not account for increased risk of death in RA for non–COVID-19-related causes, which might have contributed to the OR of 1.9 (Table 3). However, any inflation would have been countered by adjustment for multiple comorbid conditions in analysis C. A final limitation is that although our method of ascertainment of gout in the UK Biobank has been validated (18), this is not the case for RA.

In summary, we found evidence for an effect of RA on the risk of death from COVID-19, independent of included comorbidities and known risk factors. This needs to be further explored in large data sets in which a range of other factors can be investigated (eg, RA therapies).

ACKNOWLEDGMENTS

This research was conducted by using the UK Biobank resource under application No. 12611. We sincerely thank all participants.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merriman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Topless, Dalbeth, Stamp, Robinson, Merriman.

Acquisition of data. Topless, Phipps-Green, Leask, Merriman.

Analysis and interpretation of data. Topless, Phipps-Green, Leask, Dalbeth, Stamp, Robinson, Merriman.

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