Gout, rheumatoid arthritis and the risk of death from COVID-19: an analysis of the UK Biobank

Ruth K Topless¹, Amanda Phipps-Green¹, Megan Leask¹,5, Nicola Dalbeth², Lisa K Stamp³, Philip C Robinson⁴, Tony R Merriman¹,5,*

1 Biochemistry Department, University of Otago, Dunedin, New Zealand
2 Department of Medicine, University of Auckland, Auckland, New Zealand
3 Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand
4 University of Queensland Faculty of Medicine, University of Queensland, Brisbane, Australia
5. Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama, United States

*to whom correspondence should be addressed (tony.merriman@otago.ac.nz)
Abstract
Objectives To assess whether gout and / or rheumatoid arthritis (RA) are risk factors for coronavirus disease 19 (COVID-19) diagnosis. To assess whether gout and / or RA are risk factors for death from COVID-19.

Methods We used data from the UK Biobank. Multivariate-adjusted logistic regression was employed in the following analyses. Analysis A: to test for association between gout or RA and COVID-19 diagnosis in a population-based cohort (n=473,139). Analysis B: to test for association between gout or RA and death from COVID-19 in a case-control cohort of people who died or survived with COVID-19 (n=2,073). Analysis C: to test for association with gout or RA and death from COVID-19 in a population-based cohort (n=473,139)

Results Neither RA nor gout associated with COVID-19 diagnosis in analysis A, nor did RA or gout associate with risk of death in the COVID-19-diagnosed group in analysis B. However RA associated with risk of death from COVID-19 using the population-based cohort in analysis C independent of comorbidities and other measured risk factors (OR=1.8 [95% CI 1.2 ; 2.7]). Gout was not associated with death from COVID-19 in the same population-based analysis (OR=1.2 [95% CI 0.9 ; 1.7]).

Conclusions RA and gout are not risk factors for COVID-19-diagnosis. However RA, but not gout, is a risk factor for death from COVID-19 in a population-based analysis using the UK Biobank. These findings require replication in larger data sets that also allow inclusion of a wider range of factors.
Key messages

What is already known?
Information on the risk of death from COVID-19 for people with gout and rheumatoid arthritis is scarce.

What does this study add?
In a population-based analysis there is an increased risk of death by COVID-19 for people with rheumatoid arthritis independent of co-morbidities, but not gout.

The findings need to be replicated in other datasets where the influence of therapies for RA can be tested.

How might this impact on clinical practice?
Improved clinical management and treatment for RA patients with COVID-19.
Background

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 hospitalisation, 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 hospitalisation compared to other rheumatic diseases (1). In the OpenSAFELY study (2) that compared risk factors for 10,926 people who died from COVID-19 to the general population in the UK, RA was pooled with systemic lupus erythematosus and psoriasis, this combined group had a hazard ratio of 1.2 [95% CI: 1.1;1.3] for death. Gout was not examined in the OpenSAFELY study. In a US study comparing people with COVID-19 with systemic autoimmune rheumatic diseases, of whom 45% had RA, to people without these diseases there was increased risk of hospitalisation and admission to intensive care but not death (3). A Spanish study reported no evidence for association of chronic inflammatory arthritis (48% with RA) with poor outcome in COVID-19 (4).

Gout is caused by an exuberant auto-inflammatory interleukin-1β-driven innate immune system response to monosodium urate crystals present in joints (5). 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 IL-6, IL-8 and TNF-α (6), raising the possibility that people with gout might be at risk of a poor outcome due to the fact that they also have higher circulating levels of these factors (7). Gout is also strongly associated with cardiometabolic co-morbidities such as type 2 diabetes, kidney disease and heart disease (8), all established risk factors for COVID-19-related mortality (2). Gout medications may also influence outcomes following the development of COVID-19: two randomised control trials of colchicine, which is widely used as prophylaxis and treatment for the gout flare (9), reported better clinical outcomes including a shorter time in hospital and shorter duration requiring supplemental oxygen in people hospitalised with COVID-19 in those randomised to colchicine (10,11). There is also non-randomised evidence of the efficacy of colchicine in COVID-19 in a small case-control study (12).
Rheumatoid arthritis 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 (13). The profile of RA includes increased levels of pro-inflammatory cytokines TNF-α and IL-6 (14), a similar profile to COVID-19 (15), with the potential to lead to an increased immune response to infection by SARS-CoV-2.

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

Data availability

This research was conducted using the UK Biobank Resource (approval number 12611). SARS-CoV-2 test information, ICD-10 hospital codes, death records and general practice prescription information was obtained via the UK Biobank data portal on the 16th of September 2020. This information covered hospital diagnoses between 1991 and 30th June 2020, SARS-CoV-2 tests between 16th March and 24th August 2020, and death records up until 14th August 2020.

Gout, RA and COVID-19 definitions and case-control datasets

The criteria for COVID-19 diagnosis was defined as participants with 1. a positive SARS-CoV-2 test and / or 2. 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 2,118 individuals who were further divided into those that died (n=457) based on death records and those that were known to survive (n = 1,616). Forty-five participants who were diagnosed after the last recorded death were removed from this cohort used in Analysis B (below). Gout was ascertained by a previously validated gout definition using the following criteria: self-reported gout (visits 0-2); taking allopurinol or sulphinpyrazone therapy either by self-report or from linked general practice scripts (excluding those who also had hospital diagnosed lymphoma or leukemia ICD10 C81 - C96); or hospital-diagnosed gout (ICD code M10) (16). The gout case-control cohort (n = 473,139) consists of 13,105 cases (gout) and 460,034 controls (non-gout). RA affection was ascertained using the ICD-10 code M05 - M06. The RA cohort (n = 473,139) consists of 7,850 people with and 465,289 people without RA. For the RA and gout cohorts we have developed three case-control datasets to test for association with the following outcomes:

Dataset A (Analysis A) to test for association with COVID-19 diagnosis in a population-based cohort. There were 2,118 cases and 471,021 controls.

Dataset 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 1,616 people diagnosed with COVID-19 who survived.
Dataset C (Analysis C) to test for association with death from COVID-19 in a population-based cohort. There were 457 people diagnosed with COVID-19 who died and 472,682 others that included 1,616 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, Any other white background), Black British (African, White and Black African, Black or Black British, Caribbean, White and Black Caribbean, Any other Black background), Asian British (Asian or Asian British, Chinese, Indian, Pakistani, Bangladeshi, White and Asian, Any other Asian background), and Other (Other ethnic group, Mixed, Any other mixed background, Do not know, 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: C00 – C96 (cancer), D80 - D89 (immunodeficiencies), E08 - E13 (diabetes mellitus), E78 (disorders of lipoprotein metabolism and other lipidemias), F01-F03 (dementia), I10 - I15 (hypertensive diseases), I60 - I69 (cerebrovascular diseases), I20 - I25 (ischemic heart diseases), I26 - 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 using R v4.0.2 in RStudio 1.2.5019. Two models were used: adjustment with age, sex, ethnicity, Townsend deprivation index, BMI, smoking status (Model 1); and Model 1 plus adjustment by the 15 other co-morbidities evaluated (Model 2). A $P < 0.05$ threshold indicated nominal evidence for association.
Results

Associations with diagnosis of COVID-19

Results from the association analyses of 16 diseases (including gout and RA) with COVID-19 diagnosis (Analysis A) using Model 1 (adjustment by current age, sex, Townsend deprivation index, ethnicity groups, body mass index and smoking status) are presented in Table 2. Both gout and RA associated with an increased risk of COVID-19 diagnosis of 1.5-fold [95% CI: 1.3 ; 1.8] and 2.0-fold [1.6 ; 2.5], respectively. In comparison, data for cerebrovascular diseases were (OR 4.9 [4.3 ; 5.5]), heart failure (OR 4.2 [3.6 ; 4.8]), chronic kidney disease (OR 3.9 [3.4 ; 4.5]), pulmonary heart disease (OR 3.5 [2.9 ; 4.2]), immunodeficiencies (OR 3.2 [2.2 ; 4.7]) and chronic obstructive pulmonary disorders (OR 3.2 [2.7 ; 3.7]). Two to three-fold increases in risk were estimated for hypertensive diseases (OR 2.4 [2.2 ; 2.7]), diabetes mellitus (OR 2.4 [2.1 ; 2.7]), and lipoprotein disorders (OR 2.1 [1.9 ; 2.4]). One to two-fold increases in risk were estimated for ischemic heart diseases (OR 2.0 [1.8 ; 2.2]), cancer (OR 1.7 [1.6 ; 1.9]), asthma (OR 1.6 [1.4 ; 1.8]), osteoarthritis (OR 1.6 [1.4 ; 1.7]) and dementia strongly associated with COVID-19 (OR 20.0 [17.1 ; 23.5]). After adjustment by Model 1 variates and the additional 15 co-morbidities evaluated (Model 2), gout no longer associated with COVID-19 diagnosis, nor did RA, ischemic heart disease, asthma and osteoarthritis (Table 3). Age was associated with decreased risk of SARS-CoV-2 infection and / or COVID-19 diagnosis (OR = 0.98 [0.97 ; 0.98] (Table 3). This decreased risk may reflect a number of factors that influence exposure to SARS-CoV-2 in this age group, including public health messaging around limiting exposure for older people.

Associations with death upon diagnosis of COVID-19

When testing for association with death from COVID-19 within the cohort with COVID-19 diagnosis (Analysis B), there was no evidence for association with any disease in either of Models 1 or 2 (Tables 2 and 3) with the exception of immunodeficiencies OR=3.4 [1.5 ; 7.8] (Model 1) and OR=3.7 [1.6 ; 8.4] (Model 2). Established risk factors for death from COVID-19, namely male sex and older age, were strongly associated with death (OR=1.5 [1.1 ; 1.9] for males and OR=1.1 [1.1 ; 1.2] per additional year of age) (Table 3).

We then tested for association with death from COVID-19 comparing to the entire population-based cohort (Analysis C). Gout was associated with a 1.7-fold increase [95% CI: 1.2 ; 2.3] in COVID-19-related death under Model 1 but not in Model 2 (OR=1.2 [0.9 ; 1.7]). In contrast, RA associated with increased risk of death from COVID-19 in both models –
OR=2.9 [1.9 ; 4.2] in Model 1 and OR=1.8 [1.2 ; 2.7] in Model 2. Sex-specific analyses for death from COVID-19 related death in RA were OR=2.5 [1.4 ; 4.4] for males and OR=3.1 [1.9 ; 5.3] for females in Model 1, and OR=1.6 [0.9 ; 2.9] and OR=1.9 [1.1 ; 3.3], respectively, in Model 2. None of the sex-specific analyses in gout associated with risk of death in Analysis C.

We also assessed in Analysis C the 14 additional diseases for association with death from COVID-19 comparing to the entire population-based cohort. Dementia, immunodeficiencies, chronic obstructive pulmonary diseases, cerebrovascular diseases, heart failure, pulmonary heart disease, chronic kidney disease, hypertensive diseases, diabetes mellitus, and cancer all associated with additional risk of death in Model 2 (Table 3), with dementia and immunodeficiencies having the strongest effects (OR=9.9 [7.5 ; 13.2] and 4.5 [2.6 ; 8.0], respectively). In Model 2, people of Black British ancestry had the highest risk of death (OR=2.8 [1.8 ; 4.5]), compared to people of White British ancestry, and there was positive association of death with BMI (OR = 1.03 [1.01 ; 1.05]), and the Townsend deprivation index (OR=1.07 [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 UK (17). Ex-smokers were at an increased risk of death from COVID-19 in model 2 (OR=1.7 [1.3 ; 2.4]), consistent with the OpenSAFELY data from the UK (2), although directionality of association was different to the OpenSAFELY data for current smokers (OR=1.3 [1.0 ; 1.6]). Age was also associated with death (OR = 1.10 [1.08 ; 1.12]) in this comparison.
Discussion

We identified RA, but not gout, as a risk factor for death from COVID-19 in a multivariate adjusted population-based analysis. A parallel can be drawn with the increased risk of death from COVID-19 we observed in immunodeficiencies, in that suppression of the immune system in RA using immunosuppressive disease-modifying anti-rheumatic drugs may affect the same pathway(s) contributing to death from COVID-19. Of relevance is the implication of a type 1 interferon-mediated immune response in people who die from COVID-19 (18), including in people with mutations in regulatory genes (19) given implication of the type 1 interferon response in therapy of RA with biologics (20).

There are limitations to our analyses. Firstly, these analyses pertain to the population from which the UK Biobank was derived, predominantly the white European middle-aged ethnic group of the United Kingdom, and are not necessarily generalisable 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 COVID-19 diagnosed group in Analysis B. In addition to this COVID-19 outcomes will have been influenced over the time period of this study (March-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 anti-rheumatic treatments, particularly biologic disease-modifying anti-rheumatic drugs, could not be assessed in this study. 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 asymptomatic or mild COVID-19 to those with more severe disease. The UK Biobank dataset is also limited to those aged age 49 years to 86 years of age as of 2020, a demographic with a higher infection fatality ratio (21). This undoubtedly will have contributed to the inflated infection fatality ratio in the UK Biobank cohort of 22%, well above general population estimates of 0.5 to 1.5% (e.g. (22)). Therefore our findings cannot be generalised to those under 50 years of age. Finally, 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 towards the null (23). However this limitation was addressed using the population-based approach in Analysis C.

It is important that the findings presented here are replicated in larger administrative datasets (eg. US-based National COVID Cohort Collaborative (www.ncats.nih.gov/n3c) and the UK
OpenSAFELY cohort (2)). These datasets 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 with COVID-19 who also had RA or SLE or psoriasis (2) – the number of people with RA in this group is likely to be at least 10-fold greater than in UK Biobank data set used here. If our association 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. It will also be important to test for association with death from COVID-19 of RA alone, i.e. not with other autoimmunities with rheumatological sequelae, as was done in the OpenSAFELY cohort (2).

In summary, we found evidence for an effect of RA on the risk of a COVID-19 related death independent of comorbidities and known risk factors. We found an increased risk of death from RA, and this needs to be further explored in large datasets where a range of other factors can be investigated (e.g. RA therapies).
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Figure legend

Figure 1 Data sources of COVID-19-diagnosed individuals

Of the 2,118 COVID-19-diagnosed individuals, 1,712 were identified from positive SARS-CoV-2 test results (880 unique to this group), 1057 identified from hospital records (242 unique to this group), and 457 identified from death records (133 unique to this group).
### Table 1 Characteristics of participants with gout and rheumatoid arthritis

|                          | Gout      | Non-Gout  | Rheumatoid Arthritis | Non-RA    |
|--------------------------|-----------|-----------|----------------------|-----------|
| n                        | 13,105    | 460,034   | 7,850                | 465,289   |
| Age, mean (SD)           | 71.4 (7.2)| 68.1 (8.1)| 71.2 (7.2)           | 68.1 (8.1)|
| Males (%)                | 11,253 (85.9)| 200,374 (43.6)| 2,359 (30.1)       | 209,268 (45.0) |
| Females (%)              | 1,852 (14.1) | 259,660 (56.4) | 5,491 (70.0)      | 256,021 (55.0) |
| BMI, mean (SD)           | 30.4 (5.0) | 27.3 (4.7) | 28.7 (5.6)          | 27.4 (4.7) |
| Townsend deprivation index, mean (SD) | -1.07 (3.2) | -1.34 (3.1) | -0.87 (3.2)      | -1.34 (3.1) |
| White British ethnicity (%) | 12,321 (94.2) | 432,226 (94.1) | 7,311 (93.4)   | 437,236 (94.1) |
| Black British ethnicity (%) | 368 (2.8)   | 11,458 (2.5) | 225 (2.9)         | 11,601 (2.5) |
| Asian British ethnicity (%) | 189 (1.5)   | 8,599 (1.9)  | 177 (2.3)         | 8,611 (1.9)  |
| Other ethnicities (%)    | 196 (1.5)  | 6,940 (1.5)  | 115 (1.5)         | 7,021 (1.5)  |
| Never smoke (%)          | 5,612 (43.2) | 256,879 (56.2) | 3663 (47.1)     | 258,828 (55.9) |
| Current smoker (%)       | 6,202 (47.7) | 154,574 (33.8) | 3167 (40.7)     | 157,609 (34.1) |
| Ex-smoker (%)            | 1,190 (9.2) | 46,005 (10.1) | 950 (12.2)      | 46,245 (10.0) |
| Asthma (%)               | 1,562 (11.9) | 39,336 (8.6)   | 1,564 (19.9)    | 39,334 (8.5)  |
| Cancer (%)               | 2,653 (20.2) | 64,197 (14.0) | 1,619 (20.6)    | 65,231 (14.0) |
| Cerebrovascular diseases (%) | 939 (7.2)   | 11,489 (2.5)  | 571 (7.3)        | 12,526 (2.7)  |
| Chronic kidney disease (%) | 1,844 (14.1) | 13,724 (3.0)   | 807 (10.3)      | 13,739 (3.0)  |
| Chronic obstructive pulmonary diseases (%) | 932 (7.1)   | 13,154 (2.9)  | 917 (11.7)      | 13,522 (2.9)  |
| Dementia (%)             | 140 (1.1)  | 2,208 (0.5)   | 116 (1.5)        | 2,232 (0.5)   |
| Diabetes mellitus (%)    | 2,552 (19.5) | 30,595 (6.7)   | 1,173 (14.9)    | 31,974 (6.9)  |
| Gout (%)                 | -         | -            | 403 (5.1)        | 12,702 (2.7)  |
| Heart Failure (%)        | 1,247 (9.5) | 8,712 (1.9)   | 503 (6.4)       | 9,456 (2.0)   |
| Hypertensive diseases (%) | 7,807 (59.6) | 118,291 (25.7) | 4,157 (53.0)   | 121,941 (26.2) |
| Immunodeficiencies (%)   | 102 (0.8)  | 42,250 (9.2)  | 122 (1.6)       | 43,857 (9.4)  |
| Ischemic heart diseases (%) | 3,301 (25.2) | 1,664 (0.4)   | 1,694 (21.6)    | 1,644 (0.4)   |
| Lipoprotein disorders (%) | 4,163 (31.8) | 58,824 (12.8) | 2,165 (27.6)    | 60,822 (13.1) |
| Osteoarthritis (%)       | 4,018 (30.7) | 75,353 (16.4) | 4,193 (53.4)    | 75,178 (16.2) |
| Pulmonary heart disease (%) | 463 (3.5)   | 6,002 (1.3)   | 296 (3.8)       | 6,169 (1.3)   |
| Rheumatoid arthritis (%) | 403 (3.1)  | 7,447 (1.6)   | -              | -            |

SD = standard deviation.
Table 2 Analyses A-C adjusted for current age, sex, ethnicity, Townsend deprivation index, BMI, and smoking-status (Model 1)

| Condition                      | Yes / No | OR (95% CI) | P     | Died / surviving | OR (95% CI) | P     | Died / remaining cohort | OR (95% CI) | P     |
|--------------------------------|----------|-------------|-------|------------------|-------------|-------|-------------------------|-------------|-------|
| **SARS-Cov-2 infection and / or COVID-19 diagnosis** |          |             |       |                  |             |       |                         |             |       |
| N                              | 2,118 / 471,021 | 457 / 1,616 | 0.25  | 42 / 13,063      | 1.68 ( 1.21 ; 2.34 ) | 0.95  |                       |             |       |
| Gout                           | 117 / 12,988 | 2.810<sup>0.05</sup> | 2.810<sup>0.05</sup> | 92 / 12,988 | 1.29 ( 0.84 ; 1.98 ) | 0.76  |                       |             |       |
| - Gout male-only<sup>1</sup>   | 97 / 11,156 | 5.10<sup>0.01</sup> | 5.10<sup>0.01</sup> | 33 / 64      | 1.69 ( 0.72 ; 1.90 ) | 0.93  |                       |             |       |
| - Gout female-only<sup>1</sup> | 20 / 1,832 | 2.17 ( 1.38 ; 3.41 ) | 2.17 ( 1.38 ; 3.41 ) | 9 / 11       | 2.52 ( 0.97 ; 6.53 ) | 0.75  |                       |             |       |
| Rheumatoid arthritis           | 81 / 7,769 | 1.40<sup>0.01</sup> | 1.40<sup>0.01</sup> | 30 / 51      | 1.61 ( 0.97 ; 2.70 ) | 0.50  |                       |             |       |
| - RA male-only<sup>1</sup>     | 27 / 2,332 | 1.62 ( 1.08 ; 2.43 ) | 1.62 ( 1.08 ; 2.43 ) | 13 / 14      | 2.37 ( 1.00 ; 5.63 ) | 0.65  |                       |             |       |
| - RA female-only<sup>1</sup>   | 54 / 5,437 | 2.37 ( 1.78 ; 3.13 ) | 2.37 ( 1.78 ; 3.13 ) | 17 / 37      | 1.27 ( 0.66 ; 2.46 ) | 0.70  |                       |             |       |
| Dementia                       | 203 / 2,145 | 20.0<sup>2</sup> | 20.0<sup>2</sup> | 76 / 127     | 1.23 ( 0.88 ; 1.72 ) | 0.23  |                       |             | 1.2x10<sup>-101</sup> | 1.2x10<sup>-101</sup> |
| Cerebrovascular diseases        | 313 / 13,780 | 4.86 ( 4.28 ; 5.52 ) | 4.86 ( 4.28 ; 5.52 ) | 95 / 218     | 0.93 ( 0.69 ; 1.24 ) | 0.55  |                       |             | 3.9x10<sup>-55</sup> | 3.9x10<sup>-55</sup> |
| Heart Failure                   | 223 / 7,936 | 4.17 ( 3.59 ; 4.84 ) | 4.17 ( 3.59 ; 4.84 ) | 83 / 140     | 1.31 ( 0.94 ; 1.81 ) | 0.35  |                       |             | 3.6x10<sup>-29</sup> | 3.6x10<sup>-29</sup> |
| Chronic kidney disease          | 260 / 13,073 | 3.91 ( 3.40 ; 4.49 ) | 3.91 ( 3.40 ; 4.49 ) | 89 / 171     | 1.24 ( 0.91 ; 1.69 ) | 0.57  |                       |             | 5.7x10<sup>-27</sup> | 5.7x10<sup>-27</sup> |
| Pulmonary heart disease         | 116 / 6,349 | 2.38 ( 2.02 ; 2.86 ) | 2.38 ( 2.02 ; 2.86 ) | 32 / 84      | 0.96 ( 0.61 ; 1.52 ) | 0.87  |                       |             | 3.9x10<sup>-10</sup> | 3.9x10<sup>-10</sup> |
| Immunodeficiencies              | 28 / 1,738 | 3.20 ( 2.73 ; 4.67 ) | 3.20 ( 2.73 ; 4.67 ) | 14 / 14      | 3.40 ( 1.48 ; 7.79 ) | 0.87  |                       |             | 9.7x10<sup>-13</sup> | 9.7x10<sup>-13</sup> |
| Chronic obstructive pulmonary diseases | 241 / 14,415 | 3.15 ( 2.72 ; 3.65 ) | 3.15 ( 2.72 ; 3.65 ) | 81 / 160     | 1.15 ( 0.83 ; 1.60 ) | 0.71  |                       |             | 3.2x10<sup>-17</sup> | 3.2x10<sup>-17</sup> |
| Hypertensive diseases           | 1,076 / 125,022 | 2.44 ( 2.22 ; 2.69 ) | 2.44 ( 2.22 ; 2.69 ) | 299 / 777    | 1.04 ( 0.81 ; 1.34 ) | 0.77  |                       |             | 7.0x10<sup>-13</sup> | 7.0x10<sup>-13</sup> |
| Diabetes mellitus               | 430 / 32,717 | 2.38 ( 2.12 ; 2.68 ) | 2.38 ( 2.12 ; 2.68 ) | 132 / 298    | 1.24 ( 0.94 ; 1.65 ) | 0.69  |                       |             | 2.4x10<sup>-16</sup> | 2.4x10<sup>-16</sup> |
| Lipoprotein disorders           | 610 / 62,377 | 2.13 ( 1.92 ; 2.36 ) | 2.13 ( 1.92 ; 2.36 ) | 170 / 440    | 0.96 ( 0.75 ; 1.22 ) | 0.87  |                       |             | 3.7x10<sup>-10</sup> | 3.7x10<sup>-10</sup> |
| Ischemic heart diseases         | 438 / 45,113 | 1.98 ( 1.77 ; 2.21 ) | 1.98 ( 1.77 ; 2.21 ) | 131 / 307    | 0.99 ( 0.76 ; 1.29 ) | 0.91  |                       |             | 5.6x10<sup>-9</sup> | 5.6x10<sup>-9</sup> |
| Cancer                          | 476 / 66,374 | 1.74 ( 1.57 ; 1.94 ) | 1.74 ( 1.57 ; 1.94 ) | 127 / 349    | 0.97 ( 0.75 ; 1.26 ) | 0.87  |                       |             | 5.8x10<sup>-9</sup> | 5.8x10<sup>-9</sup> |
| Asthma                          | 306 / 40,592 | 1.10 ( 0.80 ; 1.52 ) | 1.10 ( 0.80 ; 1.52 ) | 67 / 239     | 1.10 ( 0.80 ; 1.52 ) | 0.55  |                       |             | 5.3x10<sup>-14</sup> | 5.3x10<sup>-14</sup> |
| Osteoarthritis                  | 558 / 78,813 | 1.55 ( 1.40 ; 1.72 ) | 1.55 ( 1.40 ; 1.72 ) | 144 / 414    | 0.82 ( 0.64 ; 1.07 ) | 0.44  |                       |             | 4.4x10<sup>-5</sup> | 4.4x10<sup>-5</sup> |
Table 3 Analyses A-C adjusted by all other exposures listed in the table (Model 2).

| Exposure                                      | OR (95% CI)          | P      | OR (95% CI)          | P      | OR (95% CI)          | P      |
|-----------------------------------------------|----------------------|--------|----------------------|--------|----------------------|--------|
| Male sex                                      | 1.19 (1.08; 1.31)    | 1.54E-04| 1.46 (1.14; 1.87)    | 3.0E-03| 1.70 (1.39; 2.09)    | 4.3E-07|
| Age (per year increase)                       | 0.98 (0.97; 0.98)    | 2.95E-12| 1.13 (1.11; 1.15)    | 1.8E-13| 1.10 (1.08; 1.12)    | 4.3E-24|
| Asian British 2                                | 1.83 (1.48; 2.27)    | 2.20E-08| 0.71 (0.35; 1.45)    | 0.35   | 1.14 (0.60; 2.21)    | 0.69   |
| Black British 2                                | 2.13 (1.72; 2.63)    | 2.20E-12| 1.57 (0.89; 2.77)    | 0.12   | 2.84 (1.81; 4.46)    | 6.0E-06|
| Other ethnicities 2                            | 1.54 (1.16; 2.04)    | 3.08E-10| 0.51 (0.19; 1.38)    | 0.18   | 0.84 (0.34; 2.06)    | 0.71   |
| Townsend deprivation index                    | 1.05 (1.04; 1.07)    | 6.79E-12| 1.03 (1.00; 1.07)    | 0.067  | 1.07 (1.04; 1.10)    | 4.7E-06|
| BMI (per increase in kg/m²)                   | 1.02 (1.01; 1.03)    | 8.27E-10| 1.03 (1.00; 1.05)    | 0.035  | 1.03 (1.01; 1.05)    | 8.7E-04|
| Current smoker 3                               | 1.18 (1.07; 1.29)    | 1.06E-10| 1.07 (0.82; 1.40)    | 0.60   | 1.28 (1.03; 1.58)    | 0.026  |
| Ex-smoker 3                                   | 1.08 (0.94; 1.25)    | 0.30   | 1.56 (1.07; 2.27)    | 0.021  | 1.74 (1.29; 2.37)    | 3.5E-04|
| Gout                                          | 1.01 (0.83; 1.23)    | 0.92   | 1.25 (0.80; 1.94)    | 0.33   | 1.19 (0.85; 1.67)    | 0.32   |
| - Gout male-only 1                            | 1.01 (0.81; 1.26)    | 0.93   | 1.16 (0.70; 1.92)    | 0.56   | 1.16 (0.79; 1.71)    | 0.44   |
| - Gout female-only 1                          | 0.97 (0.60; 1.56)    | 0.90   | 2.41 (0.88; 6.60)    | 0.086  | 1.51 (0.74; 3.09)    | 0.26   |
| Rheumatoid arthritis                          | 1.27 (1.0; 1.62)     | 0.051  | 1.61 (0.95; 2.72)    | 0.079  | 1.80 (1.20; 2.70)    | 4.6E-05|
| - RA male-only 1                              | 0.99 (0.65; 1.51)    | 0.96   | 2.57 (1.07; 6.21)    | 0.036  | 1.59 (0.86; 2.92)    | 0.14   |
| - RA female-only 1                            | 1.47 (1.09; 1.97)    | 0.011  | 1.24 (0.62; 2.52)    | 0.54   | 1.89 (1.09; 3.29)    | 0.025  |
| Dementia                                      | 10.17 (8.54; 12.11)  | 6.78E-10| 1.23 (0.87; 1.74)    | 0.24   | 9.94 (7.46; 13.24)   | 1.5E-03|
| Cerebrovascular diseases                      | 2.35 (2.04; 2.71)    | 4.23E-02| 0.90 (0.67; 1.22)    | 0.50   | 2.06 (1.58; 2.67)    | 7.3E-04|
| Heart Failure                                 | 1.79 (1.50; 2.12)    | 5.33E-11| 1.29 (0.90; 1.87)    | 0.17   | 2.01 (1.49; 2.71)    | 4.6E-06|
| Chronic kidney disease                        | 1.73 (1.48; 2.02)    | 4.82E-12| 1.16 (0.83; 1.62)    | 0.40   | 1.68 (1.28; 2.21)    | 2.2E-04|
| Pulmonary heart disease                       | 1.95 (1.59; 2.40)    | 2.21E-06| 0.90 (0.56; 1.44)    | 0.65   | 1.80 (1.22; 2.64)    | 2.8E-05|
| Immunodeficiencies                            | 1.93 (1.31; 2.84)    | 9.55E-04| 3.66 (1.59; 8.44)    | 2.4E-00| 4.54 (2.59; 7.95)    | 1.2E-07|
| Chronic obstructive pulmonary diseases        | 1.66 (1.41; 1.95)    | 1.20E-09| 1.07 (0.76; 1.53)    | 0.69   | 1.66 (1.24; 2.22)    | 6.3E-04|
| Hypertensive diseases                         | 1.57 (1.40; 1.76)    | 2.76E-13| 1.02 (0.77; 1.35)    | 0.92   | 1.53 (1.20; 1.94)    | 6.2E-04|
| Diabetes mellitus                             | 1.35 (1.19; 1.53)    | 5.47E-06| 1.24 (0.92; 1.67)    | 0.15   | 1.51 (1.18; 1.93)    | 9.0E-04|
| Lipoprotein disorders                         | 1.16 (1.03; 1.31)    | 0.015  | 0.88 (0.67; 1.16)    | 0.37   | 1.03 (0.82; 1.30)    | 0.81   |
| Ischemic heart diseases                       | 0.93 (0.81; 1.07)    | 0.28   | 0.88 (0.65; 1.19)    | 0.40   | 0.84 (0.66; 1.09)    | 0.19   |
| Cancer                                        | 1.46 (1.31; 1.62)    | 1.35E-11| 1.00 (0.77; 1.30)    | 0.99   | 1.28 (1.03; 1.58)    | 0.028  |
| Asthma                                        | 1.06 (0.93; 1.21)    | 0.39   | 1.10 (0.79; 1.54)    | 0.57   | 1.01 (0.78; 1.34)    | 0.96   |
| Osteoarthritis                                | 1.09 (0.98; 1.22)    | 0.11   | 0.77 (0.59; 1.00)    | 0.047  | 0.91 (0.73; 1.14)    | 0.42   |

1 Sex stratified analysis; 2 Reference group was white British; 3 Reference group was never smokers.
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