**Title:** Association between serum urate, gout and comorbidities: case-control study using data from the UK Biobank

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**Key Messages**

- Cardiovascular comorbidities, and CKD associate independently with increasing serum urate.
- Diabetes mellitus associates negatively with serum urate level.
- Association between gout and cardiovascular comorbidities, diabetes mellitus and hypercholesterolemia is independent of serum urate.

**Abstract**

**Objectives:** To examine the association between comorbidities and serum urate (SU); gout and comorbidities; and to determine if the association between gout and comorbidities is independent of SU.

**Methods:** Case-control study using UK Biobank data. Two separate analyses were conducted: [1] excluding participants with gout to investigate the association between comorbidities and SU, and [2] participants with gout as the index condition to examine association between gout and comorbidities. SU was measured at baseline visit. Self-reported physician-diagnosed illnesses were used to define gout and comorbidities, except for chronic kidney disease (CKD) defined using eGFR cut-off. Additionally, participants prescribed urate lowering treatment were classified as gout. Logistic regression was used to examine the associations. Odds ratios (OR) and 95% confidence intervals (CI) were calculated and adjusted for covariates including comorbidities and SU.

**Results:** Data for 458,781 UK Biobank participants were used to examine the association between comorbidities and SU. There was an association between hypertension, ischaemic heart disease (IHD), congestive cardiac failure (CCF), hyperlipidaemia, CKD and SU with aOR 1.10-3.14 for 1 mg/dl SU increase. 10,265 gout cases and 458,781 controls were included in the analysis of association between gout and comorbidities. Gout associated independently with hypertension, IHD, CCF, hyperlipidaemia, and diabetes with aORs 1.21-4.15 after adjusting for covariates including SU.

**Conclusion:** Modest elevations in SU associates with comorbidities. The association between gout and cardio-metabolic comorbidities was independent of SU levels

suggesting separate urate-independent mechanisms such as inflammation driven by crystal deposition, pro-inflammatory genotype, or dietary and lifestyle factors.

## Background

Gout is a common inflammatory arthritis with a prevalence of 2.5-3.9% in Europe and North America (1, 2). Hyperuricaemia is even more common, being present in 20% of the over 20s in the United States of America (1). Gout associates with comorbidities such as hyperlipidaemia, hypertension, ischaemic heart disease (IHD), congestive cardiac failure (CCF) and chronic kidney disease (CKD), often in distinct comorbidity clusters (3-7). Recent Mendelian randomisation studies have reported association between serum urate variants and IHD, hypertension, hypercholesterolemia, and CCF but not with CKD or diabetes (8-11). However, it is unclear whether the association between gout and comorbidities is independent of serum urate. This is because most observational studies are conducted using data from electronic health records, and serum urate levels are rarely available for controls unless measured for clinical reasons such as suspected gout, pre-eclampsia, or CKD thus precluding valid attempts at association studies using these databases.

The UK Biobank contains data on serum urate for all participants that gave blood for biomarker measurement at the baseline research assessment visit. Thus, the objectives of this study were to examine the association between [1] cardiovascular diseases, CKD, diabetes mellitus, hypercholesterolemia and serum urate level; [2] gout and cardiovascular diseases, CKD, diabetes mellitus, and hypercholesterolemia; and [3] to evaluate whether the association between gout and comorbidities is independent of serum urate.

## Methods

*Study design:* Case-control study

*Data source:* The UK Biobank, a large population-based prospective study, recruited ~500,000 participants, aged 40-69 years. Participants were recruited between 2006 and 2010 across England, Wales and Scotland. They attended a baseline visit, which comprised electronic questionnaires and interviews that aimed to collect data such as sociodemographic characteristics, lifestyle factors, health status, family history, cognitive function etc. Physical and functional measurements were recorded, and biological samples (blood, urine and saliva) were also collected for measuring biomarkers including serum urate. Details about recruitment and data processing can be found in the key documents section on the UK Biobank website (www.ukbiobank.ac.uk).

*Ethical approval:* UK Biobank Review board (Project ID 45987).

Study-1*:* Association between comorbidities and serum urate

*Population:* UK Biobank Participants without gout at the baseline visit.

Gout was defined as present if the participants met any of the following criteria (12): self-reported physician diagnosed gout, urate lowering treatment (ULT) prescription, or hospital diagnosis of gout using the following ICD-10 codes: M10 (gout), M100 (idiopathic gout), M101 (lead-induced gout), M102 (drug-induced gout), M103 (gout due to impaired renal function), M104 (other secondary gout) and M109 (gout, unspecified). Participants on ULT without gout diagnosis either via self-reporting or on hospital records, and with either a primary or a secondary diagnosis of leukaemia (ICD-10 codes C90-C96) or lymphoma (ICD-10 codes C81-C88) were not classified as having gout.

*Cases:* Participants with hypertension, diabetes mellitus, IHD, CCF, CKD or hypercholesterolemia respectively.

*Case definition:* Hypertension, diabetes mellitus, IHD, hypercholesterolemia, and CCF were categorised as present or absent if they were self-reported as being diagnosed by a doctor; and CKD was defined as present if the eGFR was <45 ml/min using the CKD-EPI calculator.

*Controls:* No self-report of physician-diagnosed conditions, and eGFR > 45 ml/min for CKD respectively.

*Covariates:* Serum urate, age, sex, body mass index (BMI), Townsend deprivation index, alcohol intake, smoking status.

Townsend deprivation index is a local area level composite index of deprivation derived from employment status, home ownership, car ownership and overcrowding, and was based on the preceding national census data, with each participant assigned a score corresponding to the postcode of their home dwelling. Higher score indicates more deprivation. It was included in the model as social deprivation associates with incidence and prevalence of gout, and also with frequent gout flares (13, 14).

Study-2: Association between gout and comorbidities

*Population:* All UK Biobank participants.

*Cases:* Participants with gout as defined for Study-1 above.

*Controls:* Participants contributing data to the UK Biobank at the baseline visit and not classified as gout.

*Covariates:* hypertension, diabetes mellitus, IHD, CCF, CKD, hypercholesterolemia, age, sex, BMI, Townsend deprivation index, alcohol intake, smoking, and serum urate.

Statistical analysis: N (%) and mean (standard deviation (SD)) were calculated for descriptive purposes. Independent sample t-test and chi-square test were used for comparing continuous and categorical data respectively.

Logistic regression was used to examine the association between individual comorbidities and serum urate levels increasing in 1 mg/dl increments, adjusted for age (years), sex (male/female), BMI ($kg/m^2$), smoking (categorised as non-smoker, ex-smoker, and current-smoker), alcohol consumption (categorised as never or only on special occasions, up to thrice a month, once or twice a week, thrice or four times a week, and daily or almost daily), and Townsend deprivation index score. Non-smoker, and drinking alcohol never or only on special occasions were the reference categories. Serum urate for participants in Study-1 was categorised into quintiles, and the association between comorbidities and quintiles of serum urate was examined with the lowest quintile referent. This was adjusted for the covariates listed above. Odds ratios (OR) and 95% confidence intervals (95%CI), and adjusted OR and 95% CI were calculated to measure the strength of associations. Bonferroni correction was used to adjust for multiple testing, and $p<0.008$ was regarded as statistically significant.

Logistic regression was used to examine the association between gout and individual comorbidities and adjusted for age (years), sex (male/female), BMI ($kg/m^2$), alcohol-intake (categorised as above), smoking status (categorised as above), Townsend deprivation index score, and comorbidities (present/absent) (Model 1). This was additionally adjusted for serum urate (mg/dl) (Model 2). For this analysis, CKD was graded using eGFR calculated from creatinine values using the CKD-EPI formula and categorised as G1 eGFR>90 ml/min, G2 (eGFR 60-90 ml/min), G3a (eGFR 45-59 ml/min), G3b (eGFR 30-44 ml/min), G4 (eGFR 15-29 ml/min) and G5 (eGFR <15 ml/min) as per the National Institute of Health and Care Excellence (NICE) guidelines

CG182. A post-hoc sensitivity analysis was performed excluding gout cases prescribed ULT. Odds ratios (OR) and 95% confidence intervals (95%CI), and adjusted OR and 95% CI were calculated to measure associations. Statistical significance was $p<0.05$. Data were managed and analysed using STATA-MP.

## Results

Data for 458,781 UK Biobank participants with baseline serum urate and without gout were included in the analysis of association between comorbidities and serum urate. There were 55.18% females. Their mean (SD) age, BMI and serum urate were 56.46 (8.10) years, 27.35 (4.75) kg/m$^2$ and 5.17 (1.32) mg/dl respectively. The prevalence of self-reported physician diagnosed comorbidities in this population was as follows: hypertension 25.86%, hypercholesterolemia 12.00%, diabetes mellitus 4.31%, ischaemic heart disease 4.30%, and congestive cardiac failure 0.05%. CKD stage 3b or higher was present in 0.33%.

The demographic and lifestyle characteristics of UK Biobank participants with and without each comorbidity is included in Tables S1-S6. All comorbidities associated with increasing serum urate level on univariate and adjusted analyses with the notable exception of diabetes for which there was a positive association on univariate analysis that became negative on adjusting for covariates (Table 1). These associations remained statistically significant ($p<0.008$) on Bonferroni correction. The association between IHD, CCF and increasing serum urate remained statistically significant on further adjustment for covariates with aOR (95%CI) 1.11 (1.09-1.12) and 1.66 (1.52-1.82) respectively for each 1-mg/dl increase in serum urate.

Data for 10,265 gout cases (11% female) were included in the analysis examining association between gout and comorbidities. Their mean (SD) age, BMI and serum urate were 59.92 (7.00) years, 30.61 (5.02) kg/m$^2$ and 6.67 (1.78) mg/dl respectively. The prevalence of self-reported physician diagnosed comorbidities in people with gout was as follows: hypertension 57.20%, hypercholesterolemia 27.56%, diabetes mellitus 12.47%, ischaemic heart disease 13.49%, and congestive cardiac failure 0.60%. CKD stage 3b or higher was present in 3.96%. Gout associated independently with age,

male sex, BMI, and with hypertension, diabetes, IHD, hypercholesterolemia, CCF, and CKD (Table 2). These associations were diminished in magnitude, but remained statistically significant ($p<0.001$) on multivariate analysis including serum urate in the model (Table 2).

In a post-hoc sensitivity analysis, association between gout and comorbidities was examined after excluding gout cases prescribed ULT. Age, male sex, BMI, hypertension, diabetes, IHD, hypercholesterolemia, and CCF associated with gout on univariate and adjusted analyses, including when adjusted for serum urate levels (Table 3). However, the positive association between gout and increasing CKD grades became negative on adjusting for the serum urate level (Table 3). Similarly, on adjusting for serum urate only daily or almost-daily alcohol intake associated significantly with gout.

## Discussion

This study reports that gout associates independently with comorbidities, and, that the association between gout and hypertension, IHD, CCF, hypercholesterolemia and diabetes mellitus is independent of serum urate. This is a novel finding and has not been reported before. This study also reports that hypertension, IHD, CCF, CKD, and hypercholesterolemia associate with serum urate, and that diabetes mellitus associates negatively with serum urate. There was a dose response in the association between comorbidities and serum urate, and, a significant independent association with even a modest increase in serum urate for all comorbidities except for diabetes. Finally, this study reports an association between gout and male-sex, age, BMI, alcohol intake and socio-economic deprivation as reported previously (1, 2, 13, 14).

The association between serum urate and hypertension, IHD, CCF, and CKD is well recognised and has been subject of several systematic reviews and prospective cohort studies (15-19). However, over 90% of the studies included in previous systematic reviews defined hyperuricaemia as serum urate level >6 or even >7 mg/dl and, in some prospective studies only relatively high serum urate levels such as >7 mg/dl in men and >6 mg/dl in women, and >6.3 mg/dl in either sexes associated with incident CKD and CCF respectively (15, 19). Our finding of an association between comorbidities and modest increases in serum urate, and even at lower concentrations is a novel finding. It is consistent with the results of a prospective cohort study that reported an association between serum urate levels of 5-6 mg/dl and incident hypertension (20). As this is a case-control study, further research is required to corroborate this observation in a prospective cohort study.

We observed an association between diabetes mellitus and increasing serum urate on univariate analysis that became negative on adjusting for covariates. This is

consistent with the results of a prospective cohort study using data from the UK primary-care database that reported a negative association between both type 1 and type 2 diabetes and incident gout (21). Our finding is also consistent with findings from Mendelian randomisation studies, which do not report a causal association between serum urate and diabetes mellitus (10, 11).

Many researchers use a different definition for hyperuricaemia for men and women. While this approach is understandable when studying the prevalence of “abnormal” blood-test result e.g. +/- 1 SD or greater, and sex-specific cut-offs can be justified, such an approach is not necessary when examining the association between comorbidities and serum urate as there is no reason to suspect a differential association between the two sexes.

Our study has confirmed an independent association between gout and several comorbidities. Hyperuricaemia is hypothesized to be the mediator of the association between gout and cardiovascular comorbidities (22, 23). However, we found that the association between gout and cardiovascular comorbidities, hypercholesterolemia, and diabetes was independent of the serum urate levels. These findings are consistent with the results of large prospective observational studies that do not report a protective effect of ULT on all-cause or cardiovascular mortality in people with gout (24). There are several potential mechanisms that explain this urate-independent association between gout and comorbidities. Firstly, monosodium urate (MSU) crystal deposition occurs in the heart and major vessels in people with gout and may promote local inflammation (25). We previously reported that people with asymptomatic hyperuricaemia with ultrasound proven MSU crystal deposits in their joints have significantly higher expression of several pro-inflammatory genes in the peripheral blood mononuclear cells compared to people with hyperuricaemia but without

ultrasound evidence of MSU crystal deposits (26). The inflammatory milieu may explain the association between gout and comorbidities independent of serum urate levels. Additionally, other shared biological mechanisms among gout and these comorbidities may explain this observation. Chronic inflammation in cardiovascular diseases has been attributed to an increased synthesis of the pro-inflammatory cytokines IL-1β and IL-18 via assembly of the NLRP3 inflammasome and the activation of the toll-like receptor (TLR) pathways (27, 28) that are also involved in the immune response to MSU crystals. Functional genetic variants in genes involved in such mechanisms have been linked to a higher risk of developing hypercholesterolemia, hypertension and heart failure. For instance, a study by Kunnas *et al.* observed an association of the single nucleotide polymorphism (SNP) rs7512998 in the NLRP3 gene with hypertension (29). Whereas the SNP rs4986790 in TLR4 gene that affects the extracellular domain of the receptor, and results in a decreased response to damage molecular patterns has been identified as a protective variant for hypertension in individuals with coronary heart disease (30). Additionally, other SNPs in NLRP3 and CASP1 genes have also been associated with an increased risk of atherosclerosis in different populations (31, 32). Several variants in the genes involved in the innate immune response (e.g. NLRP3, TLR2, MyD88, IL1β, TXNIP, CARD8 and P2XR7) are recognised as gout susceptibility loci (33). It is possible that these underlying pro-inflammatory genetic changes explain the association between gout and comorbidities that are independent of serum urate levels. Genome and phenome wide association studies have provided additional evidence of the polygenic nature of cardiometabolic diseases, and a shared genetic architecture between them and hyperuricaemia – and consequently gout. Among the common loci driving the associations of hyperuricaemia with gout are variants located in urate transporters,

mainly ABCG2 and SLC2A9 (34); while those driving the associations between hyperuricaemia and other metabolic diseases are located in genes involved in haemostasis pathways and glucose transport (PTPN11 and GCKR genes respectively) (35, 36). Determining whether those associations are due to a causal relationship has been controversial. However, recent PheWAS and Mendelian randomisation studies have suggested that the coexistence of hyperuricaemia, gout and their comorbidities is a consequence of genetic variants exerting a pleiotropic effect (8, 37). Thus, further studies in this field are needed. Additionally, dietary factors such as low intake of omega-3 fatty acids may also contribute to the association between gout and comorbidities (38, 39).

This study reports an urate-independent positive association between gout and CKD when data for all 10,265 gout cases were included in the analysis. However, this became negative when gout patients treated with ULT were excluded from the analysis. This may be due to the fact that urate lies in the causal pathway between CKD and gout and adjusting for serum urate removes any positive association.

Strengths of this study include large sample size, community-based recruitment, and adjustment for demographic factors that associate with hyperuricaemia and gout. Unlike other studies using data from consultation-based databases such as the Clinical Practice Research Datalink and Veterans Administration, or administrative claims database such as MarketScan participants had data for serum urate, BMI, eGFR collected for research purposes unrelated to clinical need.

However, there are several limitations to this study. Firstly, gout status was ascertained using self-report and prescription data, and participants were not required to meet the 2010 ACR/EULAR gout classification criteria. UK Biobank data collection precedes the development of this criteria. Similarly, the comorbidity status was

ascertained from self-report based on prior-physician diagnosis, which might introduce recall bias. However, this self-reported information is valid and reliable predicting all-cause and cause-specific mortality and out- performed the Charlson comorbidity index in a previous study (40). Additionally, the classification of serum urate levels was based on a single urate measurement, from the samples collected at the same visit and may be influenced by the diet and lifestyle activities in the previous few days. The used single serum urate measurement does not reflect the level at the time of comorbidity incidence.

In conclusion, hyperuricaemia and gout associate with several cardiometabolic comorbidities and CKD, and, even a modest elevation in serum urate e.g. by 1 mg/dl associated with significantly increased risk of comorbidities. As this was a case-control study, further prospective cohort studies are needed to examine whether such mildly elevated urate levels associate with incident comorbidities. The association between gout and cardiometabolic diseses was independent of the serum urate level. This is a novel finding and further research is required to ascertain and better understand the underlying mechanisms so that they can be addressed.

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**Ethics approval:** UK Biobank has approval from the North West Multi-Centre Research Ethics Committee (REC reference 16/NW/0274). This study did not involve recontacting participants and no separate ethics approval was required.

**Data availability statement:** Raw data used for this study are available from the UK Biobank resource.

**Competing interests:** Dr A Abhishek has received departmental research grants from AstraZeneca and Oxford Immunotec, speaker bureau fees from Menarini, scientific meeting support from Pfizer, author royalties from UpToDate and Springer, and has consulted for Inflazome unrelated to this work.

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Table 1: Association between comorbidities and serum urate

| | Hypertension | | OR (95% CI) | aOR (95% CI)[1] |
|---|---|---|---|---|
| Serum urate | Yes, n (%) | No, n (%) | | |
| 1-mg/dl increase | | | 1.45 (1.44-1.45) | 1.29 (1.28-1.30) |
| Quintile 1 (1.500-4.000) | 13,279 (11.19) | 78,520 (23.08) | 1 | 1 |
| Quintile 2 (4.005-4.728) | 18,116 (15.27) | 73,787 (21.69) | 1.45 (1.42-1.49) | 1.17 (1.14-1.20) |
| Quintile 3 (4.729-5.425) | 22,535 (19.00) | 69,180 (20.34) | 1.93 (1.88-1.97) | 1.36 (1.32-1.39) |
| Quintile 4 (5.427-6.273) | 27,698 (23.35) | 63,966 (18.81) | 2.56 (2.50-2.62) | 1.67 (1.63-1.72) |
| Quintile 5 (6.274-17.947) | 37,004 (31.19) | 54,696 (16.08) | 4.00 (3.91-4.09) | 2.37 (2.31-2.44) |

| | Diabetes Mellitus | | | |
|---|---|---|---|---|
| | Yes, n (%) | No, n (%) | | |
| 1-mg/dl increase | | | 1.26 (1.25-1.27) | 0.89 (0.88-0.90) |
| Quintile 1 (1.500-4.000) | 2,533 (12.81) | 89,266 (20.33) | 1 | 1 |
| Quintile 2 (4.005-4.728) | 3,158 (15.98) | 88,745 (20.21) | 1.25 (1.19-1.32) | 0.78 (0.74-0.83) |
| Quintile 3 (4.729-5.425) | 3,806 (19.25) | 87,909 (20.02) | 1.53 (1.45-1.61) | 0.66 (0.63-0.70) |
| Quintile 4 (5.427-6.273) | 4551 (23.02) | 87,113 (19.84) | 1.84 (1.75-1.93) | 0.60 (0.57-0.64) |
| Quintile 5 (6.274-17.947) | 5,719 (28.93) | 85,981 (19.59) | 2.34 (2.23-2.46) | 0.55 (0.52-0.59) |

| | Ischaemic Heart Disease | | | |
|---|---|---|---|---|
| | Yes, n (%) | No, n (%) | | |
| 1-mg/dl increase | | | 1.43 (1.41-1.44) | 1.11 (1.09-1.12) |
| Quintile 1 (1.500-4.000) | 1,741 (8.83) | 90,058 (20.51) | 1 | 1 |
| Quintile 2 (4.005-4.728) | 2,646 (13.42) | 89,257 (20.33) | 1.53 (1.44-1.63) | 1.03 (0.97-1.11) |
| Quintile 3 (4.729-5.425) | 3,624 (18.38) | 88,091 (20.06) | 2.13 (2.01-2.25) | 1.06 (0.99-1.12) |
| Quintile 4 (5.427-6.273) | 4,794 (24.31) | 86,870 (19.79) | 2.85 (2.70-3.02) | 1.13 (1.06-1.20) |
| Quintile 5 (6.274-17.947) | 6,912 (35.06) | 84,788 (19.31) | 4.22 (4.00-4.45) | 1.33 (1.25-1.42) |

| | High Cholesterol | | | |
|---|---|---|---|---|
| | Yes, n (%) | No, n (%) | | |
| 1-mg/dl increase | | | 1.29 (1.28-1.30) | 1.10 (1.09-1.11) |
| Quintile 1 (1.500-4.000) | 6,453 (11.72) | 85,346 (21.14) | 1 | 1 |
| Quintile 2 (4.005-4.728) | 8,795 (15.97) | 83,108 (20.59) | 1.40 (1.35-1.45) | 1.10 (1.06-1.14) |
| Quintile 3 (4.729-5.425) | 10,875 (19.75) | 80,840 (20.02) | 1.78 (1.72-1.84) | 1.18 (1.14-1.22) |
| Quintile 4 (5.427-6.273) | 12,974 (23.56) | 78,690 (19.49) | 2.18 (2.11-2.25) | 1.27 (1.23-1.32) |
| Quintile 5 (6.274-17.947) | 15,965 (28.99) | 75,735 (18.76) | 2.79 (2.70-2.87) | 1.43 (1.38-1.48) |

| | Cardiac failure | | | |
|---|---|---|---|---|
| | Yes, n (%) | No, n (%) | | |
| 1-mg/dl increase | | | 1.73 (1.60-1.87) | 1.66 (1.52-1.82) |
| Quintile 1 (1.500-4.000) | 19 (7.60) | 91,780 (20.02) | 1 | 1 |
| Quintile 2 (4.005-4.728) | 23 (9.20) | 91,880 (20.04) | 1.21 (0.66-2.22) | 1.02 (0.55-1.90) |
| Quintile 3 (4.729-5.425) | 34 (13.60) | 91,681 (19.99) | 1.79 (1.02-3.14) | 1.45 (0.81-2.59) |
| Quintile 4 (5.427-6.273) | 59 (23.60) | 91,605 (19.98) | 3.11 (1.85-5.21) | 2.50 (1.44-4.34) |
| Quintile 5 (6.274-17.947) | 115 (46.00) | 91,585 (19.97) | 6.07 (3.73-9.86) | 4.45 (2.57-7.70) |

| | CKD stage 3b or higher | | | |
|---|---|---|---|---|
| | Yes, n (%) | No, n (%) | | |
| 1-mg/dl increase | | | 2.66 (2.58-2.75) | 3.14 (3.02-3.26) |
| Quintile 1 (1.500-4.000) | 40 (2.68) | 91,322 (20.08) | 1 | 1 |
| Quintile 2 (4.005-4.728) | 51 (3.42) | 91,389 (20.09) | 1.27 (0.84-1.93) | 1.41 (0.93-2.15) |
| Quintile 3 (4.729-5.425) | 104 (6.98) | 91,114 (20.03) | 2.60 (1.81-3.75) | 3.29 (2.26-4.79) |
| Quintile 4 (5.427-6.273) | 188 (12.61) | 90,954 (20.00) | 4.72 (3.35-6.64) | 7.07 (4.96-10.09) |
| Quintile 5 (6.274-17.947) | 1,108 (74.31) | 90,042 (19.80) | 28.09 (20.49-38.52) | 52.88 (37.74-74.09) |

[1]Adjusted for age, sex, BMI, smoking status, alcohol intake and Townsend deprivation index

Table 2: Association between gout and comorbidities

| | Gout (10,265) | No gout (458,781) | OR (95% CI) | aOR (95% CI)[1] | aOR (95% CI)[2] |
|---|---|---|---|---|---|
| Age (mean (SD)), years | 59.92 (7.00) | 56.46 (8.10) | 1.06 (1.05-1.06) | 1.03 (1.02-1.03) | 1.03 (1.03-1.04) |
| Male sex, n (%) | 9,132 (88.96) | 205,603 (44.82) | 9.93 (9.33-10.56) | 8.30 (7.78-8.85) | 5.87 (5.48-6.28) |
| BMI (mean (SD)), kg/m$^2$ | 30.61 (5.02) | 27.35 (4.75) | 1.11 (1.10-1.11) | 1.11 (1.11-1.12) | 1.09 (1.08-1.09) |
| Townsend index (mean (SD)) | -1.03 (3.20) | -1.32 (3.08) | 1.03 (1.02-1.04) | 1.02 (1.01-1.03) | 1.02 (1.01-1.02) |
| Alcohol intake, n (%)* | | | | | |
| Never or only on special | 1,328 (12.94) | 90,175 (19.66) | 1 | 1 | 1 |
| <1/week | 658 (6.41) | 51,459 (11.22) | 0.87 (0.79-0.95) | 0.96 (0.87-1.06) | 0.94 (0.85-1.04) |
| 1-2/week | 2,299 (22.40) | 118,533 (25.84) | 1.32 (1.23-1.41) | 1.33 (1.23-1.43) | 1.27 (1.17-1.36) |
| 3-4/week | 2,662 (25.92) | 105,478 (22.99) | 1.71 (1.60-1.83) | 1.73 (1.62-1.87) | 1.58 (1.47-1.70) |
| Daily or almost daily | 3,289 (32.04) | 92,129 (20.08) | 2.42 (2.27-2.59) | 2.24 (2.09-2.41) | 1.95 (1.81-2.10) |
| Smoking, n (%)* | | | | | |
| Non-smoker | 4,241 (41.32) | 251,142 (54.74) | 1 | 1 | 1 |
| Ex-smoker | 4,986 (48.57) | 157,059 (34.23) | 1.88 (1.80-1.96) | 1.10 (1.05-1.15) | 1.07 (1.03-1.12) |
| Current-smoker | 978 (9.53) | 48,259 (10.52) | 1.20 (1.12-1.29) | 0.95 (0.88-1.02) | 0.97 (0.90-1.04) |
| Hypertension, n (%) | 5,870 (57.18) | 118,632 (25.86) | 3.83 (3.68-3.98) | 1.89 (1.81-1.98) | 1.75 (1.67-1.83) |
| | | | | | |
| Diabetes Mellitus, n (%) | 1,280 (12.47) | 19,767 (4.31) | 3.16 (2.98-3.36) | 1.10 (1.02-1.17) | 1.21 (1.13-1.30) |
| | | | | | |
| IHD, n (%) | 1,384 (13.48) | 19,717 (4.30) | 3.47 (3.27-3.68) | 1.22 (1.15-1.31) | 1.21 (1.13-1.29) |
| | | | | | |
| High Cholesterol, n (%) | 2,830 (27.57) | 55,062 (12.00) | 2.79 (2.67-2.92) | 1.27 (1.21-1.34) | 1.28 (1.22-1.35) |
| | | | | | |
| Heart Failure, n (%) | 62 (0.60) | 250 (0.05) | 11.15 (8.43-14.73) | 5.03 (3.63-6.97) | 4.15 (2.98-5.79) |
| CKD, n (%)* | | | | | |
| G1 (>90 ml/min | 4,171(40.88) | 273,745 (59.99) | 1 | 1 | 1 |
| G2 (60-90 ml/min) | 4,913 (48.15) | 173,121 (37.94) | 1.86 (1.79-1.94) | 1.44 (1.38-1.51) | 1.22 (1.16-1.28) |
| G3a (45-59 ml/min) | 712 (6.98) | 7,955 (1.74) | 5.87 (5.41-6.38) | 3.53 (3.22-3.87) | 2.28 (2.07-2.51) |
| G3b (30-44 ml/min) | 274 (2.69) | 1,147 (0.25) | 15.67 (13.69-17.95) | 8.22 (7.05-9.61) | 4.18 (3.56-4.91) |
| G4 (15-29 ml/min) | 95 (0.93) | 240 (0.05) | 25.98 (20.45-33.01) | 13.52 (10.25-17.84) | 6.19 (4.66-8.22) |
| G5 (<15 ml/min) | 38 (0.37) | 104 (0.02) | 23.98 (16.51-34.81) | 16.14 (10.43-24.97) | 12.49 (7.95-19.64) |

[1]Adjusted for age, sex, BMI, hypertension, diabetes mellitus, IHD, heart failure, CKD, smoking, alcohol, Townsend deprivation index; [2]Additionally adjusted for serum urate. *Data for smoking status and alcohol intake were missing for 0.58% and 0.28% cases with gout and 0.51%, and 0.21% controls respectively. CKD status was missing for 0.60% cases and 0.54% controls.

Table 3. Association between gout –excluding cases on ULT- and comorbidities.

| | Gout (4,627) | No gout (458,781) | OR (95% CI) | aOR (95% CI)[1] | aOR (95% CI)[2] |
|---|---|---|---|---|---|
| Age (mean (SD)), years | 59.54 (7.25) | 56.46 (8.10) | 1.05 (1.05-1.06) | 1.02 (1.02-1.03) | 1.04 (1.04-1.05) |
| Male sex, n (%) | 3,947 (85.30) | 205,603 (44.82) | 7.14 (6.59-7.76) | 6.12 (5.62-6.66) | 1.87 (1.70-2.05) |
| BMI (mean (SD)), kg/m$^2$ | 30.23 (5.04) | 27.35 (4.75) | 1.10 (1.09-1.10) | 1.10 (1.09-1.11) | 1.01 (1.00-1.02) |
| Townsend index (mean (SD)) | -1.00 (3.20) | -1.32 (3.08) | 1.03 (1.02-1.04) | 1.02 (1.01-1.03) | 1.00 (0.99-1.01) |
| Alcohol intake, n (%) | 42 | | | | |
| Never or only on special | 673 (14.55) | 90,175 (19.66) | 1 | 1 | 1 |
| <1/week | 319 (6.89) | 51,459 (11.22) | 0.83 (0.73-0.95) | 0.90 (0.79-1.04) | 0.85 (0.73-0.98) |
| 1-2/week | 1,031 (22.28) | 118,533 (25.84) | 1.16 (1.06-1.28) | 1.16 (1.04-1.28) | 0.97 (0.87-1.08) |
| 3-4/week | 1,107 (23.92) | 105,478 (22.99) | 1.40 (1.28-1.55) | 1.39 (1.25-1.54) | 098 (0.88-1.09) |
| Daily or almost daily | 1,478 (31.94) | 92,129 (20.08) | 2.15 (1.96-2.36) | 1.94 (1.75-2.14) | 1.14 (1.03-1.27) |
| Smoking, n (%) | 69 | | | | |
| Non-smoker | 1,929 (41.69) | 251,142 (54.74) | 1 | 1 | 1 |
| Ex-smoker | 2,165 (46.79) | 157,059 (34.23) | 1.80 (1.69-1.91) | 1.12 (1.05-1.20) | 1.00 (0.94-1.08) |
| Current-smoker | 501 (10.83) | 48,259 (10.52) | 1.35 (1.22-1.49) | 1.09 (0.99-1.21) | 1.14 (1.03-1.27) |
| | | | | | |
| Hypertension, n (%) | 2,396 (51.78) | 118,632 (25.86) | 3.08 (2.91-3.26) | 1.66 (1.55-1.77) | 1.15 (1.08-1.24) |
| | | | | | |
| Diabetes Mellitus, n (%) | 479 (10.35) | 19,767 (4.31) | 2.56 (2.33-2.82) | 0.96 (0.87-1.07) | 1.19 (1.06-1.33) |
| | | | | | |
| IHD, n (%) | 584 (12.62) | 19,717 (4.30) | 3.22 (2.95-3.51) | 1.26 (1.15-1.39) | 1.16 (1.04-1.28) |
| | | | | | |
| High Cholesterol, n (%) | 1,108 (23.95) | 55,062 (12.00) | 2.31 (2.16-2.47) | 1.14 (1.05-1.22) | 1.16 (1.07-1.25) |
| | | | | | |
| Heart Failure, n (%) | 25 (0.54) | 250 (0.05) | 9.96 (6.60-15.05) | 4.37 (2.77-6.88) | 2.21 (1.34-3.63) |
| CKD, n (%)* | | | | | |
| G1 (>90 ml/min | 1,876 (40.85) | 273,745 (59.99) | 1 | 1 | 1 |
| G2 (60-90 ml/min) | 2,238 (48.74) | 173,121 (37.94) | 1.89 (1.77-2.01) | 1.52 (1.42-1.62) | 0.85 (0.79-0.91) |
| G3a (45-59 ml/min) | 324 (7.06) | 7,955 (1.74) | 5.94 (5.27-6.70) | 3.81 (3.34-4.33) | 0.75 (0.65-0.87) |
| G3b (30-44 ml/min) | 116 (2.53) | 1,147 (0.25) | 14.76 (12.13-17.96) | 7.99 (6.46-9.90) | 0.54 (0.42-0.70) |
| G4 (15-29 ml/min) | 29 (0.63) | 240 (0.05) | 17.63 (11.96-25-99) | 9.25 (6.09-14.04) | 0.31 (0.19-0.51) |
| G5 (<15 ml/min) | 9 (0.20) | 104 (0.02) | 12.63 (6.38-24.99) | 7.67 (3.68-15.99) | 0.91 (0.36-2.32) |

[1]Adjusted for age, sex, BMI, hypertension, diabetes mellitus, IHD, heart failure, CKD, smoking, alcohol, Townsend deprivation index; [2]Additionally adjusted for serum urate.

*Data for smoking status and alcohol intake were missing for 0.69% and 0.42% cases with gout and 0.51%, and 0.21% controls respectively. CKD status was missing for 0.76% cases and 0.54% controls.

Table S1 Demographic and lifestyle characteristics for UK Biobank participants with and without hypertension

| | Hypertension + | Hypertension - | *p* value |
|---|---|---|---|
| Age (mean (SD)), years | 59.63 (7.01) | 55.41 (8.17) | <0.0001 |
| Male sex (n (%)) | 65,119 (52.30) | 149,616 (43.42) | <0.0001 |
| BMI (mean (SD)), kg/m$^2$ | 29.44 (5.22) | 26.69 (4.39) | <0.0001 |
| SU (mean (SD)), mg/dL | 5.69 (1.41) | 5.02 (1.28) | <0.0001 |
| Townsend deprivation index (mean (SD)) | -1.07 (3.22) | -1.40 (3.03) | <0.0001 |
| Alcohol intake (n (%))* | | | |
| Never or only on special | 28,086 (22.61) | 63,417 (18.45) | <0.0001 |
| <1/week | 13,044 (10.50) | 39,073 (11.37) | |
| 1-2/week | 29,901 (24.07) | 90,931 (26.45) | |
| 3-4/week | 26,584 (21.40) | 81,556 (23.72) | |
| Daily or almost daily | 26,618 (21.43) | 68,800 (20.01) | |
| Smoking (n (%))* | | | |
| Non-smoker | 62,194 (54.73) | 193,189 (56.34) | <0.0001 |
| Ex-smoker | 49,718 (40.16) | 112,327 (32.76) | |
| Current-smoker | 11,880 (9.60) | 37,357 (10.90) | |

*The following data were missing: alcohol intake for 1,036 (0.22%), and smoking status for 2,381 (0.51%).

Table S2 Demographic and lifestyle characteristics for UK Biobank participants with and without diabetes mellitus

| | Diabetes + | Diabetes - | *p* value |
|---|---|---|---|
| Age (mean (SD)), years | 59.74 (7.05) | 56.38 (8.11) | <0.0001 |
| Male sex (n (%)) | 13,369 (63.52) | 201,366 (44.95) | <0.0001 |
| BMI (mean (SD)), kg/m$^2$ | 31.38 (5.83) | 27.23 (4.64) | <0.0001 |
| SU (mean (SD)), mg/dL | 5.62 (1.47) | 5.18 (1.34) | <0.0001 |
| Townsend deprivation index (mean (SD)) | -0.38 (3.43) | -1.35 (3.06) | <0.0001 |
| Alcohol intake (n (%))* | | | |
| Never or only on special | 7,226 (34.33) | 84,277 (18.85) | <0.0001 |
| <1/week | 2,495 (11.89) | 49,622 (11.10) | |
| 1-2/week | 4,891 (23.31) | 115,941 (25.94) | |
| 3-4/week | 3,294 (15.70) | 104,846 (23.45) | |
| Daily or almost daily | 3,075 (14.66) | 92,343 (20.66) | |
| Smoking (n (%))* | | | |
| Non-smoker | 9,445 (45.26) | 245,938 (55.17) | <0.0001 |
| Ex-smoker | 9,122 (43,71) | 152,923 (34.30) | |
| Current-smoker | 2,301 (11.03) | 46,936 (10.53) | |

*The following data were missing: alcohol intake for 1,036 (0.22%), and smoking status for 2,381 (0.51%).

Table S3 Demographic and lifestyle characteristics for UK Biobank participants with and without IHD

| | IHD + | IHD - | *p* value |
|---|---|---|---|
| Age (mean (SD)), years | 61.95 (5.98) | 56.28 (8.09) | <0.0001 |
| Male sex (n (%)) | 15,037 (71.26) | 199,698 (44.58) | <0.0001 |
| BMI (mean (SD)), kg/m$^2$ | 29.48 (5.03) | 27.32 (4.75) | <0.0001 |
| SU (mean (SD)), mg/dL | 5.86 (1.43) | 5.17 (1.34) | <0.0001 |
| Townsend deprivation index (mean (SD)) | -0.59 (3.41) | -1.34 (3.07) | <0.0001 |
| Alcohol intake (n (%))* | | | |
| Never or only on special | 5,606 (26.63) | 85,897 (19.22) | <0.0001 |
| <1/week | 2,154 (10.23) | 49,963 (11.18) | |
| 1-2/week | 5,065 (24.06) | 115,767 (25.90) | |
| 3-4/week | 4,160 (19.76) | 103,980 (23.26) | |
| Daily or almost daily | 4,063 (19.30) | 91,355 (20.44) | |
| Smoking (n (%))* | | | |
| Non-smoker | 7,660 (36.60) | 247,723 (55.58) | <0.0001 |
| Ex-smoker | 10,520 (50.26) | 151,525 (33.99) | |
| Current-smoker | 2,750 (13.14) | 46,487 (10.43) | |

*The following data were missing: alcohol intake for 1,036 (0.22%), and smoking status for 2,381 (0.51%).

Table S4 Demographic and lifestyle characteristics for UK Biobank participants with and without High Cholesterol

| | High cholesterol + | High cholesterol - | *p* value |
|---|---|---|---|
| Age (mean (SD)), years | 60.93 (6.37) | 55.91 (8.12) | <0.0001 |
| Male sex (n (%)) | 32,840 (56.73) | 181,895 (44.24) | <0.0001 |
| BMI (mean (SD)), kg/m$^2$ | 28.98 (4.81) | 27.20 (4.74) | <0.0001 |
| SU (mean (SD)), mg/dL | 5.62 (1.38) | 5.14 (1.34) | <0.0001 |
| Townsend deprivation index (mean (SD)) | -1.35 (3.06) | -1.00 (3.22) | <0.0001 |
| Alcohol intake (n (%))* | | | |
| Never or only on special | 13,172 (22.82) | 78,331 (19.09) | <0.0001 |
| <1/week | 5,873 (10.17) | 46,244 (11.27) | |
| 1-2/week | 13,779 (23.87) | 107,053 (26.09) | |
| 3-4/week | 12,494 (21.64) | 95,646 (23.31) | |
| Daily or almost daily | 12,406 (21.49) | 83,012 (20.23) | |
| Smoking (n (%))* | | | |
| Non-smoker | 26,581 (46.25) | 228,802 (55.92) | <0.0001 |
| Ex-smoker | 24,506 (42.64) | 137,539 (33.61) | |
| Current-smoker | 6,390 (11.12) | 42,847 (10.47) | |

*The following data were missing: alcohol intake for 1,036 (0.22%), and smoking status for 2,381 (0.51%).

Table S5 Demographic and lifestyle characteristics for UK Biobank participants with and without CCF

| | CCF + | CCF - | *p* value |
|---|---|---|---|
| Age (mean (SD)), years | 60.65 (6.55) | 56.53 (8.09) | <0.0001 |
| Male sex (n (%)) | 195 (62.50) | 214,540 (45.77) | <0.0001 |
| BMI (mean (SD)), kg/m$^2$ | 30.28 (6.59) | 27.42 (4.78) | <0.0001 |
| SU (mean (SD)), mg/dL | 6.58 (1.82) | 5.20 (1.35) | <0.0001 |
| Townsend deprivation index (mean (SD)) | -0.12 (3.58) | -1.31 (3.08) | <0.0001 |
| Alcohol intake (n (%))* | | | |
| Never or only on special | 103 (33.12) | 91,400 (19.54) | <0.0001 |
| <1/week | 38 (12.22) | 52,079 (11.14) | |
| 1-2/week | 64 (20.58) | 120,768 (25.82) | |
| 3-4/week | 48 (15.43) | 108,092 (23.11) | |
| Daily or almost daily | 58 (18.65) | 95,360 (20.39) | |
| Smoking (n (%))* | | | |
| Non-smoker | 126 (40.78) | 255,257 (54.73) | <0.0001 |
| Ex-smoker | 145 (46.93) | 161,900 (34.72) | |
| Current-smoker | 38 (12.30) | 49,199 (10.55) | |

*The following data were missing: alcohol intake for 1,036 (0.22%), and smoking status for 2,381 (0.51%).

Table S6 Demographic and lifestyle characteristics for UK Biobank participants with and without CKD 3b or higher

| | CKD + | CKD - | *p* value |
|---|---|---|---|
| Age (mean (SD)), years | 62.28 (6.47) | 56.51 (8.09) | <0.0001 |
| Male sex (n (%)) | 1,032 (54.37) | 212,360 (45.71) | <0.0001 |
| BMI (mean (SD)), kg/m$^2$ | 29.68 (5.83) | 27.41 (4.77) | <0.0001 |
| SU (mean (SD)), mg/dL | 7.45 (1.90) | 5.19 (1.34) | <0.0001 |
| Townsend deprivation index (mean (SD)) | -0.69 (3.26) | -1.32 (3.08) | <0.0001 |
| Alcohol intake (n (%)) | | | |
| Never or only on special | 714 (37.74) | 90,256 (19.44) | <0.0001 |
| <1/week | 214 (11.31) | 51,686 (11.13) | |
| 1-2/week | 439 (23.20) | 119,962 (25.84) | |
| 3-4/week | 258 (13.64) | 107,507 (23.16) | |
| Daily or almost daily | 267 (14.11) | 94,778 (20.42) | |
| Smoking (n (%)) | | | |
| Non-smoker | 851 (45.31) | 253,542 (54.78) | <0.0001 |
| Ex-smoker | 859 (45.74) | 160,528 (34.68) | |
| Current-smoker | 168 (8.95) | 48,804 (10.54) | |

Creatinine measurements were not available for 2,531 participants; therefore, CKD status was missing for 0.54% of participants.

*The following data were missing: alcohol intake for 1,036 (0.22%), and smoking status for 2,381 (0.51%).