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Sodium-glucose cotransporter 1 inhibition and gout: Mendelian randomisation study

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ABSTRACT

Objective: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduce serum urate, but their efficacy depends on renal function which is often impaired in people with gout. SGLT1 is primarily expressed in the small intestine and its inhibition may be a more suitable therapeutic target. We aimed to investigate the association of genetically proxied SGLT1i with gout risk, serum urate levels and cardiovascular safety using Mendelian randomisation (MR).

Methods: Leveraging data from a genome-wide association study of 344,182 individuals in the UK Biobank, we identified a missense variant in the *SLC5A1* gene that associated with glycated haemoglobin (HbA1c) to proxy SGLT1i. Outcome genetic data comprised 13,179 gout cases and 750,634 controls, 457,690 individuals for serum urate levels, and up to 977,323 individuals for cardiovascular safety outcomes. We applied the Wald ratio method and investigated potential genetic confounding using colocalization.

Results: The rs17683430 missense variant was selected to instrument SGLT1i. Genetically proxied SGLT1i was associated with 75% reduction in gout risk (OR 0.25; 95%CI 0.06, 0.99; $p = 0.048$) and 32.0 μmol/L reduction in serum urate (95%CI −56.7, −7.3; $p = 0.01$), per 6.7 mmol/mol reduction in HbA1c. SGLT1i was associated with increased levels of low-density lipoprotein cholesterol (0.37 mmol/L; 95%CI 0.17, 0.56; $p = 0.0002$) but not risk of coronary heart disease, stroke, or chronic kidney disease. Colocalization did not suggest that results are attributable to genetic confounding.

Conclusion: SGLT1 inhibition may represent a novel therapeutic option for preventing gout in people with or without comorbid diabetes. Randomised trials are needed to formally investigate efficacy and safety.

Introduction

Gout affects up to 4% of adults in high-income countries, with over 7 million new cases each year worldwide [1]. Around a quarter of people with gout have concomitant type 2 diabetes [2]. In diabetes trials, participants randomised to sodium-glucose cotransporter 2 inhibitors (SGLT2i) had on average 38 μmol/L lower serum urate than comparator arms [3].

Repurposing SGLT2i for management of gout and its comorbidities is appealing. Observational studies reported lower risk of gout in initiators of SGLT2i than either glucagon-like peptide 1 receptor agonists [4,5] or dipeptidyl peptidase 4 inhibitors [6]. Post hoc analysis of randomised

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trials for canagliflozin showed lower risk of gout flares compared to placebo [7]. However, interpretation is restricted to populations with type 2 diabetes. A further limitation is that the glucose and urate lowering efficacy of SGLT2i are dependent on renal function. Chronic kidney disease (CKD) is a key risk factor for gout, and around one in six people diagnosed with gout develop stage ≥3 CKD over a median of 6 years [8]. SGLT2i have little to no uricosric effect when estimated glomerular filtrate rate (eGFR) is below 60 mL/min/1.73 m^2 (i.e., stage ≥3 CKD) [3].

SGLT1 is primarily expressed in the small intestine [9], and SGLT1i may offer advantages over SGLT2i for gout management in renal impairment. The dual SGLT1 and 2 inhibitor, sotagliflozin, improved cardiovascular outcomes in diabetes with heart failure or CKD similar to SGT2i trials [10,11]. Furthermore, it reduced glucose and glycated haemoglobin (HbA1c) by similar degrees in patients with estimated GFR (eGFR) above and below 30 mL/min/1.73 m^2 [10,11]. However, no previous studies have investigated the repurposing potential of SGLT1i for gout to our knowledge.

Natural variation in the genes that encode drug targets can offer insight into mechanism-based efficacy and adverse effects [12]. Such genetic instrumental variable analysis, or Mendelian randomisation (MR), is more robust against confounding than traditional epidemiologic designs [13]. Since genetic variants are randomly allocated at conception, MR can be conceptualised as a quasi-randomised natural experiment comparing gout risk according to levels of genetically proxied SGLT1 activity. Our aim in this study was to use MR to investigate the therapeutic potential of SGLT1 inhibition for the management of gout.

Methods

Genetic proxies for SGLT1 inhibition

SGLT2i and dual SGLT1/2i have consistently been shown to reduce HbA1c in randomised controlled trials (RCTs) of type 2 diabetes [10,11,14]. We chose HbA1c as the biomarker of SGLT1i action because of the established effect of SGLT inhibition on this marker of glycaemic control [15]. Alternative traits to proxy SGLT1i have important limitations; diabetes is a binary trait which presents methodological limitations in MR [16], while genome-wide association studies (GWAS) of other glycaemic traits (e.g., 2 hour glucose tolerance or fasting glucose; maximum GWAS sample size 63,396 to 200,622 [17]) are less likely to yield sufficiently strong instruments given their smaller sample sizes. Moreover, HbA1c is a common measure of glycaemic control in clinic practice.

To instrument SGLT1, we selected missense (protein coding) variants within the *SLC5A1* gene (build GRCh37/hg19: chromosome 22: 32439019–32509016) that were associated with HbA1c at genome-wide significance ($p < 5 \times 10^{-8}$) and uncorrelated (linkage disequilibrium threshold of $r^2 < 0.1$ using PLINK and phase 3 version 5 of the 1000 genomes project as reference panel). The HbA1c GWAS comprised 344,182 participants of European ancestry in the UK Biobank [18]. Approximately 5% of this population had type 2 diabetes at enrolment (prevalence estimate consistent between ICD10 code E11 and self-reported physician diagnosis). HbA1c was inverse-normal transformed (overall mean ± standard deviation was 36.1 ± 6.7 mmol/mol) [18].

Genetic proxies for HbA1c

Given the observational association between type 2 diabetes and gout, we investigated whether genetically predicted HbA1c overall (rather than specifically through SGLT1i) is associated with gout and urate as outcomes. We instrumented HbA1c modification using variants throughout the genome, except variants from the *SLC5A1* gene ± 20 kilobases that had associations with HbA1c at $p < 5 \times 10^{-8}$ and pairwise correlations of $r^2 < 0.001$. This stricter correlation was used because variants were selected from throughout the genome, rather than a single gene locus.

Genetic association for primary outcomes: gout and serum urate level

Full details of each outcome GWAS are summarised in Table 1. Genetic association data for gout and urate were both obtained from the GWAS meta-analysis by Tin et al. [19]; the details of demographics, genotyping and urate assay methods for each study were reported in the original publication. Data were available for 13,179 gout cases (self--reported, urate-lowering drugs or ICD codes for gout) and 750,634 controls. Half of gout cases were from the UK Biobank; 98% of cases were of European ancestry. In this study, urate (mg/dL, multiplied by 59.5 to convert to μmol/L) data were available for 457,690 individuals; there was no overlap with the UK Biobank but 37% were of non-European ancestry.

Table 1
Summary of genome-wide association studies.

Study	N (case/ controls)	Phenotype definition / unit	Ancestry
Gout (Tin) [19]	13,179/ 750,634	Self-reported, urate-lowering drugs, ICD codes for gout detailed in [19]	Mixed; 98% EUR
Urate (Tin) [19]	457,690	mg/dL (converted to μmol/L by multiplying by 59.5)	Mixed, 63% EUR
Glycated haemoglobin (HbA1c) (UKBB) [18]	344,182	SD = 6.7 mmol/mol	EUR
Heart failure (Shah) [39]	47,309/ 930,014	Clinical diagnosis of any aetiology with no specific inclusion criteria based on left ventricular ejection fraction	EUR
Coronary artery disease (Nikpay) [40]	60,801/ 123,504	Clinically confirmed CAD, eg, myocardial infarction, acute coronary syndrome, chronic stable angina or coronary stenosis of >50%	Mixed; 77% EUR
Myocardial infarction (Nikpay) [40]	43,676/ 128,199	Clinically confirmed myocardial infarction	Mixed; 68% EUR
Stroke (Malik) [41]	40,585/ 406,111	World Health Organization definition	EUR
Systolic blood pressure (Evangelou) [42]	757,601	mmHg	EUR
Diastolic blood pressure (Evangelou) [42]	757,601	mmHg	EUR
BMI (Pulit) [43]	806,834	SD = 4.8 kg/m^2	EUR
LDL (UKBB) [44]	440,546	SD = 0.87 mmol/L	EUR
HDL (UKBB)[44]	403,943	SD = 0.38 mmol/L	EUR
Triglycerides (UKBB) [44]	441,016	SD = 1.11 mmol/L	EUR
Estimated glomerular filtration rate (Wuttke) [45]	567,460	log eGFR (mL/min/1.73 m^2) estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation	EUR
Chronic kidney disease (Wuttke) [45]	41,395/ 439,303	eGFR < 60 mL/min/1.73 m^2	EUR
Type 2 diabetes (Xue) [46]	61,714/ 596,424	Meta-analysis of many studies that use combinations of self-report, HbA1c, and/or diagnostic codes	EUR

Abbreviations: eGFR, estimated glomerular filtration rate; EUR, European; HDL, high density lipoprotein; ICD, International Classification of Diseases; LDL, low density lipoprotein; SD, standard deviation.

Genetic association for supplementary cardiorenal outcomes

SGLT1 is expressed in multiple tissues including the heart, brain, liver and renal tubules, and clinical trials of SGLT2i have shown protective cardiorenal effects [15]. The effects of SGLT1i on these outcomes are unclear. We therefore investigated the effect of SGLT1i on heart failure, coronary artery disease, myocardial infarction, stroke; blood pressure, body mass index (BMI), low/high density lipoprotein (LDL/HDL) cholesterol, triglycerides; chronic kidney disease and eGFR (using serum creatinine). Lastly, we included type 2 diabetes as a positive control outcome. Details of each GWAS are summarised in Table 1.

All summary statistics from prior GWAS are publicly available and had previously received appropriate patient consent and ethical approval. Full details are available in the original publications. One-sample MR using UK Biobank data was performed under application number 72723.

Statistical analysis and MR assumptions

We used the Wald ratio method to estimate the association of genetically proxied SGLT1i with each outcome, whereby the exposure-outcome estimate is derived from the variant-outcome association divided by the variant-exposure association (further details provided in supplementary Fig. S1-2 and accompanying text). MR estimates were scaled to a 1 standard deviation (SD), i.e., 6.7 mmol/mol reduction in HbA1c. Analysis using multiple instruments for genetically predicted HbA1c was performed using the inverse-variance weighted (IVW) method, which provides a weighted average of variant estimates analogous to a fixed-effect meta-analysis [20].

Valid instrumental variables are defined by three assumptions [21] which we interrogated as follows. First, variants must be associated with the exposure of interest ("relevance"). Variance explained (r^2) was calculated using $2EAF(1-EAF)\beta^2$, where EAF is the effect allele frequency. F statistic was derived using $(r^2/K)/[(1-r^2)(N-K-1)]$, where K is the number of SNPs and N the sample size. F statistic >10 is suggestive of adequate instrument strength [22].

Second, the variants should share no common cause with the outcome (i.e., no unmeasured confounders, or "independence"). This assumption is not empirically verifiable, although a prior study of *SLC5A1* missense variants showed that they were not associated with smoking, alcohol or total energy intake [23]. Bias arising from underlying population structure was reduced through use of European ancestry populations where possible in primary or sensitivity analyses.

Third, variants should not affect the outcome except through the risk factor ("exclusion restriction"). Use of a missense variant with plausible biology reduces risk of this bias. We also performed colocalization analysis to examine possible genetic confounding through linkage disequilibrium (LD). We used Bayesian colocalization with the default prior probabilities of 10^{-4}, 10^{-4} and 10^{-5} for a variant within the *SLC5A1* genomic locus being associated with the exposure trait, outcome trait, or both traits, respectively. The primary outputs of interest are posterior probability of distinct causal variants (H3), shared causal variant (H4), and the probability of colocalization conditional on the presence of a causal variant for the outcome (H4/(H3+H4)). Further details are provided in supplementary methods.

The above two-sample MR analyses of genetically proxied SGLT1i vs gout/urate may be susceptible to bias from sample overlap and population heterogeneity. The primary analysis was repeated using individual level data from the UK Biobank (i.e., one-sample MR), again using the Wald ratio method. We obtained the instrument-exposure association by regressing inverse-normal transformed HbA1c against the instrument, and the instrument-outcome association by regressing (logistic model for gout and linear model for urate) outcome against the instrument; each model was adjusted for age, sex, recruitment centre, and the first ten principal components. Gout was defined using a combination of ICD code, urate lowering medication, self-report and primary care codes (see supplementary methods).

Analyses were performed in R using the *TwoSampleMR, coloc* and *ivreg* packages [24,25]. The study was reported in accordance with the STROBE-MR guidelines [26] (supplementary Table S5).

Results

Three missense variants in high LD ($r^2 = 1$) were identified in the *SLC5A1* gene. The lead variant, rs17683430 (F statistic 59), was used to instrument SGLT1i. In the primary (two-sample) analysis, genetically proxied SGLT1i was associated with 75% reduction in risk of gout (OR 0.25; 95%CI 0.06, 0.99; $p = 0.048$) and 32.0 μmol/L reduction in serum urate (95%CI −56.7, −7.3; $p = 0.01$), per 6.7 mmol/mol reduction in HbA1c. Genetic associations between rs17683430 and each trait are summarised in supplementary Table S1-2.

Genetically predicted HbA1c (instrumented using 318 variants with mean F statistic of 141) did not provide evidence of a strong association with gout risk (OR 0.89; 95%CI 0.75, 1.07; $p = 0.23$) or urate (−0.53 μmol/L; 95%CI −3.25, 4.32; $p = 0.78$) (supplementary Table S3).

One-sample MR analysis

One-sample MR using individual level UK Biobank data showed similar results between genetically proxied SGLT1i and gout (OR 0.08 per standard deviation reduction in HbA1c; 95%CI 0.02, 0.27; $p = 5.5 \times 10^{-5}$) and urate (−46.2 μmol/L; 95%CI −62.7, −29.6; $p = 4.4 \times 10^{-8}$)

Supplementary cardiorenal outcomes

Genetically proxied SGLT1i was associated with increased LDL cholesterol (0.4 mmol/L per 6.7 mmol/mol reduction in HbA1c; 95%CI 0.2, 0.6; $p = 2.0 \times 10^{-4}$) (Fig. 1). There was suggestive MR evidence that it reduced blood pressure, but none of the other cardiorenal outcomes examined. Genetically proxied SGLT1i was associated with reduced risk of the positive control, type 2 diabetes. Full results are shown in supplementary Table S2.

Colocalization

For HbA1c and gout, the posterior probability of a shared causal variant (8.8%) within the *SLC5A1* gene was greater than the probability of distinct variants (1.3%); probability of colocalization conditional on the presence of a causal variant for the outcome was 87%. For HbA1c and urate, the respective posterior probabilities were 10%, 1.8%, and 86%. Taken together, this suggests that the MR estimates for the effect of SGLT1i on gout and serum urate are unlikely to be confounded by a variant in LD. Locus plots and full results are shown in supplementary Fig. S3 and Table S4.

For the supplementary outcomes, HbA1c colocalised with diabetes and LDL cholesterol but not systolic or diastolic blood pressure. The associations between SGLT1i and blood pressure in MR are therefore likely confounded by a variant in LD.

Discussion

This study provides genetic evidence to support that SGLT1 inhibition reduces risk of gout and serum urate levels among a population predominantly without diabetes. Given that we did not observe evidence of an overall effect of HbA1c on either gout or serum urate, this finding is unlikely to be related to glycaemic control, and other mechanisms specific to SGLT1 may be driving the association. Genetically proxied SGLT1 inhibition was associated with increased LDL cholesterol, but not with selected adverse cardiovascular or renal outcomes.

To our knowledge, this is the first genetic study to directly investigate the therapeutic potential of SGLT1 for gout. It is biologically plausible that the link between glucose and uric acid transport for SGLT1

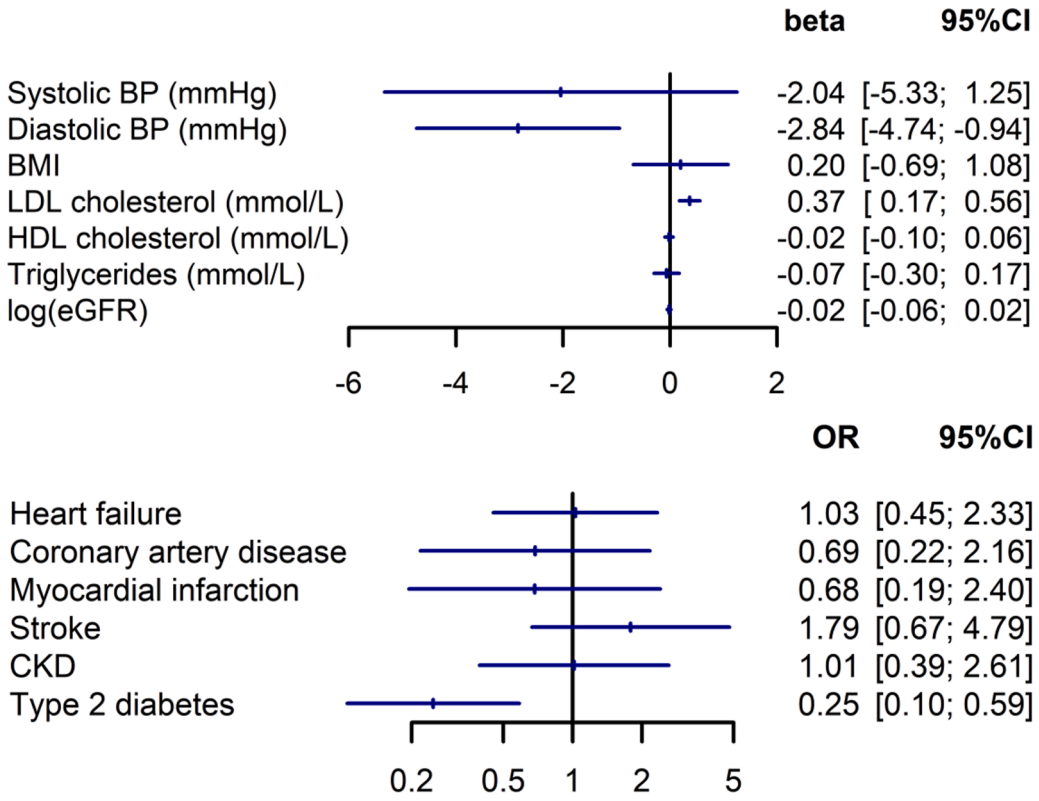

Fig. 1. Mendelian randomisation estimates of the association of genetically proxied SGLT1 inhibition with cardiovascular and renal outcomes.
Legend: BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate (log transformed); HDL: high density lipoprotein; LDL: low density lipoprotein; OR: odds ratio; CI: confidence interval.

resembles that of SGLT2 seen in the kidney. SGLT2 is expressed in the proximal renal tubules and accounts for approximately 97% of renal glucose reabsorption. Rather than directly transporting urate itself, SGLT2i is thought to increase urate excretion via osmotic uricosuria, inhibition of urate reabsorption or inflammasome suppression [27–29]. SGLT1i may analogously modulate intestinal urate transport. GLUT9 (glucose transporter 9) is a renal and intestinal urate transporter, which has been shown *in vitro* to accelerate urate efflux in the presence of extracellular glucose [30]. SGLT1 inhibition may indirectly upregulate ABCG2 (ATP-binding cassette subfamily G member 2) which is a key transporter for intestinal urate excretion [31–33]. In rat models of CKD, increased intestinal *ABCG2* expression and urate excretion was hypothesised to compensate for reduced renal elimination [34]. Increased glucose delivery to the colon may also alter microbiome composition and metabolite production with complex sequelae on systemic metabolism and inflammation [35]. Further mechanistic studies will be required to understand the molecular basis of SGLT1i on serum urate and gout.

HbA1c is a proxy for general glycaemic control, of which glucose reduction is one component. Our analysis did not investigate the causal effect of glucose elimination at the kidneys or bowel specifically on urate or gout. MR investigates causal associations (rather than correlations), which may explain why previously described observational correlations (HbA1c and urate) did not replicate.

We did not observe evidence to support any potential adverse effects of SGLT1i on cardiovascular or renal outcomes, which is important because SGLT1 action in these tissues are not well understood. This contrasts with the protective effects of SGLT2i in heart failure and CKD [15]. Several factors may explain this discrepancy. One possibility is that SGLT1i alone does not produce the diuretic/natriuretic effects and putative alterations to the autonomic nervous system that at least partly explain the protective effects of SGLT2i on heart failure [36,37], or the effects on renal filtration/haemodynamics that explain renal protection [38]. A previous one-sample MR study of SGLT1 used 2 hour glucose tolerance as the biomarker for their genetic instrument to show that a three-variant-haplotype was associated with reduced risk of heart failure [23]. The use of a different population and biomarker (glucose tolerance vs HbA1c) may explain this discrepancy.

SGLT2i has been shown to reduce blood pressure [15,37]. The aforementioned study of *SLGT1* missense variants also reported associations with diastolic blood pressure ($p = 0.028$) [23]. However, our suggestive MR finding that SGLT1i reduces blood pressure failed to colocalize, suggesting presence of genetic confounding.

Taken together, our findings suggest that SGLT1 (e.g., mizagliflozin) or dual SGLT1/2 inhibitors (e.g., sotagliflozin or licogliflozin) may be repurposed for the management of gout. We showed the urate lowering potential of SGLT1i using data from a population mostly without diabetes. By contrast, evidence is lacking that SGLT2i has uricosuric effects in populations without diabetes. The sotagliflozin trials found similar reduction in HbA1c between subgroups with eGFR above and below 30 mL/min/1.73 m^2 [10,11]; therefore, SGLT1 and dual inhibitors have potential to lower urate in the setting of renal impairment where use and effectiveness of many existing gout treatments are limited. Moreover, SGLT1i should not be associated with common adverse events related to glycosuria (e.g., urinary tract infections) seen in SGLT2i, although further studies are needed to examine other safety signals.

When instrumental variable assumptions are met, MR estimates the causal exposure-outcome relationship with less bias from confounding or reverse causation [13]. Results of this study were robust against several sensitivity analyses using different populations and statistical methods. Use of population genetics also allowed us to examine SGLT1 without restricting to diabetes cohorts, which provides support for repurposing SGLT1i to treat gout more than as a comorbidity of diabetes.

The key limitation of our work, as with all MR studies, is that the independence and exclusion restriction assumptions are not falsifiable.

However, a prior study showed that *SLC5A1* missense variants were not associated with key confounders [23], while use of a protein coding variant reduces risk of pleiotropy. MR provides estimates of the associations of genetically predicted risk factor over a lifetime thus the numerical MR estimates may be larger than pharmacological intervention in adult life [12]. Our study population included mainly participants of European ancestry; future studies among other ethnic populations are needed to confirm the generalisability of the current findings. In colocalization analyses, the posterior probability of shared causal variant was generally low, which may be due to limited statistical power, or due to the causal variant not being included in both exposure and outcome GWAS datasets. The rs17683430 instrument is associated with expression of several genes other than *SLC5A1*, which suggests a potential for pleiotropic effects unrelated to *SLC5A1* that may violate the modelling assumptions of our analysis. However, the most strongly associated expression quantitative loci pertains to *SLC5A1*, thus any such pleiotropic effects may be relatively modest. Further mechanistic studies are required to confirm the impact of the rs17683430 variant on SGLT1 activity in relation to effects through other genes to support the conclusions of our study. Lastly, we could not directly compare effect of SGLT1i between people with and without diabetes. This should be a focus of future study and may shed light on the mechanism underpinning the observed effect.

In conclusion, this study provides genetic evidence to support the therapeutic potential of SGLT1i in the treatment of hyperuricaemia and gout. This effect appears to arise independently of glycaemic control and may pertain to patients with or without comorbid type 2 diabetes. Randomised controlled trials of currently available SGLT1i or dual SGLT1i/SGLT2i are needed to test efficacy and safety in populations at high risk of incident or recurrent gout.

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Role of the funding source

The funding sources had no input into study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

Availability of data

All summary statistics used in this study are publicly available, with relevant citations detailed. UK Biobank data are available to all bona fide researchers for use in health-related research that is in the public interest. The application procedure is described at www.ukbiobank.ac.uk. The current analysis was performed under application number 72723.

CRediT authorship contribution statement

Sizheng Steven Zhao: Conceptualization, Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision. **Skanda Rajasundaram:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Ville Karhunen:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Uazman Alam:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Dipender Gill:** Conceptualization, Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

DG is employed part-time by Novo Nordisk. All authors declare no conflicts of interest that could bias this work.

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