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## EXTENDED REPORT

# MR-PheWAS: exploring the causal effect of SUA level on multiple disease outcomes by using genetic instruments in UK Biobank

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**ABSTRACT**

**Objectives** We aimed to investigate the role of serum uric acid (SUA) level in a broad spectrum of disease outcomes using data for 120 091 individuals from UK Biobank.

**Methods** We performed a phenome-wide association study (PheWAS) to identify disease outcomes associated with SUA genetic risk loci. We then implemented conventional Mendelian randomisation (MR) analysis to investigate the causal relevance between SUA level and disease outcomes identified from PheWAS. We next applied MR Egger analysis to detect and account for potential pleiotropy, which conventional MR analysis might mistake for causality, and used the HEIDI (heterogeneity in dependent instruments) test to remove cross-phenotype associations that were likely due to genetic linkage.

**Results** Our PheWAS identified 25 disease groups/outcomes associated with SUA genetic risk loci after multiple testing correction ( $P < 8.57 \times 10^{-5}$ ). Our conventional MR analysis implicated a causal role of SUA level in three disease groups: inflammatory polyarthropathies (OR=1.22, 95% CI 1.11 to 1.34), hypertensive disease (OR=1.08, 95% CI 1.03 to 1.14) and disorders of metabolism (OR=1.07, 95% CI 1.01 to 1.14); and four disease outcomes: gout (OR=4.88, 95% CI 3.91 to 6.09), essential hypertension (OR=1.08, 95% CI 1.03 to 1.14), myocardial infarction (OR=1.16, 95% CI 1.03 to 1.30) and coeliac disease (OR=1.41, 95% CI 1.05 to 1.89). After balancing pleiotropic effects in MR Egger analysis, only gout and its encompassing disease group of inflammatory polyarthropathies were considered to be causally associated with SUA level. Our analysis highlighted a locus (*ATXN2/S2HB3*) that may influence SUA level and multiple cardiovascular and autoimmune diseases via pleiotropy.

**Conclusions** Elevated SUA level is convincing to cause gout and inflammatory polyarthropathies, and might act as a marker for the wider range of diseases with which it associates. Our findings support further investigation on the clinical relevance of SUA level with cardiovascular, metabolic, autoimmune and respiratory diseases.

**INTRODUCTION**

Uric acid (UA) is the end product of the exogenous and endogenous purine metabolism, catalysed

by the action of xanthine oxidase.<sup>1</sup> Due to the evolved loss of uricase enzyme, humans are unable to convert UA into highly soluble compounds, leaving urate circulating in the blood and resulting in a high basal level of serum uric acid (SUA).<sup>2</sup> The prevalence rate of hyperuricaemia (elevated SUA level >7.0 mg/dL) is in the range of 5%–25% across different countries.<sup>3–5</sup> A progressively rising trend of hyperuricaemia prevalence has been observed worldwide.<sup>5</sup> Concernedly, hyperuricaemia is thought to inflict multiple clinical consequences, which is believed to be causally related to gout and suggestively associated with a number of prevalent health conditions, such as cardiovascular and metabolic diseases.<sup>6–8</sup>

Our recently published umbrella review presented a comprehensive overview of the breadth of disease outcomes related to SUA level by incorporating evidence from multiple sources.<sup>9</sup> A large number of disease outcomes were reported to be associated with SUA level in observational studies, covering a wide range of diseases, including cardiovascular disease, metabolic syndrome, diabetes, cancer and neurological disorders. However, evidence as to whether these associations are actually causal is not yet well developed, given that observational associations are susceptible to a variety of biases, confounding and/or reverse causality. Although results from randomised controlled trials (RCTs) have provided some evidence about the beneficial effects of SUA-lowering therapy on some intermediate traits or biomarkers (eg, blood pressure, endothelial function, serum creatinine), there remains a lack of RCTs focusing on the more important clinical disease endpoints.<sup>10–12</sup> A number of Mendelian randomisation (MR) studies, using the genetic variants influencing SUA level as instruments, provide alternative evidence to distinguish causal from non-causal associations. However, these MR studies examined a limited set of disease outcomes and were not able to detect moderate effect size due to limited power.<sup>13–19</sup> Increasing sample size and the range of outcomes in an enlarged MR study thus offers the prospect of deeper and wider insight into the causal role of SUA.

MR analysis is typically hypothesis-driven based on prior knowledge to specify the outcome to be examined in relation to the exposure of

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interest. Traditionally, only one (or a limited number) association between the exposure and one (or a few) predefined outcome(s) is tested in an MR study. Recently, phenome-wide Mendelian randomisation (MR-PheWAS) analysis has been proposed by integrating the phenome-wide association study (PheWAS) and MR method to build a hypothesis-searching approach, which aims to explore potential causal relationships between an exposure (using genetic instruments as proxies) and a range of phenome-wide disease outcomes in a high-throughput manner.<sup>20</sup> This approach is effective in evaluating or replicating the associations reported in observational studies, as well as discovering new relationships and generating new hypotheses on the genetic architecture shared by the related phenotypes. With its wealth of genotypic and phenotypic data collected in very large numbers, the UK Biobank study provides an excellent opportunity to explore the causal role of SUA level across a broad spectrum of disease outcomes. In this study, we performed an MR-PheWAS in UK Biobank database to discover disease outcomes related to genetic variations of SUA level and to investigate if any association is causal.

## METHODS

### UK Biobank data

The UK Biobank is a large-scale, population-based, prospective cohort that enrolled over 500 000 participants aged 40–69 years. The recruited participants provided a wide range of self-reported baseline information. Blood samples were collected for biochemical tests and genotyping. Their national health records have been linked with the baseline and genotypic data for longitudinal follow-up. Genotypic and phenotypic data used in this study were obtained from UK Biobank under an approved data request application (application ID: 10775).

### Genotyping and quality control

Genotyping, quality control and genetic imputation were performed by the UK Biobank team prior to the interim release of genotypic data for 150 000 participants. The procedure of genotyping and quality control is presented in detail at [https://biobank.ctsu.ox.ac.uk/crystal/docs/genotyping\\_qc.pdf](https://biobank.ctsu.ox.ac.uk/crystal/docs/genotyping_qc.pdf). We used the field variables made available by the UK Biobank for quality control to exclude the samples that had high missingness or heterozygosity, outlying short runs of homozygosity, and sex mismatch (see online supplementary table S1). We constrained our analyses to participants who were self-reported British and confirmed to be Caucasians based on the genetic principal component analysis performed by the UK Biobank. The quality control process generated a genotypic data set output with 120 091 individuals included in the current analysis.

### Phenotyping and mapping ICD-10 or ICD-9 to phecode

We focused on phenotypes in relation to diagnostic disease outcomes. We analysed two phenotypic data sets (inpatient hospital episode records and cancer registry data) in the UK Biobank using the phecode schema (see online supplementary text for phenotyping and mapping process).<sup>21</sup> The coding for clinical diagnoses in these data sets followed the WHO's International Classification of Diseases (ICD) coding systems, but used different ICD versions (ICD-10 or ICD-9) according to the date of record. We included both ICD-10 and ICD-9 codes to define the case and control groups. Since cancer registry data overlapped with the cancer diagnosis in inpatient hospital

records, we pooled the cancer registry data into the hospital episode data as a complement to the cancer diagnosis.

### Statistical analysis

The statistical analysis included three main steps: first, we performed a PheWAS to identify disease outcomes that were associated with genetic risk loci of SUA level; second, we performed MR analysis by using both the inverse-variance weighted (IVW) method and MR Egger approach to explore causal relationship for identified PheWAS associations<sup>22 23</sup>; and third, we applied HEIDI (heterogeneity in dependent instruments) test to exclude the cross-phenotype associations caused by genetic linkage.<sup>24</sup>

### Genetic instruments

We selected 31 SUA-associated single nucleotide polymorphisms (SNPs) as genetic instruments (see online supplementary table S2), which were previously reported to be independently associated with SUA level in genome-wide association studies (GWAS).<sup>25 26</sup> We obtained the SNP effect on SUA level from the largest GWAS performed in European population.<sup>25</sup> The overall proportion of variance ( $R^2$  of SUA level explained by the selected genetic instruments) was estimated to be close to 7.0%.<sup>25</sup>

### Phenome-wide association analysis

In phenome-wide analysis, we used 31 SUA-associated SNPs as genetic instruments individually to scan across a wide range of disease outcomes defined by the phecode system.<sup>21</sup> With the PheWAS algorithm,<sup>27</sup> a series of case-control tests was performed: (1) the case group was generated by including patients with the tested phecode; (2) participants were assigned to the control group based on the absence of both the tested phecode and related phecodes (patients who had the parent, child or sibling phecodes of the tested phecode were excluded from the control group)<sup>27</sup>; and (3) to ensure statistical power, analysis was only performed for phecode with no less than 200 cases. This minimum number of cases was suggested based on a simulation of power estimates for PheWAS analysis.<sup>28</sup> We used logistic regression to test the associations between 31 individual genetic instruments (assuming an additive genetic model) and each phecode (number of cases  $\geq 200$ ) after adjusting for multiple covariates, including sex, body mass index (BMI), age, assessment centre and the principal components. Considering many phecodes were not independent, we used the false discovery rate (FDR) method to account for multiple testing.<sup>29</sup>

### MR IVW, MR Egger and HEIDI test

We then explored the identified PheWAS associations in three possible scenarios (see online supplementary figure S1): (1) causality: the observed association was causal (through the SUA pathway); (2) pleiotropy: the observed association was due to pleiotropic effect of one causal variant (ie, linked to SUA level and the particular disease outcome through pleiotropy); and (3) genetic linkage: the observed association was caused by the linkage disequilibrium (LD) between two distinct causal variants, with one affecting SUA level and the other affecting the disease outcome.

### MR IVW

To explore if there was any causal effect on identified disease outcomes, we performed the conventional MR analysis by pooling the individual effect of each SNP using the IVW method

to estimate the overall causal effect (see online supplementary text).<sup>30</sup>

### MR Egger

We then performed MR Egger to attempt to correct for any potential pleiotropic effect in the causal estimates. This approach is applied to balance the pleiotropic effects derived from multiple genetic instruments (see online supplementary text).<sup>23</sup>

### HEIDI test

We calculated HEIDI statistics for the SUA genetic loci that were associated with more than one disease outcome. This test was to examine if the cross-phenotype association was due to genetic linkage (see online supplementary text).<sup>24</sup>

### Sex stratification analysis

To account for any sex difference, we performed PheWAS and MR analyses in men and women separately. The sex-specific effects of SNPs on SUA level (see online supplementary table S2) were taken from the summary-level GWAS data provided by Köttgen *et al.*<sup>25</sup>

## RESULTS

A total of 120 091 UK Biobank participants were included in the analysis, consisting of 56 845 men and 63 246 women with a mean age of 64.86 years in 2016 (SD of 7.95) (see online supplementary table S3). Within phenotypic data sets, we identified 684 324 hospital episodes and 23 174 cancer registration records, which included 7990 unique ICD-10 codes and 1998 unique ICD-9 codes. After mapping diagnostic ICD-10 or ICD-9 codes to phecodes, the phenotypic data consisted of 1807 distinct phecodes. After filtering out disease outcomes with low prevalence (number of cases <200), 568 phecodes (median number of cases=694 (range: 200–39 142)) were included in PheWAS analysis. These 568 phecodes were classified into 17 broadly related disease categories (table 1). We noted that the distribution of phenotypes examined was skewed across the different disease categories (see online supplementary figure S2), in which a large number of disease phenotypes were included in digestive,

circulatory, endocrine and metabolic systems, but some disease categories, for example congenital anomalies, were not well represented in the study population.

### Phenome-wide association analysis

The PheWAS analysis performed 17 608 case-control tests, leading to an adjusted significance threshold of  $P < 8.57 \times 10^{-5}$  corresponding to an FDR of  $q < 0.05$  to account for the multiple testing. A total of 27 pairs of genotype-phenotype associations passed the significance threshold of FDR correction ( $P < 8.57 \times 10^{-5}$ ) in the overall PheWAS analysis with adjustment for covariates (table 2). Results of PheWAS without adjustment for BMI are shown in online supplementary table S4. The sex-stratified PheWAS analysis identified 10 pairs of genotype-phenotype association in men and 10 pairs of genotype-phenotype association in women (see online supplementary table S5). When compared with the overall PheWAS analysis, five new pairs of association were identified from the sex-stratified PheWAS analysis (see online supplementary table S5).

These identified genotype-phenotype associations were distributed across 15 SUA genetic loci, of which 5 loci were associated with more than one disease outcome: rs653178 in *ATXN2/SH2B3* locus (number of disease outcomes:  $n_{outcomes} = 10$ ), rs1165151 in *SLC17A3* locus ( $n_{outcomes} = 3$ ), rs1260326 in *GCKR* locus ( $n_{outcomes} = 3$ ), rs2231142 in *ABCG2* locus ( $n_{outcomes} = 4$ ) and rs2079742 in *BCAS3* locus ( $n_{outcomes} = 2$ ). Of note, six disease outcomes shared genetic associations with SUA level at more than one locus: gout (number of loci:  $n_{loci} = 3$ ), inflammatory polyarthropathies ( $n_{loci} = 2$ ), disorders of iron metabolism ( $n_{loci} = 2$ ), coeliac disease ( $n_{loci} = 2$ ), hypertensive disease ( $n_{loci} = 2$ ) and essential hypertension ( $n_{loci} = 2$ ).

In summary, the PheWAS analyses identified 25 unique disease groups/outcomes (corresponding to 25 unique phecodes) that shared genetic risk loci with SUA level, which included 9 disease groups (inflammatory polyarthropathies, hypertensive disease, circulatory disease, disorders of metabolism, disorders of thyroid, other diseases of respiratory system, disorder of skin and subcutaneous tissue, benign neoplasm of digestive system, and complications of labour and delivery) and 16 specific disease

**Table 1** The number of phenotypes and the number of cases in each disease category

| Disease categories               | Phenotypes (n) | Cases (n) |        |      |         |
|----------------------------------|----------------|-----------|--------|------|---------|
|                                  |                | Minimum   | Median | Mean | Maximum |
| Circulatory system               | 61             | 221       | 665    | 2937 | 39 142  |
| Congenital anomalies             | 6              | 206       | 265    | 302  | 522     |
| Dermatological diseases          | 24             | 201       | 706    | 2736 | 32 738  |
| Diseases in sense organs         | 34             | 201       | 425    | 1216 | 11 306  |
| Digestive diseases               | 73             | 201       | 949    | 2176 | 23 129  |
| Neoplasms                        | 59             | 203       | 763    | 1916 | 30 101  |
| Infectious diseases              | 16             | 205       | 787    | 975  | 3192    |
| Endocrine and metabolic diseases | 25             | 229       | 492    | 2304 | 13 592  |
| Haematopoietic diseases          | 10             | 205       | 1187   | 1600 | 3669    |
| Neurological diseases            | 21             | 229       | 452    | 1282 | 11 828  |
| Respiratory diseases             | 38             | 219       | 712    | 1713 | 19 238  |
| Mental disorders                 | 18             | 205       | 673    | 1926 | 8942    |
| Genitourinary diseases           | 77             | 200       | 666    | 1606 | 29 859  |
| Pregnancy complications          | 11             | 227       | 360    | 707  | 2531    |
| Musculoskeletal diseases         | 44             | 263       | 1076   | 2482 | 21 822  |
| Clinical symptoms                | 14             | 267       | 1237   | 2570 | 12 287  |
| Injuries and poisonings          | 37             | 211       | 589    | 911  | 4842    |

**Table 2** Genotype–phenotype associations identified from PheWAS after correcting multiple testing by FDR ( $P < 8.57 \times 10^{-5}$ )

| Phecode | Description                          | SNP_risk allele* | Allele frequency | Total (n) | Cases (n) | OR (95% CI)         | P†       |
|---------|--------------------------------------|------------------|------------------|-----------|-----------|---------------------|----------|
| 274.1   | Gout                                 | rs2231142_T      | 0.11             | 119555    | 1003      | 1.89 (1.69 to 2.12) | 5.41e-28 |
| 275.1   | Disorders of iron metabolism         | rs1165151_G      | 0.45             | 119063    | 205       | 3.56 (2.78 to 4.56) | 1.41e-23 |
| 244.4   | Hypothyroidism                       | rs653178_C       | 0.48             | 118821    | 4146      | 1.21 (1.16 to 1.27) | 3.90e-17 |
| 246     | Disorders of thyroid                 | rs653178_C       | 0.48             | 119601    | 4926      | 1.18 (1.14 to 1.23) | 8.82e-16 |
| 274.1   | Gout                                 | rs12498742_A     | 0.23             | 118960    | 1002      | 1.54 (1.37 to 1.74) | 7.94e-13 |
| 275.1   | Disorders of iron metabolism         | rs742132_A       | 0.29             | 119271    | 205       | 2.80 (2.10 to 3.74) | 3.13e-12 |
| 401     | Hypertensive disease                 | rs653178_C       | 0.48             | 119762    | 23634     | 1.06 (1.04 to 1.09) | 1.68e-08 |
| 401.1   | Essential hypertension               | rs653178_C       | 0.48             | 119688    | 23560     | 1.06 (1.04 to 1.09) | 2.00e-08 |
| 411.4   | Coronary atherosclerosis             | rs653178_C       | 0.48             | 119460    | 9526      | 1.09 (1.05 to 1.12) | 1.27e-07 |
| 411     | Ischaemic heart disease              | rs653178_C       | 0.48             | 119401    | 9467      | 1.09 (1.05 to 1.12) | 1.33e-07 |
| 211     | Benign neoplasm of digestive system  | rs11264341_C     | 0.43             | 117030    | 1504      | 0.83 (0.77 to 0.89) | 2.41e-07 |
| 274.1   | Gout                                 | rs1260326_T      | 0.39             | 119555    | 1003      | 1.26 (1.15 to 1.38) | 3.86e-07 |
| 459.9   | Circulatory disease                  | rs653178_C       | 0.48             | 119677    | 39142     | 1.05 (1.03 to 1.06) | 2.24e-06 |
| 411.2   | Myocardial infarction                | rs653178_C       | 0.48             | 113559    | 3625      | 1.12 (1.07 to 1.18) | 2.80e-06 |
| 557.1   | Coeliac disease                      | rs1165151_G      | 0.45             | 99783     | 549       | 1.33 (1.18 to 1.51) | 4.30e-06 |
| 557.1   | Coeliac disease                      | rs653178_C       | 0.48             | 99965     | 550       | 1.31 (1.16 to 1.48) | 9.28e-06 |
| 427.2   | Atrial fibrillation and flutter      | rs6598541_A      | 0.35             | 113261    | 4333      | 1.11 (1.06 to 1.16) | 9.92e-06 |
| 960     | Poisoning by antibiotics             | rs1165151_G      | 0.45             | 112343    | 1027      | 0.82 (0.75 to 0.90) | 1.22e-05 |
| 535     | Gastritis and duodenitis             | rs478607_G       | 0.15             | 115386    | 5233      | 1.12 (1.07 to 1.19) | 1.34e-05 |
| 411.3   | Angina pectoris                      | rs653178_C       | 0.48             | 114967    | 5033      | 1.09 (1.05 to 1.14) | 3.01e-05 |
| 669     | Complications of labour and delivery | rs729761_G       | 0.28             | 113240    | 2376      | 1.17 (1.09 to 1.26) | 3.78e-05 |
| 272.11  | Hypercholesterolaemia                | rs1260326_T      | 0.39             | 118921    | 10201     | 1.07 (1.03 to 1.10) | 3.82e-05 |
| 366     | Cataract                             | rs6770152_G      | 0.43             | 116218    | 4567      | 1.09 (1.05 to 1.14) | 4.14e-05 |
| 471     | Nasal polyps                         | rs10821905_A     | 0.17             | 112745    | 983       | 1.26 (1.13 to 1.40) | 4.61e-05 |
| 454.1   | Varicose veins of lower extremity    | rs2231142_T      | 0.11             | 111390    | 3204      | 0.84 (0.78 to 0.92) | 5.79e-05 |
| 401     | Hypertensive disease                 | rs2079742_T      | 0.13             | 115659    | 22832     | 1.07 (1.03 to 1.10) | 7.00e-05 |
| 401.1   | Essential hypertension               | rs2079742_T      | 0.13             | 115588    | 22761     | 1.07 (1.03 to 1.10) | 7.02e-05 |

\*Effect allele was harmonised to be the SUA-raising allele defined by Köttgen *et al.*<sup>25</sup>

†Significance threshold of  $P < 8.57 \times 10^{-5}$  corresponds to an FDR of  $q < 0.05$  after correcting the multiple testing. FDR, false discovery rate; PheWAS, phenome-wide association study; SUA, serum uric acid.

outcomes (gout, essential hypertension, angina pectoris, myocardial infarction, coronary atherosclerosis, ischaemic heart disease, atrial fibrillation and flutter, varicose veins of lower extremity, hypercholesterolaemia, disorders of iron metabolism, coeliac disease, hypothyroidism, gastritis and duodenitis, poisoning by antibiotics, cataract, and nasal polyps). The mappings of ICD codes to these 25 phecodes and their hierarchical relationships are shown in online supplementary table S6.

### MR IVW, MR Egger and HEIDI test

We then performed MR analysis using the IVW method to explore if there was any causal link between SUA level and the 25 disease groups/outcomes identified from PheWAS analysis. The MR IVW analysis suggested a potential causal link for 7 out of 25 disease groups/outcomes. The corresponding effect estimate on each disease outcome is presented in table 3. It was indicated that genetically determined higher SUA level was potentially causally linked with an increased risk of three disease groups, including inflammatory polyarthropathies (OR=1.22, 95% CI 1.11 to 1.34,  $P=1.10 \times 10^{-4}$ ), hypertensive disease (OR=1.08, 95% CI 1.03 to 1.14,  $P=0.004$ ) and disorders of metabolism (OR=1.07, 95% CI 1.01 to 1.14,  $P=0.03$ ), and of four specific disease outcomes, including gout (OR=4.88, 95% CI 3.91 to 6.09,  $P=3.55 \times 10^{-15}$ ), essential hypertension (OR=1.08, 95% CI 1.03 to 1.14,  $P=0.005$ ), myocardial infarction (OR=1.16, 95% CI 1.03 to 1.30,  $P=0.015$ ) and coeliac disease (OR=1.41, 95% CI 1.05 to 1.89,  $P=0.02$ ).

To explore and correct for any possible pleiotropic effect of multiple instruments, we then conducted the MR Egger analysis (table 3). After balancing out the potential pleiotropic effects, the putative causal link of SUA level with gout (OR=4.58, 95% CI 2.72 to 7.72,  $P_{effect}=1.76 \times 10^{-6}$ ) and its umbrella disease group, inflammatory polyarthropathies (OR=1.15, 95% CI 1.01 to 1.31,  $P_{effect}=0.03$ ), remained statistically significant and there was no indication of unbalanced pleiotropy ( $P_{pleiotropy}=0.73$  and  $P_{pleiotropy}=0.23$ , respectively). The putative causal effect of SUA level on the other five disease groups/outcomes was not statistically significant in the MR Egger model. The causal effects of each individual SNPs on these seven disease groups/outcomes are shown in online supplementary figures S3–S9. Unbalanced pleiotropy was observed for essential hypertension ( $P_{pleiotropy}=0.001$ ) and its umbrella disease group, hypertensive disease ( $P_{pleiotropy}=0.001$ ). For myocardial infarction, coeliac disease and disorders of metabolism, the putative causal effect was not statistically significant in the MR Egger model ( $P_{effect}=0.75$ ,  $P_{effect}=0.41$  and  $P_{effect}=0.80$ , respectively), although there was no evidence of unbalanced pleiotropy ( $P_{pleiotropy}=0.13$ ,  $P_{pleiotropy}=0.75$  and  $P_{pleiotropy}=0.18$ , respectively). The results of the sex-stratified MR IVW are presented in online supplementary table S7.

Finally, to distinguish the genotype–phenotype association of pleiotropy from LD, the HEIDI test was performed for the five genetic loci (rs653178 in *ATXN2/SH2B3* locus, rs1165151

**Table 3** PheWAS associations assessed by conventional MR IVW and MR Egger analysis

| Disease outcomes                          | MR IVW              |          |        | MR Egger            |          |              |        |
|---|---------------------|----------|--------|---------------------|----------|--------------|--------|
|   | OR (95% CI)         | P effect | Power* | OR (95% CI)         | P effect | P pleiotropy | Power* |
| Gout                                      | 4.88 (3.91 to 6.09) | 3.55e-15 | 1.00   | 4.58 (2.72 to 7.72) | 1.76e-06 | 0.73         | 1.00   |
| Inflammatory polyarthropathies†           | 1.22 (1.11 to 1.34) | 1.10e-04 | 0.99   | 1.15 (1.01 to 1.31) | 0.03     | 0.23         | 0.83   |
| Essential hypertension                    | 1.08 (1.03 to 1.14) | 5.07e-03 | 0.82   | 0.93 (0.83 to 1.05) | 0.23     | 1.13e-03     | 0.73   |
| Hypertensive disease                      | 1.08 (1.03 to 1.14) | 4.23e-03 | 0.82   | 0.93 (0.83 to 1.05) | 0.24     | 1.19e-03     | 0.73   |
| Myocardial infarction                     | 1.16 (1.03 to 1.30) | 0.02     | 0.70   | 1.03 (0.84 to 1.27) | 0.75     | 0.13         | 0.08   |
| Coeliac disease                           | 1.41 (1.05 to 1.89) | 0.02     | 0.72   | 1.31 (0.68 to 2.54) | 0.41     | 0.75         | 0.48   |
| Disorders of metabolism†                  | 1.07 (1.01 to 1.14) | 0.03     | 0.52   | 1.01 (0.91 to 1.14) | 0.80     | 0.18         | 0.06   |
| Coronary atherosclerosis                  | 1.07 (0.99 to 1.15) | 0.08     | 0.41   | 0.99 (0.85 to 1.17) | 0.95     | 0.20         | 0.06   |
| Ischaemic heart disease                   | 1.07 (0.99 to 1.15) | 0.09     | 0.41   | 0.99 (0.85 to 1.16) | 0.91     | 0.20         | 0.06   |
| Angina pectoris                           | 1.04 (0.94 to 1.15) | 0.41     | 0.11   | 0.95 (0.80 to 1.12) | 0.51     | 0.11         | 0.15   |
| Atrial fibrillation and flutter           | 1.01 (0.91 to 1.12) | 0.87     | 0.05   | 0.90 (0.75 to 1.08) | 0.23     | 0.07         | 0.41   |
| Circulatory disease                       | 1.04 (1.00 to 1.09) | 0.08     | 0.40   | 0.97 (0.89 to 1.07) | 0.57     | 0.05         | 0.26   |
| Varicose veins of lower extremity         | 0.86 (0.72 to 1.02) | 0.09     | 0.55   | 0.86 (0.67 to 1.10) | 0.24     | 0.97         | 0.55   |
| Disorders of iron metabolism              | 1.19 (0.74 to 1.90) | 0.45     | 0.11   | 0.79 (0.15 to 4.07) | 0.77     | 0.47         | 0.12   |
| Hypercholesterolaemia                     | 1.14 (0.96 to 1.36) | 0.12     | 0.94   | 1.18 (0.88 to 1.58) | 0.27     | 0.78         | 0.99   |
| Hypothyroidism                            | 1.10 (0.99 to 1.23) | 0.07     | 0.39   | 0.99 (0.75 to 1.32) | 0.97     | 0.30         | 0.05   |
| Disorders of thyroid                      | 1.08 (0.98 to 1.20) | 0.10     | 0.31   | 1.01 (0.79 to 1.29) | 0.94     | 0.41         | 0.05   |
| Benign neoplasm of digestive system       | 0.93 (0.78 to 1.10) | 0.36     | 0.11   | 0.90 (0.64 to 1.26) | 0.52     | 0.79         | 0.18   |
| Gastritis and duodenitis                  | 0.97 (0.88 to 1.07) | 0.53     | 0.09   | 0.95 (0.80 to 1.13) | 0.55     | 0.70         | 0.16   |
| Nasal polyps                              | 1.08 (0.88 to 1.34) | 0.45     | 0.10   | 1.09 (0.73 to 1.60) | 0.67     | 0.98         | 0.12   |
| Cataract                                  | 0.99 (0.90 to 1.09) | 0.85     | 0.05   | 0.91 (0.75 to 1.10) | 0.34     | 0.23         | 0.36   |
| Poisoning by antibiotics                  | 0.85 (0.70 to 1.04) | 0.14     | 0.25   | 1.00 (0.68 to 1.48) | 1.00     | 0.28         | 0.05   |
| Complications of labour and delivery†     | 0.89 (0.76 to 1.03) | 0.12     | 0.30   | 0.78 (0.59 to 1.02) | 0.08     | 0.20         | 0.83   |
| Other diseases of respiratory system†     | 1.11 (0.94 to 1.31) | 0.19     | 0.22   | 1.16 (0.92 to 1.46) | 0.22     | 0.64         | 0.42   |
| Disorder of skin and subcutaneous tissue† | 0.99 (0.93 to 1.06) | 0.77     | 0.06   | 0.98 (0.89 to 1.09) | 0.75     | 0.85         | 0.09   |

\*The statistical power of MR analyses was calculated by using the non-centrality parameter-based approach<sup>65</sup>; the overall proportion of variance ( $R^2$ ) of serum uric acid level explained by the genetic instruments was estimated to be 7.0%.<sup>25</sup>

†Disease outcomes identified from sex-stratified PheWAS analysis.

IVW, inverse-variance weighted; MR, Mendelian randomisation; PheWAS, genome-wide association study.

in *SLC17A3* locus, rs1260326 in *GCKR* locus, rs2231142 in *ABCG2* locus and rs2079742 in *BCAS3* locus) that were associated with multiple disease outcomes in the PheWAS analysis (see online supplementary figures S10–S14). Based on the HEIDI test, we identified 14 disease outcomes that were associated with the SUA genetic risk loci due to pleiotropy (with  $P_{HEIDI} > 0.05$ ). The strongest pleiotropic locus was the *ATXN2/SH2B3*, where three SNPs (rs653178, rs4766578 and rs3184504) in near-complete LD ( $r^2=0.99$ ) were tagged as the lead SNPs associated with 10 disease groups/outcomes as a cluster of cardiovascular diseases and autoimmune disorders (see online supplementary figure S10). Other potential pleiotropic effects included the associations of *BCAS3* locus (rs2079742) with essential hypertension ( $P_{HEIDI}=0.10$ ) and hypertensive disease ( $P_{HEIDI}=0.09$ ) (see online supplementary figure S11), the associations of *ABCG2* locus (rs2231142) with varicose veins of lower extremity ( $P_{HEIDI}=0.32$ ) (see online supplementary figure S12), and the association of *SLC17A3* locus (rs1165151) with poisoning by antibiotics ( $P_{HEIDI}=0.26$ ) (see online supplementary figure S13).

Our analysis rejected the null hypothesis of a pleiotropic model for the shared genetic association between SUA level and disorders of iron metabolism at the *SLC17A3* locus (rs1165151) ( $P_{HEIDI}=5.54e-28$ ); we identified a different causal variant (rs17342717 in *SLC17A1*) that was in LD with the SNP rs1165151 ( $r^2=0.24$ ) and strongly associated with the disorders of iron metabolism ( $P=1.69e-129$ ) (see online supplementary figure S13). Similarly, for the associations between the *SLC17A3*

locus (rs1165151) and coeliac disease ( $P_{HEIDI}=6.51e-16$ ) (see online supplementary figure S13), and the *GCKR* locus (rs1260326) and hypercholesterolaemia ( $P_{HEIDI}=3.27e-11$ ) (see online supplementary figure S14), the pattern of shared regional genetic association was more consistent with a genetic linkage model, and the SNP with the smallest P value was tagged as an index of the distinct causal variant affecting the examined disease outcome.

## DISCUSSION

In PheWAS analysis by using SUA-associated SNPs as genetic instruments, we replicated the findings of the largest GWAS performed by Köttgen and the findings of the most recent candidate gene-based association study conducted in UK Biobank, which indicated that two SUA-related SNPs (rs12498742 in *SLC2A9* locus and rs2231142 in *ABCG2* locus) are significantly associated with gout at GWAS P value threshold ( $P < 5.0e-08$ ).<sup>25 31</sup> We conducted a conventional MR analysis (using the IVW method) and an MR Egger analysis, which accounts for potential pleiotropic effects, to investigate potential causal links with SUA level. These both confirmed potential causal effects of SUA level on gout and inflammatory polyarthropathies. The latter category represents the disease group term that includes gout, and thus this finding may just reflect the causal role of SUA in gout. However, this study cannot exclude a causal association between SUA and other inflammatory polyarthropathies, and this may be worth further study. Given that many comorbidities

are commonly reported in patients with gout, it is of interest to consider the evidence for SUA sharing genetic risk loci with some of these diseases, such as cardiovascular/metabolic diseases and autoimmune disorders, and the evidence for a possible causal role for SUA in these conditions.

Overall, we identified 32 pairs of genotype–phenotype associations, which covered a wide range of phenotypic categories including endocrine/metabolic diseases, cardiovascular diseases and autoimmune disorders. Our PheWAS analysis replicated 14 pairs of previously known genotype–phenotype (or closely related phenotypic groups) associations reported in the GWAS Catalog (see online supplementary table S2 and table 2). For example, rs653178 (*ATXN2/S2HB3* locus) was previously reported to be associated with diastolic blood pressure,<sup>32</sup> myocardial infarction,<sup>33</sup> peripheral artery disease,<sup>34</sup> coeliac disease<sup>35</sup> and serum thyroid peroxidase antibody levels.<sup>36</sup> In our PheWAS, this SNP was statistically significantly associated with the same phenotypes (ie, coeliac disease, myocardial infarction) or similar phenotypic groups (ie, hypertension, circulatory and heart diseases, hypothyroidism and other disorders of thyroid). We also identified 18 novel genotype–phenotype associations (at the PheWAS threshold of  $P < 8.57 \times 10^{-5}$ ), of which the association between rs1165151 (*SLC17A3* locus) and disorders of iron metabolism had the smallest P value ( $P = 1.23 \times 10^{-19}$ ).

We performed conventional MR analysis, using the IVW method, to investigate whether there was a potential causal link between SUA level and the 25 unique disease groups/outcomes identified from PheWAS. The results of MR IVW analysis suggested a potential causal effect of SUA level on three disease groups, including inflammatory polyarthropathies (as noted above), hypertensive disease and disorders of metabolism, and four specific individual disease outcomes, including gout (as noted above), essential hypertension, myocardial infarction and coeliac disease. When adopting the advanced MR Egger analysis to account for potential pleiotropic effects, it is indicated that, except for gout and inflammatory polyarthropathies, all the other putative causal associations suggested by MR IVW analysis were probably inflated by the presence of pleiotropy. However, although the MR Egger analysis is more robust in dealing with pleiotropy, this method is not infallible.<sup>37</sup> Intuitively, the genetic instrument with larger effect on SUA level is expected to have a larger effect on disease outcome and would exert stronger influence in the MR Egger regression model. With indepth examination of the individual SNP effects on SUA level against the SNP effects on disease outcomes (see online supplementary figures S5–S8), we found that the outlying variant (rs12498742 in *SLC2A9*) that had the strongest association with SUA level showed a negative (null) effect on essential hypertension and hypertensive disease, which reversed the sign of the overall putative causal effect and led to a rejection of the intercept test. Given the influence of the outlying variant, the unbalanced pleiotropy and relatively moderate statistical power (power=0.73), we would interpret that unbalanced pleiotropy between SUA level and hypertension is an issue for their causal inference in MR Egger analysis.

Previous observational studies have reported sex difference in the association between SUA level and the development of cardiovascular diseases,<sup>38–42</sup> but few studies have addressed the sex difference by using MR approach to keep out the influence of environmental confounders. Our study identified a few more cardiovascular diseases (eg, coronary atherosclerosis, ischaemic heart disease) that were potentially causally linked with the genetic variation of SUA level in women, but not in men. These MR findings were concordant with results from observational

studies, which indicated that the relationship between SUA level and cardiovascular disease was particularly strong in women, especially for heart disease.<sup>41 43 44</sup> Although these putative causal associations specific to women were not verified by MR Egger, this may be due to the decreased statistical power of MR Egger (and a higher risk of type 2 error). The biological mechanism that can lead the association of SUA level with cardiovascular disease to be more pronounced in women than in men remains a matter for further investigation.

We also found that several PheWAS associations were likely driven by LD. For instance, the outstanding PheWAS association between disorders of iron metabolism and the SNP rs1165151 in *SLC17A3* locus was not consistent with a pleiotropic model, and further examination found the SUA-associated SNP rs1165151 was located in LD ( $r^2 = 0.24$ ), with the rs17342717 variant in *SLC17A1* locus, which was strongly associated with disorders of iron metabolism ( $P = 1.69 \times 10^{-129}$ ). This SNP (rs17342717) is also associated with red blood cell traits and serum iron levels in previous GWAS.<sup>45 46</sup> We suggest that the implications of these findings have wider relevance for PheWAS studies. Typically, associations of a single SNP with multiple phenotypes were claimed to be due to pleiotropy in previous PheWAS.<sup>47 48</sup> However, as PheWAS focused on single variant without considering the correlations between SNPs, we would suggest that an additional examination of LD is necessary when we identify pleiotropic links.

In contrast, the pattern of shared regional genetic associations of SUA level with multiple disease outcomes at *ATXN2/S2HB3* locus was more consistent with a pleiotropic model, where we interpreted this locus influenced a cluster of cardiovascular diseases and autoimmune disorders. However within the *ATXN2/S2HB3* locus, there are three leading SNPs (rs653178, rs4766578 and rs3184504) in high LD ( $r^2 = 0.99$ ). In this case, we were unable to provide an indication of whether the observed associations are due to pleiotropy or genetic linkage, as it was difficult to infer the causal variant. Although SNP rs653178 was reported as the lead variant influencing SUA level at this locus in GWAS, the potential biological mechanism underlying this effect is unclear.<sup>25</sup> Furthermore, although the implication of the rs653178 on the regulation of blood pressure, cardiovascular diseases and coeliac disease has been suggested by a few GWAS,<sup>32–35</sup> a clear biological explanation for this role could not be demonstrated. Evidence from the functional follow-up of the *S2HB3* gene indicated that rs3184504 may be the causal variant, as the *S2HB3* gene encodes one of the S2HB family proteins, which have a diverse physiological roles on haematopoiesis, immune response and signalling, and variation in rs3184504 may introduce a new phosphorylation site affecting the function of the S2HB protein.<sup>49 50</sup> We believe that further uncovering of the biological functions of this pleiotropic locus (eg, gene function follow-up, expression quantitative trait loci analysis) might be helpful to understand the complex underlying relationship of SUA level with cardiovascular and autoimmune diseases.

The sex-stratified MR IVW analysis identified that unspecified diseases in respiratory system were potentially causally linked with SUA level in women (with the MR Egger analysis showing a consistent causal effect). This finding is consistent with recently published experimental studies, which demonstrated that human airway epithelial cells and lung tissue expressed a functional UA production/secretion system and UA was crucial in mediating the development of allergic airway diseases and regulating the antigen-specific T cell proliferation.<sup>51–54</sup> It was also speculated that fine, inhaled particulate matter can induce increased UA production in the human airway, which may contribute to

allergic sensitisation and asthma pathogenesis.<sup>55</sup> Evidence from other epidemiological studies suggested that high SUA level was associated with low lung function and high risk of respiratory symptoms and chronic obstructive pulmonary disease, but the direct causal relationship has not been established.<sup>56–58</sup> Further investigation may be worth to explore the clinical relevance of SUA level in lung health and respiratory diseases.

Key strengths of our study included its potential to make novel discoveries in genotype–phenotype associations and to identify novel cross-phenotype associations, possibly reflecting common aetiology or causal mechanisms. Unlike the genome, for which genetic structure can be measured by reliable biological techniques, the definition of phenome varies across studies. Current published PheWAS have been limited primarily to billing ICD-9-clinical modification (CM) to phecode system, and the method for aggregating ICD-9-CM codes into phecodes has proven to be valuable in previous PheWAS studies.<sup>21 59</sup> Our work broadened the utility of phecode system and illustrated the process of adopting phecode system in the updated ICD-10 version to define the phenome framework. Our mapping process revealed some potential shortcomings of the current phecode system (eg, the ICD-10 codes involving the personal or family history were missing elements in the phecode system), which should be improved as a future undertaking. Recent methodological applications (eg, tree-structured phenotypic model (TreeWAS)) can be applied in future PheWAS analyses.<sup>60</sup> As we were preparing the manuscript for submission, a web resource within UK Biobank, the GeneATLAS, was released in the bioRxiv (prior to peer review).<sup>61</sup> We checked our PheWAS findings in this database, but only 10 of the 31 SUA-related SNPs were included in their database (and associations with some disease outcomes were replicated for these SNPs).<sup>61</sup> We focused on the causal relationships between SUA level and binary disease outcomes in MR analyses, and these findings were complementary to MR estimates of urate archived in the MR-Base database (<http://evm.mrbase.org/>), which mainly focused on quantitative traits.

On the other hand, our analysis was limited to phenotypes with no less than 200 cases; therefore, diseases with relatively low prevalence were not analysed. As the UK Biobank grows, we expect to perform PheWAS and MR analyses for more phenotypes, with the priority given to the ones of which the relationships with SUA level are much controversial, such as dementia.<sup>62 63</sup> Furthermore for some analysed phenotypes, our PheWAS analysis may still have low power to detect small effect size. The use of the interim release of UK Biobank data and focusing on a very homogeneous population (self-reported British confirmed by principal component analysis (PCA)) limited the power of this study. Additionally, we did not analyse the self-reported UK Biobank data to avoid information bias, but this may have impacted on the comprehensiveness of PheWAS and have reduced the precision of MR estimates. To improve this limitation, we performed a sensitivity analysis for gout by comparing the MR estimates for hospital-diagnosed gout, self-reported gout and hospital-diagnosed/self-reported gout (see online supplementary table S8). The MR estimates were consistently statistically significant in any of the cases but with differences in their effect sizes. These differences might be due to the fact that gout cases ascertained from hospital discharge coding may be unrepresentative of gout, given hospitalised gout is more likely to be complicated by comorbidities, as reported by Robinson *et al.*<sup>64</sup> While making efforts to dissect the PheWAS associations with different models, given the complexity of human genetic structure, these models are not mutually exclusive and each model has its own methodological limitations,

thus strong conclusions are not always possible. Therefore, the realistic goal for the present study was to assess different lines of evidence (ie, causality, pleiotropy or genetic linkage) in order to characterise the identified PheWAS associations in relation to SUA level. It would be beneficial to assess whether measured SUA level, rather than its genetic proxy, is also associated with the observed disease outcomes, but data on the SUA biomarker are not yet available in UK Biobank.

Overall, this PheWAS analysis demonstrated that SUA level shares genetic risk loci with multiple disease outcomes, particularly cardiovascular/metabolic diseases and autoimmune disorders. These findings provide rationale for further investigation of whether these associations are causal. Our study indicated a putative causal effect of SUA level on three disease groups (inflammatory polyarthropathies, hypertensive disease and disorders of metabolism) and four specific disease outcomes (gout, essential hypertension, coeliac disease and myocardial infarction); when balancing out the pleiotropy, a robust conclusion about causality was made for gout and its encompassing disease group, inflammatory polyarthropathies. Unbalanced pleiotropy was identified as an issue for the causal inference on the association between SUA level and hypertension. Other potential causal relevance of SUA level with respiratory diseases is also worthy of further investigation. When interpreting the PheWAS associations from a view of pleiotropy, our analysis highlighted a key pleiotropic locus that influenced SUA level and multiple cardiovascular and autoimmune diseases. A further functional annotation of this locus might be helpful to understand the biological pathways that contribute to the phenotypic associations between SUA level and cardiovascular diseases (including hypertension).

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**Data sharing statement** All the data generated or analysed during this study are included in this published article and in the online supplementary information files. Further enquiry regarding data availability, analysis methods and results would be addressed to XL (xue.li@ed.ac.uk).

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## REFERENCES

- Maiuolo J, Oppedisano F, Gratterer S, *et al.* Regulation of uric acid metabolism and excretion. *Int J Cardiol* 2016;213:8–14.
- Oda M, Satta Y, Takenaka O, *et al.* Loss of urate oxidase activity in hominoids and its evolutionary implications. *Mol Biol Evol* 2002;19:640–53.
- Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum* 2011;63:3136–41.
- Liu R, Han C, Wu D, *et al.* Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2015;2015:1–12.
- Emma Smith LM. Global Prevalence of Hyperuricemia: A Systematic Review of Population-Based Epidemiological Studies. *Arthritis Rheumatol* 2015;67(suppl 10).
- Feig DI, Kang D-H, Johnson RJ. Uric Acid and Cardiovascular Risk. *N Engl J Med Overseas Ed* 2008;359:1811–21.
- Culleton BF, Larson MG, Kannel WB, *et al.* Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131:7–13.
- Nejatnamini S, Ataie-Jafari A, Qorbani M, *et al.* Association between serum uric acid level and metabolic syndrome components. *J Diabetes Metab Disord* 2015;14:70.
- Li X, Meng X, Timofeeva M, *et al.* Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. *BMJ* 2017;357:j2376.
- Agarwal V, Hans N, Messerli FH. Effect of allopurinol on blood pressure: a systematic review and meta-analysis. *J Clin Hypertens* 2013;15:435–42.
- Kanbay M, Siriopol D, Nistor I, *et al.* Effects of allopurinol on endothelial dysfunction: a meta-analysis. *Am J Nephrol* 2014;39:348–56.
- Zhang YF, He F, Ding HH, *et al.* Effect of uric-acid-lowering therapy on progression of chronic kidney disease: a meta-analysis. *J Huazhong Univ Sci Technolog Med Sci* 2014;34:476–81.
- Pfister R, Barnes D, Luben R, *et al.* No evidence for a causal link between uric acid and type 2 diabetes: a Mendelian randomisation approach. *Diabetologia* 2011;54:2561–9.
- Kleber ME, Delgado G, Grammer TB, *et al.* Uric Acid and Cardiovascular Events: A Mendelian Randomization Study. *J Am Soc Nephrol* 2015;26:2831–8.
- Sluijs I, Holmes MV, van der Schouw YT, *et al.* A Mendelian randomization study of circulating uric acid and type 2 diabetes. *Diabetes* 2015;64:3028–36.
- White J, Sofat R, Hemani G, *et al.* Plasma urate concentration and risk of coronary heart disease: a Mendelian randomisation analysis. *Lancet Diabetes Endocrinol* 2016;4:327–36.
- Keenan T, Zhao W, Rasheed A, *et al.* Causal assessment of serum urate levels in cardiometabolic diseases through a mendelian randomization study. *J Am Coll Cardiol* 2016;67:407–16.
- Hughes K, Flynn T, de Zoysa J, *et al.* Mendelian randomization analysis associates increased serum urate, due to genetic variation in uric acid transporters, with improved renal function. *Kidney Int* 2014;85:344–51.
- Palmer TM, Nordestgaard BG, Benn M, *et al.* Association of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation analysis of two large cohorts. *BMJ* 2013;347:f4262.
- Millard LA, Davies NM, Timpson NJ, *et al.* MR-PheWAS: hypothesis prioritization among potential causal effects of body mass index on many outcomes, using Mendelian randomization. *Sci Rep* 2015;5:16645.
- Denny JC, Bastarache L, Ritchie MD, *et al.* Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nat Biotechnol* 2013;31:1102–11.
- Burgess S, Scott RA, Timpson NJ, *et al.* Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. *Eur J Epidemiol* 2015;30:543–52.
- Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015;44:512–25.
- Zhu Z, Zhang F, Hu H, *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat Genet* 2016;48:481–7.
- Köttgen A, Albrecht E, Teumer A, *et al.* Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat Genet* 2013;45:145–54.
- Kolz M, Johnson T, Sanna S, *et al.* Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet* 2009;5:e1000504.
- Carroll RJ, Bastarache L, Denny JC. R PheWAS: data analysis and plotting tools for phenome-wide association studies in the R environment. *Bioinformatics* 2014;30:2375–6.
- Verma A, Verma SS, Pendergrass SA, *et al.* A simulation study investigating power estimates in Phenome-Wide Association Studies. *bioRxiv* 2017.
- Benjamini Yoav HY. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society* 1995;72:405–16.
- Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol* 2013;37:658–65.
- Cadzow M, Merriman TR, Dalbeth N. Performance of gout definitions for genetic epidemiological studies: analysis of UK Biobank. *Arthritis Res Ther* 2017;19:181.
- Newton-Cheh C, Johnson T, Gateva V, *et al.* Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet* 2009;41:666–76.
- Nikpay M, Goel A, Won HH, *et al.* A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet* 2015;47:1121–30.
- Kullo IJ, Shameer K, Jouni H, *et al.* The ATXN2-SH2B3 locus is associated with peripheral arterial disease: an electronic medical record-based genome-wide association study. *Front Genet* 2014;5:166.
- Dubois PC, Trynka G, Franke L, *et al.* Multiple common variants for celiac disease influencing immune gene expression. *Nat Genet* 2010;42:295–302.
- Medici M, Porcu E, Pistis G, *et al.* Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease. *PLoS Genet* 2014;10:e1004123.
- Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol* 2017;32.
- Yoshitomi R, Fukui A, Nakayama M, *et al.* Sex differences in the association between serum uric acid levels and cardiac hypertrophy in patients with chronic kidney disease. *Hypertens Res* 2014;37:246–52.
- Li YH, Lin GM. Sex differences in the association between serum uric acid and cardiac mortality in Asian patients with established coronary artery disease: A revisit of the ET-CHD registry in Taiwan, 1997–2003. *J Cardiol* 2016;68:461.
- Rodrigues SL, Baldo MP, Capingana P, *et al.* Gender distribution of serum uric acid and cardiovascular risk factors: population based study. *Arq Bras Cardiol* 2012;98:13–21.
- Freedman DS, Williamson DF, Gunter EW, *et al.* Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol* 1995;141:637–44.
- Kurata A, Shigematsu Y, Higaki J. Sex-related differences in relations of uric acid to left ventricular hypertrophy and remodeling in Japanese hypertensive patients. *Hypertens Res* 2005;28:133–9.
- Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008;359:1811–21.
- Kawabe M, Sato A, Hoshi T, *et al.* Gender differences in the association between serum uric acid and prognosis in patients with acute coronary syndrome. *J Cardiol* 2016;67:170–6.
- Kullo IJ, Ding K, Jouni H, *et al.* A genome-wide association study of red blood cell traits using the electronic medical record. *PLoS One* 2010;5:e13011.
- Pichler I, Minelli C, Sanna S, *et al.* Identification of a common variant in the TFR2 gene implicated in the physiological regulation of serum iron levels. *Hum Mol Genet* 2011;20:1232–40.
- Pendergrass SA, Brown-Gentry K, Dudek S, *et al.* Phenome-wide association study (PheWAS) for detection of pleiotropy within the Population Architecture using Genomics and Epidemiology (PAGE) Network. *PLoS Genet* 2013;9:e1003087.
- Hall MA, Verma A, Brown-Gentry KD, *et al.* Detection of pleiotropy through a Phenome-wide association study (PheWAS) of epidemiologic data as part of the Environmental Architecture for Genes Linked to Environment (EAGLE) study. *PLoS Genet* 2014;10:e1004678.
- Devallière J, Charreau B. The adaptor Lnk (SH2B3): an emerging regulator in vascular cells and a link between immune and inflammatory signaling. *Biochem Pharmacol* 2011;82:1391–402.
- Devallière J, Chatelais M, Fitau J, *et al.* LNK (SH2B3) is a key regulator of integrin signaling in endothelial cells and targets  $\alpha$ -parvin to control cell adhesion and migration. *Faseb J* 2012;26:2592–606.
- Peden DB, Hohman R, Brown ME, *et al.* Uric acid is a major antioxidant in human nasal airway secretions. *Proc Natl Acad Sci U S A* 1990;87:7638–42.

- 52 Kool M, Willart MA, van Nimwegen M, *et al.* An unexpected role for uric acid as an inducer of T helper 2 cell immunity to inhaled antigens and inflammatory mediator of allergic asthma. *Immunity* 2011;34:527–40.
- 53 Hara K, Iijima K, Elias MK, *et al.* Airway uric acid is a sensor of inhaled protease allergens and initiates type 2 immune responses in respiratory mucosa. *J Immunol* 2014;192:4032–42.
- 54 Webb R, Jeffries M, Sawalha AH. Uric acid directly promotes human T-cell activation. *Am J Med Sci* 2009;337:23–7.
- 55 Gold MJ, Hiebert PR, Park HY, *et al.* Mucosal production of uric acid by airway epithelial cells contributes to particulate matter-induced allergic sensitization. *Mucosal Immunol* 2016;9:809–20.
- 56 Horsfall LJ, Nazareth I, Petersen I. Serum uric acid and the risk of respiratory disease: a population-based cohort study. *Thorax* 2014;69:1021–6.
- 57 Aida Y, Shibata Y, Osaka D, *et al.* The relationship between serum uric acid and spirometric values in participants in a health check: the Takahata study. *Int J Med Sci* 2011;8:470–8.
- 58 Kobylecki CJ, Vedel-Krogh S, Afzal S, *et al.* Plasma urate, lung function and chronic obstructive pulmonary disease: a Mendelian randomisation study in 114 979 individuals from the general population. *Thorax* 2017. 10.1136/thoraxjnl-2017-210273. [Epub ahead of print 29 Nov 2017].
- 59 Denny JC, Ritchie MD, Basford MA, *et al.* PheWAS: demonstrating the feasibility of a phenome-wide scan to discover gene-disease associations. *Bioinformatics* 2010;26:1205–10.
- 60 Cortes A, Dendrou CA, Motyer A, *et al.* Bayesian analysis of genetic association across tree-structured routine healthcare data in the UK Biobank. *Nat Genet* 2017;49:1311–8.
- 61 Canela-Xandri O, Rawlik K, Tenesa A. An atlas of genetic associations in UK Biobank. *bioRxiv* 2017.
- 62 Latourte A, Soumaré A, Bardin T, *et al.* Uric acid and incident dementia over 12 years of follow-up: a population-based cohort study. *Ann Rheum Dis* 2017:e210767.
- 63 Khan AA, Quinn TJ, Hewitt J, *et al.* Serum uric acid level and association with cognitive impairment and dementia: systematic review and meta-analysis. *Age* 2016;38:16.
- 64 Robinson PC, Merriman TR, Herbison P, *et al.* Hospital admissions associated with gout and their comorbidities in New Zealand and England 1999-2009. *Rheumatology* 2013;52:118–26.
- 65 Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol* 2013;42:1497–501.