Genetics of hyperuricemia and gout: Insights from recent genome-wide association studies and Mendelian randomization studies

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ABSTRACT

Gout is the most common form of inflammatory arthritis in adults. Elevation serum uric acid (SUA) concentration is known to be the key to gout pathogenesis. Since the first genome-wide association study (GWAS) for SUA was performed in 2007, the number of gene loci known to be associated with hyperuricemia and gout has grown rapidly. GWASs and Mendelian randomization studies have also reported numerous novel results regarding the genetics of hyperuricemia and gout since 2018. We concisely review recent advances in scholarship on the effects of genetics on hyperuricemia and gout risk. We also review data from genetic association studies in Taiwan and perform GWASs of SUA levels among Taiwan Biobank participants.

KEYWORDS: Genetics, Genome-wide association study, Gout, Hyperuricemia, Mendelian randomization study

INTRODUCTION

The incidence of hyperuricemia has increased over the last century in many populations [1,2]. Hyperuricemia is central to the pathogenesis of gout [3-6]. Serum uric acid (SUA) is the end product of purine metabolism, and elevated SUA concentration resulting from hepatic overproduction or renal or intestinal underexcretion [7] may lead to the saturation of urate levels and the formation of monosodium urate (MSU) crystals. These MSU crystals are deposited in the synovial fluid of joints. Cascading inflammatory responses follow, and gout develops. Gout is currently the most common form of inflammatory arthritis in adults, and its prevalence is increasing [1,2,8]. The progression from hyperuricemia to gout can develop in four stages: hyperuricemia only, MSU crystal deposition without symptomatic gout, acute gouty flares and tophi, and chronic and advanced gouty arthritis [3,6,9]. Each stage from asymptomatic hyperuricemia (AHUA) toward gout has different etiological factors that have different causal relationships with comorbidities. Cardiometabolic comorbidities that are common in patients with gout include obesity, hypertension, type 2 diabetes mellitus, chronic kidney disease, dyslipidemia, and coronary artery disease [10-14]. However, the causal relationships between hyperuricemia, gout, and various lifestyle effects and cardiometabolic disorders remain to be determined [15-19].

Since 2007, Li et al. [20] first reported the genome-wide association study (GWAS) for SUA levels. Major et al. [4] reported an updated review of genetics of hyperuricemia and gout for both GWASs and Mendelian randomization (MR) studies in 2018. Thereafter, a lot of publications from East Asian population and from transethnic studies with meta-analysis have been reported. Herein, we will briefly summarize the data of GWAS and MR studies for hyperuricemia and gout, especially focused on publications after 2018.

HERITABILITY OF HYPERURICEMIA AND GOUT

Heritability is defined as the percentage variance in phenotype that is explained by genetic variations between individuals in a population. Heritability can be estimated by studying phenotypic correlations between related individuals—typically twins. A genome-wide association study (GWAS) can also reveal candidate gene loci that may partly explain the genetic variance of a phenotype. Twin...
studies have demonstrated that the heritability of serum urate is 45%–73% [21-23], whereas the heritability of the renal clearance of urate was estimated to be 46%–96% [24-26]. GWASs have identified gene loci by using a prevalence of >1% for each allele. The estimated heritability of SUA levels by GWAS was 45%–68% in Europeans [27]. However, index single-nucleotide polymorphisms (SNPs) explained only 5.3% of the variance in SUA concentrations in populations with European ancestry that had 28 loci identified [27]. Larger studies of up to 457,690 individuals identifying 183 loci were only estimated to explain 7.7% of SUA variance [28], which is significantly less than what is predicted to be heritable. In addition, in a general population-based pedigree study, the 183 index SNPs explained 17% of SUA heritability, in which 5% was attributed to three index SNPs on ABCG2, SLC2A9, and SLC22A12 [28]. The missing heritability may be due to copy number variants, rare or population-specific genetic variants, mitochondrial variants, epigenetic effects, and gene–gene and gene–environment interactions. The prevalence of gout increases with age and plateau at age 70. The incidence is 2–6 times higher in men than in women [8,29,30]. Some ethnic groups, such as aboriginal Taiwanese, Pacific Islanders living in New Zealand, and Maoli (native Hawaiian) people (specifically, men), have a higher prevalence of gout than other ethnic groups [8,29]. Gout is heritable and tends to cluster in families. By using segregation and linkage analysis of familial gout in aboriginal Taiwanese, an autosomal–arbitrary major gene model was found to best fit the data, indicating a genetic basis for familial gout [30]. Using data from the National Health Insurance Research Database in Taiwan, Kuo et al. [31] conducted a nationwide study enrolling more than 1,000,000 individuals with physician-diagnosed gout to estimate the degree of familial aggregation for gout. The results revealed that the relative contribution of heritability was sexually dimorphic at 35.1% in men and 17.0% in women.

**GENOME-WIDE ASSOCIATION STUDIES FOR SERUM URIC ACID LEVEL AND GOUT BEFORE 2018**

New scholarly advances on the genetic basis of hyperuricemia have improved our understanding of the pathogenesis of hyperuricemia and gout [4,32-34]. By using a genome-wide scan, Li et al. [20] first reported that GLUT9 gene variants are associated with SUA levels. Vitart et al. [35] further revealed that SLC2A9, encoded by the GLUT9 gene, is a newly identified urate transporter influencing SUA concentrations, urate excretion, and gout. Analyzing a total of 26,714 participants from the Framingham Heart Study (FHS), Rotterdam study, and the Atherosclerosis Risk in Communities (ARIC) study, Dehghan et al. [36] revealed that three gene loci, ABCG2, SLC2A9I, and SLC17A3, are associated with uric acid concentrations and gout risk. A meta-analysis of 28,141 individuals discovered five new loci – SLC22A11, SLC16A9, GCKR, LRRC16A, and PDZK1 – that influence uric acid levels [37]. Two more loci, RBE1 and INHBC, were also reported to be associated with gout by Yang et al. [38]. In 2013, by combining data from >140,000 individuals of European ancestry, 18 new gene regions for SUA concentrations were later identified and replicated in or near TRIM46, INHBB, SFMBT1, TMEM171, VEGFA, BAZ1B, PRKAG2, STC1, HNF4G, A1CF, ATXN2, UBE2Q2, JGF1R, NFAT5, MAF, HLF, ACVR1B-ACVR1L, and B3GNT4 gene loci [27]. In an updated review of genetics of hyperuricemia and gout in 2018 [4], the authors summarized earlier GWAS findings and reported that 28 GWAS loci for serum urate levels were detected in European populations, whereas only four loci were detected in East Asian populations and three in African-American populations, suggesting that the molecular genetics of hyperuricemia and gout had been underestimated in Asian and African populations in earlier studies.

**RECENT GENOME-WIDE ASSOCIATION STUDIES FOR HYPERURICEMIA AND GOUT**

Since 2018, many new GWASs have used more Asians participants and have recruited transethnic populations or used meta-analyses to discover more genome-wide loci that are related to hyperuricemia and gout. Kanai et al. [39] conducted a GWAS investigating 58 quantitative traits in 162,255 individuals from the Biobank Japan Project and identified 27 gene loci for SUA levels in Japanese people. A total of 10 loci were novel including MAFFTR, AC022166.1, AC092130.1, AC099159.1, LRP2, and several other gene loci (NXRN2, SLC22A11-SLC22A12, and others) were located in chromosome 11. By performing a transethnic GWAS of serum urate for 457,690 individuals, Tin et al. [28] identified 183 loci (with 147 novel loci) for serum urate levels that improve the prediction of gout in an independent cohort of 334,880 individuals. By conducting a GWAS investigating SUA levels among 6881 Korean individuals, Cho et al. [40] identified two low-frequency and six common independent variants including LC22A12 p.W258X and an East Asian-specific missense variant (rs671) in ALDH2 associated with SUA. The NHGRI-EBI GWAS Catalog is a publicly available resource for GWAS, and it contains useful visualizations of variant-trait associations. All variants are mapped onto chromosomal positions on the human genome (https://www.ebi.ac.uk/gwas/). When the keywords of “gout” and “uric acid measurement” were searched, a total of 193 associations from 23 studies regarding gout and 380 associations from 38 studies regarding uric acid were identified in the GWAS Catalog. The identified gene loci were compared; in an analysis of only protein-coding genes, a total of 41 gene loci were found to overlap the categories of “gout” and “uric acid measurement” [Table 1].

Urate excretion is regulated by the kidney and gut, and urate excretion in the kidneys is controlled by a suite of urate transporters. Variations in SLC2A9, ABCG2, and SLC22A12 gene loci are most strongly associated with both SUA levels and gout in multiple populations. Dysfunction in ABCG2 also mediates the underexcretion of urate in the gut and causes an overload of renal urate [4]. Four distinct subtypes of gout have been classified according to patient clinical parameters. These subtypes are classified according to the causes of gout and are renal underexcretion (RUE), renal overload, combined, and normal [41]. GWAS meta-analyses of clinically defined gout were performed to identify subtype-specific susceptibility loci using 3053 clinically
Table 1: Gene loci associated with uric acid measurement and/or gout: Data derived from genome-wide association study catalog

| Phenotype/disease | Protein-coding gene loci |
|-------------------|-------------------------|
| Uric acid measurement only | A1CF, ALDH3B1, ANRD33-FIGNL2-AT, ABHGAP26, B4AGTA1, BANF1-CST6, BAZ1B, BCA1, BCC1, BRAP, C11orf80, C1QTNFR9-BKRD304199, CARMILL1, CCDC18, CNTN4, COMMD4-ANP32BP1, CPS1, CYSB-BNAT5, DACH1, DCDC2, DIP7C-AL1577091, DNEA3, DEPE1, EIF1AD, ETT5, F5, FATK-ANKRD50, FLRT1-MACROD1, FRAS1, FRMD8, GAD1, GAREMI, GNAS, GPD1J, HECTD4, HLA-DQA1-HLA-DQB1, HLF, HNF4A, IGFR1, INHBC, INS, IPI01-ISCAP1J, KCE1, KIAA0319, KLH5, RNU1-130P, LMAN2-RXPD2, LRP2, MAPTRR, MAJIN, MALAT1, MAP4K2, MAPKAPK5-ADAM1A, MARK4-EXOC3L2, METTL6, MPPED2-MUTYH, MUC1, MYO9A, MYOF, NDUFA6, NFAT2, NFKB1, NRG2, NRC1-BINDR5, ORC4, OVL1, PCNX3, PIGN, PKD2, PLAAT2-PLAAT4, PLAAT5, PNPLA3, POLA2, PPP2R5B, PSORS1C1-PSORS1C2, PCYD1, QIRC2, RAIA1, RBM14-RBM4, RGS20, RNS7KP182, RNASEH2C-KRT8P26, RN115, RNU1-148P-SC1, RPH3A, RPL21P41, RPL32P31, RPL7P27, RPS5K1A4, RBRE1-AL393901, RPS3G, RTN4RL1-RAP1, RBP2, SLENOO, SENS2, SED1, SHOOM1, SIP1AL3, SLC10A2, SLC14A2, SLC17A4, SLC22A10, SLC22A24, SLC25A26-LRIG1, SLC27A5, SLC29A2, STK32B, SYN3, TENM2, TMC6, TMED171, TMEM18, TSGA10IP-DRAP1, TSHR, TTL1, UMOD, UNCX, USP2, USP34, VEGFA, VPS37D-MIYX1L, VPS4A, VPS51, WDR1, WDR72, WNT7A, ZNF38, ZNF584 |
| Gout only | AADACL2-AS1, ABCA1, ABCC8, ABCG1, AC002463, ARBOX1, BRF32, ZNF724, RNS7KP193, CNDN24, ACSM2B, HAC5, AL1378661, OR13C8, ALDH11A2, ALX4, LINCO2724, ARID5B, ASB10, ATIP1A4, BDKRB2, CTRI, CNH2, CNP14, CNT5, CYBSAP4, CYP2C8, CYP2E1, DST, EFIP1P, EVA1A, FAM3A, FGFR2, FSTL4, FTH1P1, GABP1, GLUD1, GRID1, HGF, JAZF1, LHPL3, MCAM1D-AS1, MIR21, MFSD6P2, MSC-AS1, NIPAL1, NSUN3-ARMC10P1, NTG2-MED27, PDEF1, PFB1, POLD3, PPAR, PPARYC1-DLX15, PRKAG2, PRKACB, PTN3R, PXDNL, RARB, RFX3-AS1, RUNX2-CJLC5, SLC13A4, SLC22A1, SLC22A18AS, SLC3A1, SMARC1C1, SMT3D, SV2B, TPS1, TDR, WNT5B |
| Both uric acid measurement and gout | ABCG2, BCA3A, RNS7L469P, CACNA2D3, SFMBT1, ZMYM6, ACAD10, THEM4, TRIM46, ALDH2, ANO2, BAIAP2, CCDC75P1, CAC428BG-MEN1, CUX2, FAAHP1, PDM6-FFG3, GCKR-C2orf16, GEM2, KCNQ1, MYL2, MAP3K1, MKAP6, MLXIP, MRPS3P3-RPFP22, MYH11, NA2A5, NALCN, NRXN2, OR4D5-OR5D4, OR6M1-OR6M2P, CD160-PDZK1, PKNOX2, RAB27B, SHLD2, SLC16A9, SLC17A1, SLC22A11-SLC22A12, SLC22A9, SNCX1P26-CYP4F34P, WWOX |

defined gout cases and 4554 controls from Japanese men. Both ABCG2 and ALDH2 were associated with all gout subtypes; SLC2A4, SLC22A11-SLC2A12, and SHLD2 were associated with the RUE and combined gout subtypes; BCA3 was associated with the combined gout subtype, and CD2-PGFRN and SLC28A3-NTRK2 were associated with normal gout cases [41,42]. These findings, including two novel genes CD2-PGFRN and SLC28A3-NTRK2, can elucidate the molecular pathophysiology of different gout subtypes and facilitate the development of precision medicines for gout and hyperuricemia prevention and therapy. Elevated SUA concentrations are known to be central to the pathogenesis of gout, however, most individuals with AHUA do not develop gout. By analyzing a total of 2860 gout cases and 3149 AHUA controls in Japanese men, Kawamura et al. [43] revealed that six gene loci (SLCA29, ABCG2, CNTN5, ALDH2, MIR302F, and ZNF724) were associated with crystal-induced inflammation (i.e., the final stage of gout development). Sandoval-Plata et al. [44], in the analysis of 4934 gout cases and 56,948 AHUA controls as the discovery cohort and 2115 gout cases and 24,406 AHUA controls as the replication cohorts from the UK Biobank, further revealed 13 independent SNPs in ABCG2, SLC249, SLC22A11, GCKR, MEPE, PPM1K-DT, LOC103577323, and ADH1B, which were also associated with the combined gout subtype, and led to the combined gout subtypes and led to the combined gout subtypes and led to the combined gout subtypes and led to the combined gout subtypes.

**Ethnic heterogeneity for genetics of hyperuricemia and gout**

Several studies have revealed ethnic heterogeneity in the genetics of hyperuricemia and gout. In a GWAS of SUA levels, ABCG2 variants were reported to have a prominent effect (≈1%) on SUA levels in East Asian and European populations, whereas the ABCG2 lead SNP rs22331142, Gln141Lys, is associated with hyperuricemia and gout in the African-American population but with a similar effect size [36]. ALDH2 rs671 (Glu504Lys) is another variant prevalent in East Asian populations associated with hyperuricemia and gout [45,46]. The Lys allele causes substantially reduced ALDH2 activity, and by reducing plasma and urinary hypoxanthine levels, it is associated with reduced SUA after alcohol ingestion; it, therefore, reduces the risk of gout. However, ALDH2 rs671 is rare in many other populations and Glu allele-positive individuals have elevated hypoxanthine and urate levels, which increase the risk of gout. Liu et al. [47] reported interactive effects between body mass index and alcohol intake on the association between rs671 genotypes and risk of gout. Sulem et al. [48] identified a low-frequency missense variant (c.1580C>G) in ALDH11A1 (rs150414818, Pro476Arg) associated with gout in the Icelandic population, which was not reported in other populations. Multiple gene loci identified by GWAS as controlling urate are common across multiple populations, indicating the critical role of urate excretion in the pathogenesis of hyperuricemia and gout [4].

**Studies of genetic basis of hyperuricemia and gout from Taiwan**

We have analyzed 459 participants from cardiovascular health examination and found the association between...
**NEW PERSPECTIVES FOCUSED ON NONCODING RNA AND ITS IMPACT ON FUTURE THERAPEUTIC STRATEGY**

Noncoding RNA is a type of RNA, such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) that does not encode protein. Although initially considered redundancy, many studies have revealed that noncoding RNA plays a critical role in many diseases and has the potential to be a new target for therapy [59]. Multiple miRNAs and lncRNAs are involved in various stages of gout development [60]. GWASs also identified several noncoding RNA as candidate gene loci [39,43,44]. Ko et al. [50] showed that the candidate ALPK1 gene variant for gout was identified as being able to effectively interfere with microRNA target recognition and to modulate mRNA expression. Medications for hyperuricemia and gout, such as colchicine, allopurinol, and benzbromarone, may upregulate different miRNAs [60]. Noncoding RNAs can directly regulate the transcriptional level of coding genes and display faster regulation of the occurrence and development of diseases. Therefore, exploration of miRNAs and lncRNAs may be considered as a target for future gout therapy.

**RISK OR COMORBIDITY ASSOCIATED WITH HYPERURICEMIA AND GOUT: EVALUATED BY MENDELLIAN RANDOMIZATION STUDY**

Although observational studies are commonly used to discover correlations between quantitative traits and disease status, the causality of the associations is uncertain in these studies due to their inability to control for confounding factors and biases from reverse causation. An MR study is performed by using either genetic variants or genetic risk scores as an instrumental variable for modifiable exposure. MR is widely used in GWASs to investigate causality [61,62]. In an umbrella review of evidence from observational studies, randomized controlled trials, and MR studies, Li et al. [63] comprehensively analyzed 107 MR studies identified from 36 publications (with a median number of 7158 participants and 2225 cases) from before 2017 with SUA level as an...
Since 2018, MR studies have used SUA level or gout as an exposure or outcome [Table 3]. Larsson et al. [66] and Larsson et al. [65], analyzing data from the Global Urate Genetics Consortium, reported that coffee intake may lower the risk of gout and that obesity, as determined by body mass index, causes increased SUA levels and an increased likelihood of gout attacks. By contrast, a genetically higher waist–hip ratio (adjusted for body mass index) was not associated with SUA levels or gout risk [66]. This result is similar to that reported by Lyngdoh et al. [77], which suggested that elevated SUA levels are a consequence rather than a cause of adiposity. Yuan et al. [69] reported genetically high iron status, such as high serum iron, ferritin, and transferrin saturation, and low transferrin levels (causally) increase the odds of gout but lower the odds of rheumatoid arthritis in 48,972 individuals of European descent. By contrast, Lee [67] reported that smoking is not causally associated with gout in a study involving data from 85,997 individuals of European descent as the exposure and data from 2115 patients with gout and 67,259 controls as the outcome. By analyzing data regarding 106,147 individuals from the Copenhagen General Population Study, Kobylecki et al. [64] discovered that genetically high plasma Vitamin C is not causally related to SUA levels. In addition, with 333,214 participants from UK Biobank, Nicolopoulos et al. [68] demonstrated no causal association between coffee intake and gout. Topless et al. [70] used data from the ARIC study, the FHS, the Coronary Artery Risk Development in Young Adults (CARDIA) study, the Cardiovascular Health Study (CHS), and the UK Biobank (419,060 individuals in total) and found only weak causal effects of four dietary habits – preferentially drinking skim milk, consuming tub margarine, preferentially drinking milk with higher fat content, and consuming dried fruit – on SUA levels. These effects were mediated by body mass index. These results indicate that diet has a relatively minor effect on SUA levels, whereas urate-lowering therapy is the largest factor for hyperuricemia leading to gout. When SUA was used as an exposure in MR studies, gout and inflammatory polyarthropathies were the most consistent outcomes for hyperuricemia [71,72]. Chronic kidney disease, reduced bone mineral density, and urolithiasis were also not demonstrated to be outcomes of hyperuricemia [72,74,76], and neither bone mineral density nor Alzheimer’s disease [74,75] was demonstrated to be outcomes of gout. Biradar et al. [15] analyzed 10,000 TWB participants and found that elevated SUA levels may increase blood pressure and triglyceride levels and decrease high-density lipoprotein cholesterol levels, resulting in a higher risk of metabolic syndrome, whereas high waist circumference may be causative for all the components of metabolic syndrome including hyperuricemia. By analyzing the same study population, Chiang et al. [16] also found that high SUA levels are a precursor to the development of cardiometabolic diseases. However, by using a phenome-wide association study together with a Bayesian analysis of a tree-structure phenotypic model, Li et al. [73] identified 13 distinct phecodes associated with genetically determined SUA levels after using multiple testing correction. These results, and the conclusions of Kanai et al. [39], either suggest that a range of interrelated disease outcomes is associated or that the genetic correlations are, in fact, due to the existence of common upstream pathological elements that influence both SUA levels and metabolic traits but may not themselves be causal.

**Conclusion**

Since 2018, the rapid expansion of GWAS and MR studies has increased our understanding for the genetics of hyperuricemia and gout. With Biobank studies and transethnic analysis, gene loci of East Asian as well as other populations have been greatly expanded. The understanding of the molecular basis of gout has progressed from initially urate transporter genes to many gene loci for different stages of gout development, from AHUA to gout and from different etiology of hyperuricemia to gout. The elucidation of noncoding RNA as candidate loci for hyperuricemia and gout also provides a hope for future target drug therapy. Till now, gout as an outcome of elevated uric acid levels was confirmed in most MR studies. When uric acid level or gout was used as an exposure or as an outcome, the causal relationships with other lifestyle factors, phenotypes, or diseases have made much progress in recent large population studies, however, we still need more replication studies to reach final conclusions.

Studies of the genetics of hyperuricemia and gout are ongoing. By comparing 35 different blood and urine laboratory measurements of individuals in the UK Biobank (n = 363,228 individuals, mostly British or non-British individuals of European descent), Sinnott-Armstrong et al. [17] found 363 independent loci associated with SUA levels. In these 363 gene variants, 3 were protein-truncating variants, 40 were protein-altering variants, and 320 were noncoding variants. These results further expand our understanding of novel gene loci for hyperuricemia and for gout in transethnic studies. We believe that efforts to include different ethnic populations, especially in Biobank studies, and performing meta-analyses will facilitate the discovery of gene loci for hyperuricemia and gout and also in understanding more of the causal inference between SUA level/gout and various candidate exposures and outcomes in the future.

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Table 3: Risk or comorbidity associated with hyperuricemia and gout: Evaluated by recent mendelian randomization studies

| Author/year/reference number | Dominant ancestry | Number of study participants | Exposure | Outcome | Conclusions |
|-----------------------------|------------------|------------------------------|----------|---------|-------------|
| **Hyperuricemia or gout as an outcome** | | | | | |
| Kobylecki et al., 2018 [64] | EA | 106,147 from CGPS (24,099 with HUA) | Plasma Vitamin C | SUA | No causal relationships detected |
| Larsson and Carlström, 2018 [65] | EA | 110,347 from GUGC | Coffee | SUA | OR=−0.15 mg/dl (95% CI−0.22—−0.09, \(P=7.9\times10^{-4}\)) for SUA, for 1 cup/day coffee consumption |
| Larsson and Carlström, 2018 [65] | EA | 2115 gout and 110,347 controls, from GUGC | Coffee | Gout | OR=0.56 (95% CI 0.38-0.84; \(P=0.005\)) for gout, for 1 cup/day coffee consumption |
| Larsson et al., 2018 [66] | EA | 110,347 from GUGC | Adiposity | SUA | OR=0.30 mg/dl (95% CI 0.25-0.35, \(P=1.6\times10^{-36}\)) for SUA, for each SD increase of BMI |
| Larsson et al., 2018 [66] | EA | 2115 gout and 67,259 controls from GUGC | Adiposity | Gout | OR=2.24 (95% CI 1.70-2.95; \(P=8.4\times10^{-9}\)) for gout, for each SD increase of BMI |
| Lee, 2018 [67] | EA | Exposure dataset: 85,997 | Smoking | Gout | No causal relationships detected |
| Nicolopoulos et al., 2020 [68] | EA | 333,214 from UKB | Coffee | MR-PheWAS for 1117 phecodes | Association with gout was due to pleiotropy. Causal association for increased odds of osteoarthrosis, other arthropathies, and overweight, and lower odds of postmenopausal bleeding |
| Yuan and Larsson, 2020 [69] | EA | 140,000 (2115 gout) from GUGC | Iron status* | Gout, rheumatoid arthritis and inflammatory bowel disease | Genetically high iron status was positively associated with gout and inversely associated with rheumatoid arthritis |
| Topless et al., 2021 [70] | EA | 419,060 (ARIC, FHS, CARDIA, CHS) and UKB | Diet | Hyperuricemia | Weak causal effect of four dietary habits, such as preferentially drinking skim milk, consuming tub margarine, preferentially drinking milk with a higher fat content and dried fruit, on SUA levels, which were mediated by BMI |
| **Hyperuricemia or gout as an exposure** | | | | | |
| Li et al., 2018 [71] | EA | 120,091 from UKB | SUA | MR-PheWAS for 568 phecodes | OR=4.58 (95% CI 2.72-7.72) for gout |
| Jordan et al., 2019 [72] | EA | 110,347–335,212 (from GUGC, EMR-linked UKB, ARIC, FHS, CARDIA, CHS) | SUA | CKD, eGFR, Gout | OR=3.41-6.04 for gout, per 1 mg/dl increase in SUA, all \(P<0.001\) |
| Biradar et al., 2020 [15] | Taiwan | 10,000 TWB participants | SUA | MetS components | SUA increment may augment the risk of MetS through increase blood pressure and triglyceride levels and decrease high-density lipoprotein cholesterol levels |
| Chiang et al., 2019 [16] | Taiwan | 10,000 TWB participants | SUA | CVD | OR=1.62 (95% CI 1.17-2.23), \(P=0.003\) for high versus. low SUA WGRS group |
| Li et al., 2019 [73] | EA | 339,256 from UKB | SUA | MR-PheWAS for 1431 disease outcomes | Associations with circulatory and metabolic disorders were due to pleiotropy. For the association with inflammatory polyarthropathies, only gout had a significant association in PheWAS analysis |
| Lee and Song, 2019 [74] | EA | Exposure dataset: 28,141, Outcome dataset: 4807 gout, 332,352 controls | SUA, gout | Bone mineral density | No causal relationships detected |

Contd...
Table 3: Contd...

| Author/year/reference number | Dominant ancestry | Number of study participants | Exposure | Outcome | Conclusions |
|------------------------------|------------------|------------------------------|----------|---------|-------------|
| Lee, 2019 [75]              | EA               | 17,008 Alzheimer’s disease and 37,154 controls | Gout     | Alzheimer’s disease | No causal relationships detected |
| Narang et al., 2021 [76]    | EA               | 359,827 (6398 uricolithiasis) from UKB | SUA      | Uricolithiasis      | No causal relationships detected |

*Including serum iron, ferritin, transferrin saturation, and transferrin levels. ARIC: Atherosclerosis risk in communities, CARDIA: Coronary artery risk development in young adults, CGPS: Copenhagen general population study, CHS: Cardiovascular health study, CI: Confidence interval, CKD: Chronic kidney disease, CVD: Cardiovascular disease, EA: European ancestry, eGFR: Estimated glomerular filtration rate, EMR: Electronic medical record, FHS: Framingham heart study, GUGC: Global urate genetics consortium, HUA: Hyperuricemia, MetS: Metabolic syndrome, OR: Odds ratio, PheWAS: Phenome-wide association study, SD: Standard deviation, SUA: Serum uric acid, TWB: Taiwan Biobank, UKB: UK Biobank, WGRS: Weighted genetic risk score, BMI: Body mass index

Conflicts of interest

Dr. Yu-Lin Ko, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process or of decision to publish this article.

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