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Advances in multidimensional risk factors and comorbidities of gout based on UK Biobank data

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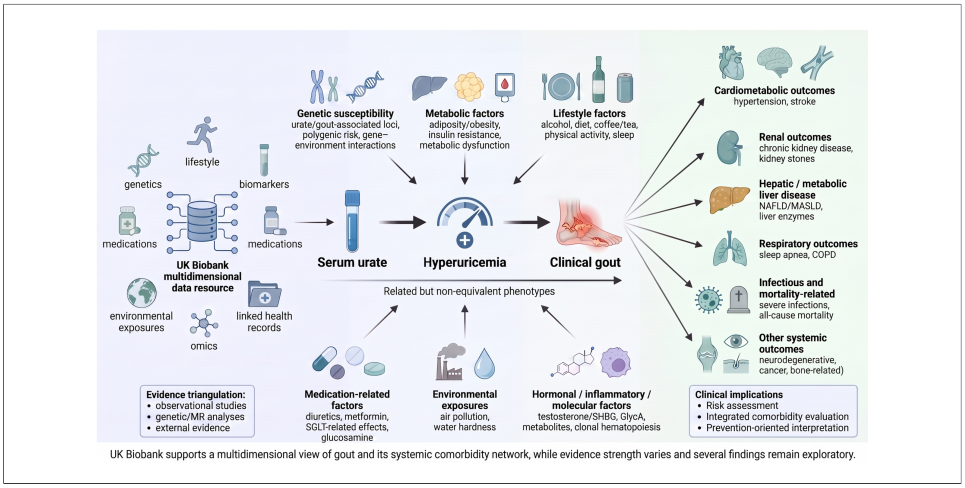

UK Biobank supports a multidimensional view of gout and its systemic comorbidity network, while evidence strength varies and several findings remain exploratory.

Abstract

Gout is an increasingly prevalent inflammatory arthritis that substantially affects quality of life and contributes to a growing public health burden. Understanding its complex network of risk factors is crucial for effective prevention and management. The emergence of large-scale cohorts, particularly the UK Biobank, has facilitated etiologic, genetic, and clinical research on gout and related urate phenotypes. By providing multidimensional lifestyle, clinical, and omics data, the UK Biobank serves as a powerful resource for dissecting the multifaceted nature of gout. Here, we provide a critical narrative review of UK Biobank-based gout research, focusing on multidimensional determinants, convergent and conflicting evidence, comorbidity networks, clinical implications, and methodological limitations and potential biases. This review aims to provide an evidence-based framework for informing gout prevention, comorbidity assessment, and future research.

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INTRODUCTION

Gout is a chronic inflammatory arthritis caused by deposition of monosodium urate crystals in and around joints, usually in the setting of sustained hyperuricemia[1-4]. Its burden is increasing globally, but gout risk is not explained by serum urate alone. Genetic susceptibility, renal and intestinal urate handling, adiposity, diet, alcohol exposure, physical activity, medications, sex hormones, environmental exposures, and comorbid metabolic or cardiovascular disease may all shape the transition from hyperuricemia to clinical gout. Existing reviews and individual studies often examine these domains separately, which makes it difficult to compare observational associations, genetic findings, Mendelian randomization evidence, multi-omics signals, and clinically actionable implications in a single framework. With the vast scale of over 500,000 participants, deeply integrated genetic and multi-omics data, comprehensive phenotypic information, and long-term follow-up records, the UK Biobank (UKB) provides an unparalleled opportunity to investigate the mechanisms underlying the development and progression of complex diseases, including gout[5,6].

This critical narrative review summarizes the landscape and latest advancements of gout research using UKB data, while selectively incorporating evidence from external cohorts, genetic studies, mechanistic research, and clinical studies to place UKB findings within a broader scientific and clinical context. We integrate evidence on gout epidemiology, phenotype definition, multidimensional determinants, comorbidity networks, causal directionality, and therapeutic and preventive implications. We distinguish observational associations from findings derived from causal-inference approaches and evaluate whether the available evidence is consistent, conflicting, or insufficient. By summarizing these themes, this review aims to clarify how UKB-based evidence can inform gout prevention, risk stratification, comorbidity assessment, and future translational research, while avoiding overinterpretation of observational associations.

SEARCH STRATEGY

A structured literature search was conducted in PubMed and Web of Science to identify studies investigating gout and related urate phenotypes using UK Biobank data. Both databases were searched from inception through December 31, 2025. The primary search combined terms for the data source and disease-related phenotypes as follows: ("UK Biobank" OR UKB) AND (gout OR hyperuricemia OR "serum urate"). Eligibility was determined according to the date on which an article was available online in the searched databases. Therefore, studies that were available online on or before December 31, 2025 were included even if their final volume, issue, or page information was assigned to a 2026 publication year. After the relevant UK Biobank-based studies had been identified, targeted supplementary searches were conducted to identify non-UK Biobank studies addressing comparable exposures, outcomes, genetic factors, comorbidities, or clinical questions. These external studies were included selectively to compare findings across populations, help explain inconsistent results, provide mechanistic or clinical interpretation, and assess the broader relevance of the UK Biobank evidence. Because this was a critical narrative review rather than a systematic review, we did not apply a screening framework based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) or claim exhaustive study identification.

EVOLUTION OF GOUT RESEARCH USING UK BIOBANK RESOURCE

UK Biobank-derived gout research has progressed from phenotype validation and genetic discovery toward multidimensional risk assessment and clinically relevant comorbidity research [Figure 1]. Studies establishing the methodological and genetic foundation of UK Biobank-based gout research addressed the performance of different gout definitions[7] and genetically informed analyses of serum urate, gout susceptibility, and urate-related disease outcomes[8-13]. These studies indicated that gout, hyperuricemia, and serum urate are related but non-equivalent phenotypes, and that phenotype selection can substantially influence case ascertainment and downstream genetic findings.

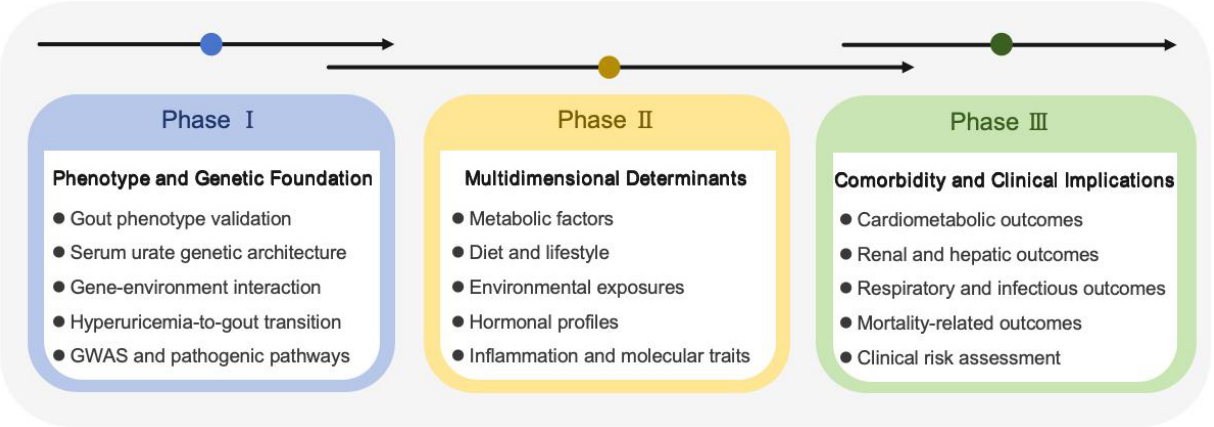

Figure 1. Evolution of gout research based on UK Biobank data. The figure illustrates three overlapping stages of gout research using UK Biobank resources: phenotype and genetic foundation, multidimensional determinants, and comorbidity and clinical implications. Each stage lists representative research themes.

Subsequent work expanded from single associations to a broader etiological framework integrating inherited susceptibility, adiposity, insulin resistance[14-16], lifestyle factors[17,18], medication use[19,20], environmental exposures[21,22], hormones[23], inflammatory biomarkers, and molecular traits[24,25]. During this phase, prospective cohort analyses were increasingly combined with Mendelian randomization and other genetically informed approaches to distinguish observational correlations from potential causal relationships. This transition helped clarify which factors are more consistently linked to serum urate, hyperuricemia, or clinical gout, while also highlighting discrepancies caused by exposure definition, confounding, pleiotropy, and phenotype heterogeneity. More recent studies have positioned gout within wider networks of cardiometabolic and renal outcomes[26-28], as well as hepatic, respiratory, and infectious outcomes[29-31]. This shift reflects a growing recognition that gout is not merely an isolated inflammatory arthritis but also a clinical signal of systemic metabolic and inflammatory burden. Overall, the evolution of UK Biobank-based gout research shows a clear movement from defining phenotypes and genetic risk toward integrating longitudinal exposures, multi-omics data, causal-inference methods, and comorbidity outcomes.

MULTIDIMENSIONAL DETERMINANTS OF GOUT AND HYPERURICEMIA: CONVERGENT AND CONFLICTING EVIDENCE

The breadth of phenotypic, genetic, biomarker, medication, and environmental data available in the UK Biobank has enabled gout research to move beyond the study of isolated risk factors. Current evidence supports a multidimensional model in which inherited susceptibility interacts with adiposity, metabolic dysfunction, lifestyle, medication use, environmental exposures, hormonal profiles, and inflammatory processes. However, the consistency of evidence varies substantially across these factors. Some associations have been reproduced across UK Biobank analyses, external cohorts, and genetically informed studies, whereas others differ according to the phenotype studied, exposure definition, population, or analytical method. A further distinction is required between factors associated with serum urate or hyperuricemia and those associated with progression to clinically manifest gout, because changes in urate concentration do not necessarily translate into equivalent changes in gout incidence or flare risk.

Genetic risk factors

Large-scale cross-population genome-wide association study (GWAS) meta-analyses have substantially enhanced the statistical power to uncover novel disease/phenotype-associated genetic loci and facilitate disease risk prediction. A trans-ancestry GWAS meta-analysis of 457,690 individuals identified 183 serum

urate-associated loci, including 147 novel loci, and validated the regulatory effect of HNF4A on urate metabolism. These urate-associated loci were further combined into a weighted genetic risk score (GRS) that improved gout risk prediction among 334,880 UK Biobank participants. The GRS alone showed moderate discrimination, whereas its addition to age and sex increased the cross-validated area under the receiver operating characteristic curve (AUC) from 0.78 to 0.83, suggesting that genetic information may complement conventional risk factors in identifying individuals with a high inherited susceptibility to gout[8].

Complementing this large-scale locus discovery, a trans-ancestry study integrating European and East Asian serum urate GWAS data used UK Biobank data for linkage disequilibrium estimation and replication of gout associations. Subsequent expression quantitative trait locus (eQTL) colocalization and functional fine-mapping identified candidate causal genes at 24 serum urate-associated loci, providing further insight into the molecular mechanisms underlying urate control[32]. Additionally, by using large-cohort genotypic and phenotypic data from the UK Biobank, twelve novel single nucleotide polymorphisms (SNPs), located in ABCG2, SLC2A9, SLC22A11, GCKR, MEPE, PPM1K-DT, LOC105377323 and ADH1B, associated with the progression from hyperuricemia to gout were identified in 2021, providing novel insights into the underlying pathogenic mechanisms of gout[11]. More recent studies have further refined the genetic architecture of clinical gout. A large multi-ancestry GWAS meta-analysis of 2.6 million individuals, including UK Biobank participants, identified 377 loci and 410 genetically independent signals and prioritized pathways involving epigenetic remodeling, cellular osmolarity, and NLRP3 inflammasome regulation, thereby extending genetic research beyond urate transport and metabolism to gout-specific inflammatory mechanisms[12]. Using a refined gout phenotype derived from the 2019 UK Biobank pain questionnaire, another GWAS identified 13 gout-associated loci, 10 of which were replicated in FinnGen, and also revealed sex-specific patterns of genetic association[13].

From a clinical perspective, genetic risk scores may complement established clinical factors in identifying individuals with a high inherited susceptibility to gout, but their routine use for gout risk stratification remains premature. Gout-specific intervention thresholds and prospective evidence that polygenic risk score (PRS)-guided risk stratification improves clinical outcomes have not yet been established, and appropriate validation, calibration, and interpretation are required before clinical implementation[33]. Ethical implementation also requires careful communication of probabilistic genetic risk, informed decision-making, protection against misuse of genetic information, and attention to potential inequities in PRS performance across populations[33,34].

Adiposity, insulin resistance, and biological aging

Adiposity is among the most consistently supported modifiable determinants of hyperuricemia and gout. UK Biobank-based and genetically informed analyses have linked higher body mass index and obesity to elevated serum urate and a greater risk of gout[15,35]. These findings are broadly consistent with external prospective cohorts in both men and women, which identified obesity as an important predictor of incident gout and of progression from asymptomatic hyperuricemia to clinical disease[36,37]. The agreement between observational and genetically informed evidence makes adiposity one of the more robust risk factors identified in this field.

The metabolic consequences of obesity may be as important as body size. Bidirectional Mendelian randomization analyses supported a directional effect of hyperinsulinemia on serum urate and gout, whereas evidence for an effect in the reverse direction was weaker[14]. An external study combining Mendelian randomization with network pharmacology suggested insulin resistance as a potential mechanistic link between obesity and hyperuricemia[38]. Hyperinsulinemia may reduce renal urate excretion and frequently coexists with dyslipidemia, hypertension, and visceral fat accumulation. These findings support a metabolic pathway linking adiposity, insulin resistance, hyperuricemia, and gout, although the relative contributions of

renal urate handling, dietary intake, inflammation, and other metabolic abnormalities remain difficult to separate.

Genetic susceptibility also remains relevant across different levels of adiposity. UK Biobank analyses showed that urate-associated variants continued to influence gout risk across body mass index categories[10]. This indicates that obesity and genetic predisposition should not be viewed as mutually exclusive explanations. Instead, they may contribute jointly to disease development. However, existing studies do not establish a specific body mass index or visceral adiposity threshold that can be used to guide gout prevention.

Age-related biological changes have emerged as a related but less established area of research. A UK Biobank cohort study associated accelerated biological aging with progression from hyperuricemia to gout[39]. Separately, a cross-sectional and Mendelian randomization study reported an association between frailty and gout[40]. Other analyses have examined relationships among serum urate, telomere length, and inflammatory markers[41]. Although these findings point in a broadly consistent direction, biological age, frailty, and telomere length measure different aspects of aging and cannot be treated as interchangeable exposures. Evidence that biological aging independently drives progression to gout remains preliminary and requires validation in cohorts with repeated measurements and well-defined hyperuricemia-to-gout transitions.

Alcohol, diet and other lifestyle factors

Alcohol is one of the clearest examples of concordant UK Biobank and external evidence. In the UK Biobank, higher total alcohol consumption and several beverage-specific exposures were associated with a higher risk of incident gout, with variation by sex, dose, and beverage type[18]. In this analysis, among current drinkers, consuming alcohol five or more times per week, compared with less than once per week, was associated with a higher risk of gout in both men (HR: 2.05, 95%CI: 1.84-2.30) and women (HR: 1.34, 95%CI: 1.12-1.61). UK Biobank genetic analyses also suggested gene-environment interactions involving alcohol-related loci and gout susceptibility[42]. These findings are consistent with external prospective cohort evidence showing that alcohol intake, particularly beer and spirits, increased incident gout risk in men[43]. External case-crossover evidence further showed that alcohol intake shortly before an attack was associated with recurrent gout flares[44]. Therefore, alcohol can be discussed as a relatively well-supported modifiable risk factor, although the magnitude of risk depends on dose, beverage type, sex, and baseline metabolic status.

Coffee shows a more complex pattern. UK Biobank observational evidence supports an inverse association between coffee consumption and gout risk. A UK Biobank prospective analysis found nonlinear inverse associations between tea or coffee intake and incident gout[45]. External prospective cohorts in men and women reported similar inverse associations between coffee consumption and incident gout[46,47]. However, genetically informed studies have produced less consistent conclusions. The UK Biobank mediation analysis suggested that shared genetic variants largely influenced gout directly rather than through coffee intake[48]. A UK Biobank Mendelian randomization-phenome-wide association study (MR-PheWAS) of habitual coffee consumption also provided limited evidence that genetically predicted coffee intake produced broad disease-protective effects[49]. In contrast, external Mendelian randomization and mediation MR studies reported a potential protective association of coffee intake with gout, possibly involving serum urate, urea, or sex hormone-binding globulin[50,51]. These differences may reflect the choice of genetic instruments, pleiotropy, exposure definition, coffee subtype, caffeine content, and differences between lifelong genetic predisposition and actual drinking behavior. Thus, coffee consumption is consistently associated with lower gout risk in observational studies, but current causal evidence remains insufficient to recommend increased coffee intake specifically for gout prevention.

Evidence for tea is more limited and should be interpreted separately from coffee. The UK Biobank prospective analysis suggested that tea intake was associated with gout risk in a nonlinear manner, with the lowest risk observed at relatively high intake levels. In that study, participants consuming more than six cups of tea per day had a lower risk of incident gout than non-tea drinkers (HR: 0.77, 95%CI: 0.66-0.91), and spline analyses suggested that the inverse association became apparent at approximately six cups per day[45]. However, Mendelian randomization evidence was less consistent. A separate MR study reported no clear causal association of tea intake with overall gout, idiopathic gout, or serum urate, although a weak inverse association was observed for gout due to impaired renal function[52]. Therefore, current tea-related evidence suggests a possible inverse association but remains insufficient to support a firm conclusion regarding gout prevention.

Studies of broader dietary patterns highlight the need to distinguish specific dietary components from the overall contribution of diet to serum urate variability. Several UK Biobank studies have examined dietary quality or specific food groups. Higher consumption of ultra-processed foods was associated with a higher risk of gout in the UK Biobank and appeared to have an additive effect with genetic susceptibility[53]. Compared with participants in the lowest quartile of ultra-processed food consumption, those in the highest quartile had a higher risk of gout (HR: 1.16, 95%CI: 1.01-1.33). Participants with both high ultra-processed food consumption and high genetic predisposition had an even higher risk than those with low consumption and low genetic predisposition (HR: 1.90, 95%CI: 1.39-2.60). UK Biobank analyses of carbohydrate intake further showed that carbohydrate quality and source were more informative than total carbohydrate intake alone, with free sugars and less favorable carbohydrate profiles associated with higher gout risk[54]. A UK Biobank-derived low-urate dietary index was also associated with lower incident gout risk and was further evaluated in external cohorts, where the overall direction of association was broadly consistent[55]. These findings support the relevance of dietary quality, but most individual dietary exposures require further replication.

At the same time, non-UKB and mixed-cohort evidence suggests that diet explains only a limited proportion of serum urate variation compared with genetic and metabolic determinants. A diet-wide meta-analysis based on five United States cohorts, not the UK Biobank, found that dietary factors explained only a small fraction of variation in serum urate levels[56]. A subsequent multi-cohort analysis including UK Biobank and external cohorts similarly concluded that diet had a relatively weak causal contribution to hyperuricemia compared with genetic, metabolic, and clinical factors[57]. These findings are not necessarily inconsistent with UK Biobank studies identifying specific dietary risk factors. A broad dietary contribution to serum urate variation can be modest while particular foods, nutrients, or dietary patterns still show meaningful associations with gout risk.

Fatty acid research represents another emerging dietary direction. UK Biobank-based cohort and Mendelian randomization analyses associated higher circulating or dietary linoleic acid and some n-6 polyunsaturated fatty acid measures with lower gout risk[58,59]. The direction of evidence is internally consistent across these UK Biobank-related analyses, but these findings should not be generalized to all polyunsaturated fatty acids, because different fatty acid subtypes may have distinct associations. External replication and intervention studies are still needed before these results can be translated into gout-specific dietary recommendations.

Observational evidence from the UK Biobank generally supports an inverse association between physical activity and incident gout. Greater purposeful steps combining walking volume and intensity, a more regular weekly distribution of accelerometer-measured moderate-to-vigorous physical activity, and higher walking activity across polygenic risk strata were each associated with a lower risk of incident gout[60-62]. However, genetically informed evidence is less consistent and appears to vary according to the outcome assessed. One

Mendelian randomization study found that genetically predicted physical activity was associated with lower serum urate but not with gout[63], whereas another suggested that moderate-intensity physical activity may reduce gout risk without a clear effect on serum urate[64]. Differences in physical activity definitions, genetic instruments, outcome datasets, and statistical power may partly explain these divergent findings. Taken together, current evidence supports physical activity as part of a favorable gout risk profile, but does not yet establish an independent causal effect on gout.

Sleep has received less attention. A UK Biobank prospective study found that healthier sleep patterns were associated with a lower risk of new-onset gout[17]. Compared with participants with poor sleep patterns, those with healthy sleep patterns had a 21% lower risk of new-onset gout (HR: 0.79, 95%CI: 0.70-0.91). A separate UK Biobank analysis focusing on sleep duration and hyperuricemia reported that short sleep duration was associated with hyperuricemia, particularly among women[65]. These findings are directionally compatible, but sleep duration, sleep quality, chronotype, insomnia, and sleep apnea are distinct exposures. Their relationships with gout may also be confounded or mediated by obesity, depression, cardiometabolic disease, shift work, and medication use. Current evidence supports considering sleep health as a potential component of overall gout risk, but not as a single well-defined causal factor.

Smoking remains one of the least consistent lifestyle-related factors. In UK Biobank gout research, smoking has mainly been included as part of composite healthy lifestyle scores rather than evaluated as an independent exposure. A UK Biobank analysis showed that a healthier lifestyle score was associated with lower gout risk and attenuated part of the excess risk associated with genetic susceptibility[16]. However, this does not prove that non-smoking alone independently lowers gout risk. External studies have reported conflicting findings: one prospective study in men observed a lower incidence of gout among current smokers[66], whereas another study in older adults found that some smoking-related measures were associated with a higher subsequent risk of gout[67]. These counterintuitive and inconsistent results may reflect differences in smoking definitions, former-smoker classification, competing risks, body weight, and residual confounding. Smoking should still be discouraged because of its well-established systemic harms, but the current literature does not support presenting smoking avoidance as an independently proven gout-specific preventive factor.

Medication-related factors

Medication-related evidence in UK Biobank studies has focused mainly on diuretics, metformin, sodium-glucose cotransporter inhibition, and glucosamine supplementation. These medications and related exposures may influence serum urate or gout risk through renal urate transport, metabolic pathways, or interactions with genetic susceptibility. Among them, the most consistent evidence concerns diuretics. UK Biobank research showed that serum urate-associated genetic variants continued to contribute strongly to gout risk among individuals taking diuretics[68]. Another UK Biobank genome-wide analysis of thiazide-induced adverse metabolic effects found genetic determinants of thiazide-associated hyperuricemia[69]. These UK Biobank findings are supported by external cohort evidence from the Atherosclerosis Risk in Communities (ARIC) study, which reported a urate gene-by-diuretic interaction and higher gout risk among hypertensive participants using thiazide or loop diuretics[70]. Earlier external prospective cohorts also identified diuretic use as a predictor of incident gout in men and women[36,37]. Overall, diuretic exposure is one of the medication-related factors with relatively consistent evidence. Clinically, this supports careful risk assessment rather than discontinuation of necessary antihypertensive therapy.

The evidence for metformin is less consistent and depends on the outcome. A UK Biobank analysis found that metformin use was associated with lower serum urate, but evidence for a corresponding reduction in incident gout was less convincing[19]. In contrast, an external target-trial emulation study in adults with

prediabetes reported that metformin initiation was associated with a lower risk of gout[71]. Differences in baseline metabolic status, comparator groups, medication adherence, exposure duration, and endpoint definition may explain this discrepancy. Therefore, metformin should be described as a drug with potential urate-lowering relevance, but not as an established gout-preventive therapy.

Sodium-glucose cotransporter inhibition provides a related but distinct example. A genetic proxy analysis using a UK Biobank-derived SGLT1 instrument found that genetically proxied SGLT1 inhibition was associated with lower serum urate and gout risk[72]. External comparative-effectiveness studies of clinical SGLT2 inhibitor use reported lower risks of incident or recurrent gout compared with several other glucose-lowering therapies[73,74]. These findings are directionally coherent, but they do not evaluate the same exposure: SGLT1 genetic proxies and SGLT2 inhibitor treatment differ biologically and clinically. Randomized trials or well-designed comparative studies with gout-specific endpoints would be required before drawing therapeutic conclusions.

Habitual glucosamine supplementation was associated with a lower incidence of gout among women in a UK Biobank study, whereas no clear association was observed among men[20]. No directly comparable independent replication was identified in the targeted external search. This finding should therefore be presented as a sex-specific, hypothesis-generating drug-repurposing signal rather than established evidence of benefit. Healthy-user behavior and differences in healthcare engagement may partly explain the association.

Environmental exposures

Air pollution is the environmental exposure with the clearest convergence between UK Biobank and external evidence. Two UK Biobank prospective studies associated long-term exposure to particulate matter, nitrogen dioxide, nitrogen oxides, or combined air pollutants with higher incident gout risk[21,22]. For example, each interquartile-range increase in $PM_{2.5}$ and NO_2 exposure was associated with a 5% (HR: 1.05, 95%CI: 1.02-1.09) and 8% (HR: 1.08, 95%CI: 1.05-1.12) higher risk of incident gout, respectively[21]. Some analyses suggested that the associations varied by age, genetic risk, or circulating biomarkers[22]. External studies in non-UKB populations similarly linked ambient air pollution to higher serum urate concentrations or increased hyperuricemia risk[75-77]. The direction of evidence is therefore broadly consistent across populations.

However, the evidence remains predominantly observational. In the UK Biobank, air pollution exposure is generally estimated from residential location and may not fully capture migration, indoor pollution, occupational exposure, commuting patterns, or individual time-activity behavior. Air pollution is also correlated with socioeconomic status, urbanization, noise, physical activity opportunities, and healthcare access. Thus, air pollution can be described as a consistent environmental correlate of hyperuricemia and gout, but not yet as an independently established causal factor.

Domestic water hardness is a relatively new and underexplored exposure. A UK Biobank study linked higher domestic water hardness and higher calcium- or magnesium-related water metrics to incident or recurrent gout[78]. No directly comparable external gout studies were identified, and existing non-UKB research has focused on urinary electrolytes or kidney stone outcomes rather than gout[79]. Thus, this finding remains exploratory and requires independent validation.

Hormones, inflammatory, and molecular factors

Sex hormone evidence illustrates why exposure definitions matter. A UK Biobank cohort analysis found that higher total testosterone was associated with lower gout risk in men, whereas free testosterone and bioavailable testosterone showed associations in the opposite direction[23]. Genetically informed analyses also

supported inverse associations of total testosterone and sex hormone-binding globulin (SHBG) with gout risk[80], although free and bioavailable testosterone were not evaluated in the same manner. These measure-specific findings suggest that total testosterone, free testosterone, bioavailable testosterone, and SHBG capture different hormonal and metabolic states and should not be interpreted as interchangeable exposures.

UK Biobank research has also increasingly investigated circulating biomarkers associated with gout development and recurrence. A UK Biobank prospective metabolomic study found that prediagnostic GlycA concentrations were associated with incident gout and recurrent flares after accounting for serum urate, with Mendelian randomization analyses in the same study providing additional support for a potential inflammatory pathway[24]. The internal consistency between prospective and genetic analyses strengthens the finding, but no directly comparable external replication was identified. GlycA should therefore be described as a promising inflammatory marker beyond serum urate, not as a clinically validated prediction tool.

Metabolomic evidence is also emerging. A UK Biobank metabolome-wide study identified several amino acids and related metabolites associated with incident or hospitalized gout, accounting for serum urate[81]. However, the direction of association differed across metabolites, and the findings may be sensitive to multiple testing, renal function, diet, and correlated metabolic traits. Because no directly comparable external replication was identified, these results should be presented as exploratory and hypothesis-generating.

Clonal hematopoiesis provides a stronger example of convergence across data sources. A study using UK Biobank and Mass General Brigham Biobank data found that TET2-mutant clonal hematopoiesis was associated with a higher risk of gout, and experimental work supported a potential NLRP3-interleukin-1β inflammatory mechanism[25]. This combination of UKB evidence, an external biobank, and mechanistic validation provides stronger support than a single-cohort association. Nevertheless, the finding should not be generalized to all forms of clonal hematopoiesis, and its implications for clinical screening or prevention remain uncertain.

Impaired pulmonary function is another emerging factor mainly supported by UK Biobank evidence. An integrated UK Biobank study combining longitudinal observation, Mendelian randomization, and mediation analysis associated impaired pulmonary function with higher gout risk and suggested possible roles for serum urate and inflammatory biomarkers[30]. The use of multiple analytical strategies improves internal consistency, but no directly comparable external replication was identified. This topic should therefore be described as a novel research direction rather than an established gout risk factor.

Overall interpretation of the evidence

Overall, the available evidence does not support treating all gout-related factors as equally established. Adiposity, insulin resistance, alcohol consumption, diuretic use, and air pollution show relatively consistent associations across UK Biobank and external studies, although causal certainty varies by exposure. Coffee consumption, physical activity, smoking, metformin use, and sex hormone measures require more cautious interpretation because findings differ according to exposure definition, analytical method, or clinical endpoint. Other factors, including biological aging, domestic water hardness, GlycA, amino acid metabolites, glucosamine, and pulmonary function, are best regarded as emerging areas that require independent replication. These patterns are summarized in Table 1, which distinguishes relatively consistent, partially concordant, conflicting, and emerging evidence.

COMORBIDITY NETWORKS AND CLINICALLY RELEVANT OUTCOMES IN GOUT AND HYPERURICEMIA

Whereas the preceding section reviewed determinants of gout and hyperuricemia, this section focuses on the comorbidity profile and broader clinical implications of gout and serum urate. Gout rarely presents solely as an articular disorder and commonly coexists with cardiometabolic, renal, hepatic, respiratory, and inflammatory conditions. UK Biobank-based studies have been particularly useful for mapping these associations at scale, but they also show that not all comorbidities should be interpreted as direct consequences of serum urate or gout. Figure 2 summarizes clinically relevant comorbidity networks associated with serum urate, hyperuricemia, and clinical gout, emphasizing outcomes that may guide cardiometabolic, renal, hepatic, respiratory, infectious, and mortality-related risk assessment in clinical practice.

Cardiometabolic comorbidities and cardiovascular outcomes

Cardiometabolic disease represents the most clinically relevant comorbidity cluster in gout. A UK Biobank case-control study showed that hypertension, ischemic heart disease, congestive heart failure, hyperlipidemia, and diabetes were more common among individuals with gout than among controls. Some associations persisted after accounting for serum urate, suggesting that the systemic burden of gout may not be explained by urate concentration alone[26]. Earlier external cohort evidence also indicated that hypertension may predict incident gout independently of serum urate, supporting a bidirectional clinical relationship between blood pressure, urate metabolism, and gout risk[82].

Large-scale UK Biobank and genetic studies further indicate that hyperuricemia and gout are associated with higher cardiovascular risk, but causal interpretation remains complex. A cohort and Mendelian randomization analysis found that individuals with hyperuricemia or gout had increased risks of several cardiovascular diseases, although genetic evidence did not uniformly support a direct causal effect of gout itself across all cardiovascular outcomes[27]. Similarly, Mendelian randomization and phenome-wide analyses suggested that serum urate may act partly as a marker of shared cardiometabolic pathways rather than a universal causal driver of cardiovascular disease[83-85].

From a clinical perspective, these findings support systematic cardiovascular risk assessment in patients with gout, including evaluation of blood pressure, lipid levels, diabetes, obesity, renal function, and medication use. However, they do not justify assuming that urate-lowering therapy alone will reduce cardiovascular risk. More recent UK Biobank studies suggest that favorable lifestyle and metabolic profiles are associated with lower cardiovascular risk among individuals with gout or high genetic susceptibility to gout[86,87]. Thus, gout should be regarded as a practical cue for broader cardiometabolic prevention rather than merely as an indication for serum urate control.

Renal and hepatic comorbidities

The relationship between serum urate, gout, and kidney disease is clinically important but causally uncertain. Observational studies consistently link higher serum urate with lower estimated glomerular filtration rate and higher chronic kidney disease risk. However, Mendelian randomization analyses using UK Biobank-linked and external genetic data did not support a causal effect of serum urate on estimated glomerular filtration rate or chronic kidney disease risk[88]. A UK Biobank Mendelian randomization analysis similarly found no convincing causal effect of serum urate on urolithiasis, despite observational associations between hyperuricemia and stone disease[28]. These findings suggest that renal comorbidities in gout may often reflect shared risk factors, including hypertension, diabetes, obesity, diuretic use, and reduced renal urate excretion.

Table 1. Analytical approaches and evidence consistency for major determinants of gout and hyperuricemia

Category	Factor or exposure	Study outcome	Direction of association/effect	UKB analytical approach	UKB evidence	External evidence
Genetic factors	Serum urate-associated loci	Serum urate; clinical gout/gout susceptibility	Risk alleles associated with higher urate or gout risk	Genetic risk score validation/gout risk stratification[8]	Supportive	Supportive mixed-cohort and external genetic evidence[8,105-107]
	Gout-associated genetic variants	Clinical gout/gout susceptibility	Higher genetic risk	UKB-inclusive GWAS/genetic analysis[12,13]	Supportive	Supportive multi-cohort and external replication evidence[12,13,106,108]
	Hyperuricemia-to-gout transition loci	Hyperuricemia-to-gout progression	Higher progression risk	GWAS[11]	Supportive	No direct external evidence identified
	Gene-sex interaction	Clinical gout/gout susceptibility; serum urate	Sex-specific effect	Gene-sex interaction analysis[9]	Supportive	No direct external evidence identified
	Gene-alcohol interaction	Clinical gout/gout susceptibility	Interaction-dependent higher risk	Gene-environment interaction analysis[42]	Supportive	No direct external evidence identified
	BMI strata	Clinical gout/gout susceptibility	Genetic urate effects persist across BMI strata	Gene-BMI interaction analysis[10]	Supportive	No direct external evidence identified
Adiposity and metabolic factors	BMI	Serum urate; clinical gout/gout susceptibility	Higher risk/higher serum urate	Mendelian randomization analysis[35]	Supportive	Supportive external prospective evidence[36,37]
	Obesity	Serum urate; clinical gout/gout susceptibility	Higher risk	Mendelian randomization analysis[15]	Supportive	Supportive[36,37]
	Insulin resistance	Serum urate; clinical gout/gout susceptibility	Higher risk/higher serum urate	Bidirectional Mendelian randomization with UKB-based analysis[14]	Supportive	Supportive same-study external genetic evidence[14]; indirect supportive evidence[38]
	Hyperinsulinemia	Serum urate/hyperuricemia susceptibility	Higher serum urate	UKB observational and gene-environment interaction analysis[109]	Supportive	Supportive same-study clinical and mechanistic evidence[109]
Aging-related factors	Biological aging	Clinical gout/gout susceptibility	Higher risk	Prospective cohort analysis[39]	Supportive but preliminary	No direct external evidence identified
Lifestyle and dietary factors	Alcohol consumption	Incident gout	Higher risk	Prospective cohort analysis[18]	Supportive	Supportive for incident gout[43]; related supportive evidence for recurrent flares[44]
	Alcohol-related genetic susceptibility	Clinical gout/gout susceptibility	Interaction-dependent higher risk	Gene-environment interaction analysis[42]	Supportive	No direct external evidence identified
	Coffee intake	Incident gout	Lower risk in observational analysis	Prospective cohort analysis[45]	Supportive	Supportive[46,47]
	Coffee intake	Clinical gout/gout susceptibility; serum urate-related outcomes	No clear causal effect	Mendelian randomization/PheWAS[49]	Not supportive for causality	Supportive but discordant external genetic evidence[50,51]
	Tea intake	Incident gout	Nonlinear/lower risk at higher intake	Prospective cohort analysis[45]	Supportive but nonlinear	Inconsistent/outcome-dependent mixed-source MR evidence[52]
	Ultra-processed food	Incident gout	Higher risk	Prospective cohort analysis[53]	Supportive	No direct external evidence identified
	Total carbohydrate intake	Incident gout	Lower risk	Prospective cohort analysis[54]	Supportive	No direct external evidence identified
	Free sugar intake	Incident gout	Higher risk	Prospective cohort analysis[54]	Supportive	No direct external evidence identified
	Dietary PUFA intake	Incident gout	Lower risk	Cohort/genetic analysis[59]	Supportive but preliminary	No direct external evidence identified
	Plasma linoleic acid	Incident gout	Lower risk	Integrated cohort and genetic analysis[58]	Supportive but preliminary	No direct external evidence identified
	Walking volume/intensity	Incident gout	Lower risk	Prospective cohort analysis[60]	Supportive	Mixed/outcome-dependent genetic evidence[63,64]
	Walking activity with genetic susceptibility	Incident gout	Lower risk across genetic risk strata	Prospective cohort/genetic-risk analysis[62]	Supportive	No direct external evidence identified
	Accelerometer-derived physical activity	Incident gout	Lower risk	Prospective cohort analysis[61]	Supportive	Mixed/outcome-dependent genetic evidence[63,64]
	Stair climbing	Hyperuricemia	Lower risk	Prospective cohort analysis[110]	Supportive	No direct external evidence identified
	Healthy sleep pattern	Incident gout	Lower risk	Prospective cohort analysis[17]	Supportive	No direct external evidence identified
	Short sleep duration	Hyperuricemia	Higher risk	Cross-sectional and linear/nonlinear Mendelian randomization analyses[65]	Supportive for hyperuricemia	No direct external evidence identified
	Smoking	Incident gout	Not independently assessed	Composite lifestyle analysis[16]	Limited as independent exposure	Conflicting[66,67]

Medication-related factors	Diuretics	Clinical gout/gout susceptibility	Higher risk	Genetic interaction analysis[68]	Supportive	Supportive[70,111]
	Thiazide-related effects	Hyperuricemia	Higher risk/higher serum urate	GWAS[69]	Supportive	Indirect supportive evidence[70,111]
	Metformin	Serum urate; incident gout	Lower serum urate; gout unclear	Observational and Mendelian randomization analyses[19]	Supportive for serum urate; less clear for gout	Partially supportive external genetic and clinical evidence[19,71]
	SGLT1 inhibition	Serum urate; clinical gout/gout susceptibility	Lower risk/lower serum urate	Mendelian randomization analysis[72]	Supportive	Supportive but not directly comparable clinical SGLT2 inhibitor evidence[73,74]
	Glucosamine supplementation	Incident gout	Lower risk in women	Prospective cohort analysis[20]	Sex-specific supportive evidence	No direct external evidence identified
Environmental exposures	Air pollution	Incident gout	Higher risk	Prospective cohort analysis[21]	Supportive	Indirect supportive evidence[75-77]
	Combined air pollutants with genetic risk	Incident gout	Higher risk/interaction-dependent risk	Prospective cohort/interaction analysis[22]	Supportive	Indirect supportive evidence for the broader air pollution-urate/hyperuricemia association[75-77]
	Domestic water hardness	Incident gout; recurrent gout flares	Higher risk	Prospective cohort analysis[78]	Supportive but preliminary	No direct external evidence identified
Hormonal factors	Total testosterone	Incident gout	Lower risk in men	Cohort analysis[23]	Supportive	Partially supportive/measure-dependent genetic evidence[80]
	Free testosterone	Incident gout	Higher risk in men	Cohort analysis[23]	Supportive	No direct external evidence identified
	Bioavailable testosterone	Incident gout	Higher risk in men	Cohort analysis[23]	Supportive	No direct external evidence identified
	SHBG	Incident gout	Lower risk	Cohort analysis[23]	Supportive but indirect	Partially supportive/measure-dependent genetic evidence[80]
Inflammatory and molecular factors	GlycA	Incident gout; recurrent gout flares	Higher risk	Prospective cohort and Mendelian randomization analyses[24]	Supportive	No direct external evidence identified
	Prediagnostic amino acid metabolites	Incident gout; hospitalized gout	Metabolite-specific	Prospective cohort and Mendelian randomization analyses[81]	Supportive but exploratory	No direct external evidence identified
	TET2-mutant clonal hematopoiesis	Incident gout	Higher risk	UK Biobank analysis[25]	Supportive	Supportive external-biobank and experimental validation within the same publication[25]
Systemic functional markers	Impaired pulmonary function	Incident gout	Higher risk	Cohort/Mendelian randomization/mediation analysis[30]	Supportive but preliminary	No direct external evidence identified

"Higher" and "lower" indicate the direction of association or effect for the corresponding gout- or urate-related outcome. "Supportive" evidence indicates consistency in the reported direction but does not necessarily imply causality. "Clinical gout/gout susceptibility" refers to gout status or genetic liability, whereas "incident gout" refers to new-onset gout during follow-up. External evidence refers to evidence derived from non-UK Biobank data, including external cohorts, biobanks, consortia, genetic datasets, comparative-effectiveness studies, and mechanistic investigations. Studies integrating UK Biobank with non-UK Biobank data may therefore contribute to both the UKB and external evidence columns; when a study includes both UK Biobank and non-UK Biobank data, evidence from the non-UK Biobank component is reported as external evidence. Evidence from separate independent studies is considered independent external replication. "No direct external evidence identified" indicates that no closely comparable external evidence was identified in the targeted search. GlycA: Glycoprotein acetyls; GWAS: genome-wide association study; MR: Mendelian randomization; PheWAS: phenome-wide association study; PRS: polygenic risk score; PUFA: polyunsaturated fatty acid; SGLT1: sodium-glucose cotransporter 1; SHBG: sex hormone-binding globulin; UKB: UK Biobank; BMI: body mass index.

For clinicians, the key message is that kidney function should be assessed routinely in patients with gout because it affects urate handling, drug selection, and cardiovascular risk. However, current genetic evidence does not support lowering serum urate solely to prevent chronic kidney disease in individuals without gout-specific indications. The clinical value of serum urate may lie more in risk stratification and integrated management than in serving as a single therapeutic target for all renal outcomes.

Hepatic and metabolic liver disease has emerged as another important component of the gout comorbidity network. UK Biobank-based prospective and causal-inference studies have examined the relationship between gout and metabolic dysfunction-associated steatotic liver disease from both directions. One study suggested that gout may contribute to metabolic dysfunction-associated steatotic liver disease (MASLD) through gut microbiota and inflammatory mediators, whereas another found that MASLD was associated with a higher subsequent risk of gout[31,89]. These findings support a bidirectional metabolic-inflammatory

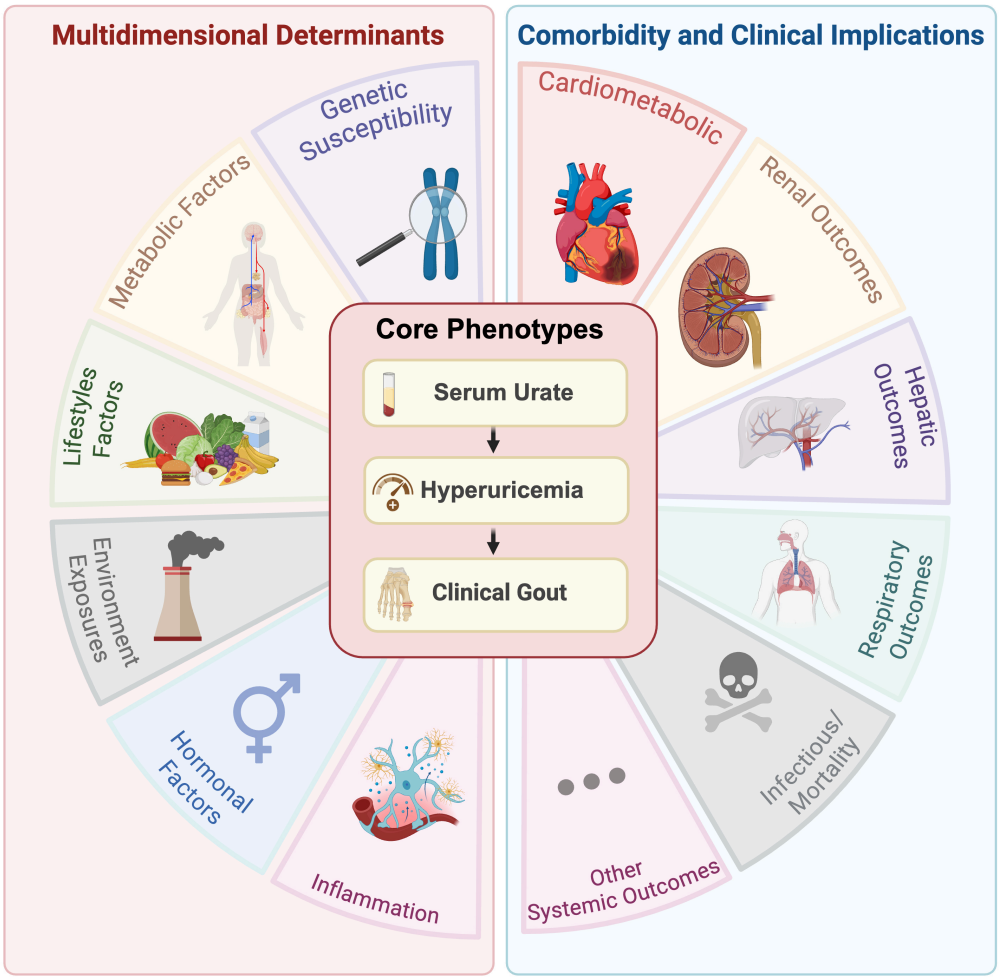

Figure 2. Clinically relevant comorbidity networks associated with serum urate, hyperuricemia, and clinical gout. The figure summarizes two connected dimensions of UK Biobank-based gout research. The left panel shows multidimensional determinants, including genetic susceptibility, metabolic factors, lifestyle factors, environmental exposures, hormonal factors, and inflammation. The center shows the core phenotypes of serum urate, hyperuricemia, and clinical gout. The right panel shows comorbidity and clinical implication domains, including cardiometabolic, renal, hepatic, respiratory, infectious/mortality-related, and other systemic outcomes. Created in BioRender. Fang X (2026) https://BioRender.com/7y3wkim.

framework rather than a simple one-way causal pathway. Clinically, patients with gout, especially those with obesity, diabetes, or dyslipidemia, may benefit from evaluation of liver metabolic health as part of comprehensive risk management.

Respiratory, infectious, and mortality-related outcomes

UK Biobank studies have also extended gout research beyond traditional metabolic and cardiovascular outcomes. An integrated cohort, Mendelian randomization, and mediation analysis suggested that impaired pulmonary function was associated with a higher risk of gout, with possible mediation through serum urate and inflammatory biomarkers[30]. Another UK Biobank analysis examined the joint association of serum urate and healthy diet with chronic obstructive pulmonary disease incidence[90]. These studies suggest that respiratory health may be connected to urate metabolism and systemic inflammation, although the clinical directionality remains under investigation.

During the COVID-19 pandemic, UK Biobank analyses reported that gout was associated with increased risks of COVID-19 diagnosis or COVID-19-related death, with some evidence of stronger relative associations among women[29,91]. These findings should be interpreted cautiously because the association may

reflect comorbid obesity, kidney disease, cardiovascular disease, health-care access, vaccination status, and treatment availability. Nevertheless, they reinforce the broader clinical point that patients with gout often carry a high burden of conditions that may increase vulnerability during systemic illness.

Mortality-related analyses further support the importance of considering serum urate within clinical context. In individuals with diabetes or chronic kidney disease, serum urate and hyperuricemia have been associated with all-cause or cardiovascular mortality, with some studies suggesting nonlinear or J-shaped patterns[92,93]. These findings imply that both very high and very low urate levels may have different prognostic meanings in high-risk populations. However, they should not be interpreted as evidence that artificially maintaining a specific urate level improves survival. Rather, serum urate may help identify patients with a higher burden of metabolic, renal, and cardiovascular risk.

Other emerging clinical outcomes

Several UK Biobank and genetic studies have explored associations between serum urate, gout, and less traditional clinical outcomes, including neurodegenerative disorders, cancer, bone mineral density, and erectile dysfunction[94-100]. These studies broaden the clinical scope of urate and gout research, but the evidence is heterogeneous and often endpoint-specific. For example, serum urate may show different associations across neurodegenerative outcomes, cancer sites, or bone-related phenotypes. Mendelian randomization results are also not uniformly supportive of direct causal effects. At present, these findings are best viewed as hypothesis-generating rather than as indications for routine disease-specific screening in all patients with gout.

Overall, UK Biobank-based research supports a clinically useful view of gout as part of a systemic comorbidity network. The most actionable evidence relates to cardiometabolic disease, kidney function, metabolic liver disease, and high-risk infectious or mortality contexts. For clinicians, the practical implication is not to treat every reported association as causal, but to use gout as a prompt for integrated assessment of cardiovascular risk, renal function, metabolic health, liver disease risk, medication exposures, and lifestyle factors. This approach may enhance the clinical value of gout care beyond urate lowering while avoiding overinterpretation of observational associations.

STRENGTHS, LIMITATIONS, AND POTENTIAL BIASES OF GOUT RESEARCH USING UK BIOBANK DATA

Although the UK Biobank has substantially advanced our understanding of the mechanisms underlying gout development and progression through its large prospective cohort design, linked health records, biochemical measurements, lifestyle information, genetic data, and multiple omics and imaging resources[5,101], several limitations should be considered when interpreting UK Biobank-based evidence.

First, the UK Biobank is not fully representative of the general population. Participants tend to be healthier, less socioeconomically deprived, and more health-conscious than the underlying UK population, reflecting a well-recognized healthy volunteer bias[102]. This may affect estimates of disease prevalence and incidence, exposure distributions, comorbidity burden, and absolute risk. For example, underrepresentation of individuals with poorer metabolic or renal health may lead to lower observed gout incidence, while lower participation by individuals with severe or disabling gout may underestimate the burden of severe disease. Although exposure-outcome associations may remain informative, participation related to both exposures and outcomes can also distort association estimates[103]. Analytical approaches such as inverse-probability weighting using population-representative external data may partially reduce volunteer-selection bias. External validation in independent cohorts can further assess the generalizability of UK Biobank-derived

incidence estimates and exposure-outcome associations. Findings should therefore be interpreted as evidence from a large volunteer cohort rather than as direct estimates for the entire UK population.

Second, phenotype and exposure definitions vary across studies. Gout may be identified using self-reported diagnoses, hospital or primary care records, medication use, or combinations of these sources. Different definitions can affect case ascertainment and downstream genetic findings[7]. Self-reported gout may be affected by recall error, whereas hospital-based definitions may preferentially identify more severe disease, and medication-based definitions may include individuals treated for asymptomatic hyperuricemia. In addition, many lifestyle and clinical exposures were measured only at baseline and may change over time. This may introduce measurement error and reverse causation, particularly when participants alter their behavior or treatment in response to early symptoms or comorbidities.

Third, residual confounding remains difficult to exclude. Obesity, kidney function, hypertension, medication use, diet, alcohol consumption, socioeconomic status, and healthcare access are closely interrelated. Associations between gout and cardiovascular, renal, hepatic, or other outcomes may therefore reflect shared metabolic and inflammatory pathways rather than direct effects of gout or serum urate. Medication-related analyses are additionally susceptible to confounding by indication. Genetic and Mendelian randomization studies can strengthen causal inference, but their findings may still be affected by pleiotropy, weak instruments, population stratification, sample overlap, and phenotype misclassification. They should therefore be considered as part of evidence triangulation rather than as definitive proof of causality.

Fourth, ancestry imbalance limits generalizability. Most UK Biobank participants are of European ancestry, and many genetic analyses are restricted to European-ancestry populations. Although this reduces population stratification, it limits the transferability of genetic associations and polygenic risk scores to Asian, African, and other underrepresented populations, particularly East Asian populations, as well as other underrepresented groups. This is particularly relevant to gout because the frequencies and effects of urate-related variants, including those in ABCG2 and SLC2A9, may differ across ancestries. Consequently, European-derived PRSs may show reduced predictive performance in East Asian populations because of differences in allele frequencies, linkage disequilibrium patterns, and variant effect sizes, highlighting the need for population-specific validation and calibration[104]. Several international consortia and organized initiatives provide complementary resources for addressing this limitation. The Global Urate Genetics Consortium has enabled large-scale meta-analyses of serum urate and gout, whereas the Asian Genetic Epidemiology Network has contributed East Asian data to trans-ancestry analyses and functional interpretation[32,105]. More recent gout-focused collaborations, including the GlobalGout Genetics Consortium, Asia Pacific Gout Consortium, and Japan Gout Genomics Consortium, have further supported multi-cohort analyses of gout-specific loci and inflammatory pathways[12]. Integrating UK Biobank findings with these resources may improve ancestral representation, independent replication, fine-mapping, and the distinction between serum urate-associated and gout-specific genetic signals. However, differences in phenotype definitions, case ascertainment, and analytical pipelines across resources may limit direct comparability.

Finally, several recent findings have not yet been widely replicated. Associations involving environmental exposures, metabolic biomarkers, biological aging, pulmonary function, supplement use, and dietary biomarkers are often based on one or a small number of analyses. These findings should remain hypothesis-generating until they are confirmed in independent cohorts, diverse populations, and, where appropriate, mechanistic or interventional studies.

Overall, the UK Biobank is a powerful platform for studying gout and hyperuricemia, but its findings should be interpreted with attention to selection bias, phenotype heterogeneity, exposure measurement, confounding, causal assumptions, ancestry imbalance, and external validation. The most reliable conclusions are likely to come from triangulating UK Biobank evidence with external cohorts, multi-ancestry genetic studies, mechanistic experiments, randomized trials, and real-world clinical data.

CONCLUSION

UK Biobank-based studies have expanded current understanding of how lifestyle, hormones, and environmental factors are associated with gout risk, while also highlighting the roles of genetic susceptibility, metabolic dysfunction, medication use, and inflammatory or molecular pathways. These studies also highlight a broad comorbidity burden involving cardiovascular, renal, hepatic, respiratory, infectious, and mortality-related outcomes, supporting a view of gout as part of a broader systemic comorbidity network rather than an isolated joint disease. Mendelian randomization and other genetically informed approaches help distinguish potential causal relationships from observational associations, providing an important evidence base for gout risk stratification, integrated comorbidity assessment, and future prevention-oriented clinical strategies. However, phenotype heterogeneity, selection bias, residual confounding, ancestry imbalance, and limited external validation mean that UK Biobank-based findings should be interpreted cautiously and validated in diverse populations and complementary study designs.

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Authors' contributions

Responsible for drafting and revising the manuscript: Ge L
Provided guidance on the overall conceptual framework and contributed to the critical revision of the manuscript: Qu H
Provided supervision and guidance for the manuscript and the overall research project: Fang X
All authors contributed to the article and approved the submitted version.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (version OpenAI GPT-5.4, released 2026-03-05) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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