Gout and Its Risk Factors: A Review Based on Mendelian Randomization Analysis

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Abstract: Gout and its complications have caused an enormous health and economical burden worldwide. Understanding the underlying risk factors for gout and their causality as well as interactions can provide new insights into prevention and novel therapeutic strategies. Mendelian Randomization (MR) analysis is a research method that uses genetic variants as instruments to estimate the causal effect of a risk factor on an outcome, thereby reducing confounding in observational studies, the usage of such method along with the observational studies can provide valuable information and instruction to further pathophysiology studies and clinical practice. This narrative article aims to summarize the underlying risk factors and totalizing published MR analysis on gout. The systolic blood pressure, pulse pressure in cardiovascular system, body mass index, visceral adipose tissue, high-density lipoprotein, fast insulin in metabolism, tea, coffee in lifestyle, Victivallaceae family and the Ruminococcus gnavus and other 12 taxa of intestinal microbiota has been all proven to be casually associated with the development of gout, and other diseases/trait in these systems were associated with either serum uric acid level or hyperuricemia. Gout/serum uric acid level/hyperuricemia are as well had an impact on considerably diseases. These studies provide useful data and thoughtful insights to better assisting further studies in pathophysiology and clinical practice. Though several approaches have been developed to detect pleiotropy, more new method should be invented and practiced on MR analysis.
***Keywords*:** Causality; Gout; Mendelian Randomization; Review; Risk factor; Hyperuricemia

1. Introduction

Gout has become the most common inflammatory arthritis around the globe, the worldwide prevalence of gout has significantly increased in multiple regions over the past 50 years, and its impact is considerable. Though the recent reports of the prevalence and the occurrence of gout have a large range of vary, most are ranging from a prevalence of range from a prevalence of <1% to 6.8% and an incidence of 0.58–2.89 per 1,000 person-years[1]. Data on the prevalence of gout in developing countries is limited, but it generally appears to be lower in these nations than in more affluent countries[1]. Regional epidemiology studies have been conducted in China. In aresearch conducted in the Shandong province, located in the northern coastal area of China, the adult gout prevalence was estimated to be 1.14%, surpassing estimations for the remainder of China, except for Hong Kong[2]–[4].

The pathology of gout is characterized by the excessive accumulation of serum uric acid, often attributed to a long-term unhealthy diet or metabolic disorders[5]. This elevation in serum uric acid levels can lead to hyperuricemia, typically reported when serum urate is higher or equal to 0·42 mmol/L (7 mg/dL)[6]. Typically, the lower extremities, including the foot, ankle, and knee, are predominantly affected[7]. The deposition of monosodium urate in both articular and non-articular structures subsequently leads to the crystallization of monosodium urate crystals. The formation of these crystals initiates a cascade of immune-mediated inflammatory responses (gout flares) (Figure 2.), which significantly impair the patient's mobility and result in substantial pain[6].

Although the link between exposure factors and gout has been clarified by some studies, while observational studies have shown evidence of potential exposures related to gout and hyperuricemia, our understanding of the complex factors underlying its development is limited by residual confounding and reverse causation, and the use of mendelian randomization (MR) analysis in gout research is relatively limited, highlighting the need for more extensive studies in this area. The MR uses genetic variants as instrumental variables, which are less susceptible to biases that commonly affect observational studies[8]. The use of MR may also provide more robust evidence regarding the causative factors of gout, potentially leading to more targeted treatments and preventive strategies[8]. This narrative article aims to summarize the evidence of on potential risk factorsongout and hyperuricemia and to reflect on future perspectives of MR studies on gout.

2. Causal exposures and risk factors of gout in cardiovascular system

Observational studies have shown associations between gout and hypertension, hypertension and other cardiovascular

diseases are among the most common comorbidities of gout and hyperuricemia[9][10], some have also attempted to explain the association by showing that gout or hyperuricemia is associated with arterial stiffness[11], but whether these are causal remains unclear. An MR analysis discussed systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP), and the IVW analysis implied that SBP-associated SNPs in Europeans had a causal effect on increased serum urate and risk of gout, which was also supported by weighted median analysis[12]. When setting SBP as the outcome, genetically determined serum urate and gout were not associated with SBP, alternatively, IVW MR indicated that PP was causally associated with gout which was agreed by the weighted-median and Bonferroni correction[12]. Another MR analysis has revealed the interactions between gout and the cardiovascular system, by obtaining 88,347 participants and 686,439 single-nucleotide polymorphisms (SNPs) genetic information from the Taiwan immune cells areactivated and release inflammatory cytokines like TNF, IL-1, IL-6, IL-8, and MCP-1. Mast Cell Activation: This leads to the release of histamine, which contributes to inflammation and pain. Complement Activation: The complement system, part of the immune response, becomes activated, leading to further inflammation. Synovial Cell Activation: The cells lining the joints react, which can cause joint pain and swelling characteristic of gout. The arrows indicate the direction of the biochemical and cellular responses.

Biobank, using 4 SNPs associated with gout and 10 SNPs associated with the result, the result indicated a significant positive causal effect of the liability of gout on hypertension, but the causality of hypertension on gout was denied by the MR analysis[13]. This analysis had several limitations–although MR analysis with coarsened exposures can use SNPs with pleiotropic effects to increase the efficiency of estimation, misclassification of pleiotropic SNPs as valid IVs may have introduced biased results, the PhenoScanner database was used to search for possible pleiotropic effects of SNPs, and then the unrelative SNPs was removed in the sample[13], but the final result remained the same. Another MR analysis using SNP data from GWAS has revealed a significantly positive association between genetic liability for hyperuricemia and with cardiovascular diseases (CVD) in both one-sample and two-sample MR analysis[14]. Another analysis draws a conclusion that individuals with hyperuricemia were at increased risk for several types of CVD. Because the MR analysis suggested a causal effect of hyperuricemia, but not gout, on CVD, however, the causality of genetic liability for gout to CVD was negative by the MR analysis[14]. These results suggested the possible effects of other gout-associated factors on the development of CVD[14].

Although the exact mechanisms are not yet fully determined, various potential pathways have been suggested to explain the link between hyperuricemia and a heightened risk of cardiovascular diseases. Elevated serum urate levels could lead to endothelial dysfunction, primarily due to enhanced oxidative stress and inflammation[15]. Moreover, uric acid may promote the proliferation of vascular smooth muscle cells and oxidative stress, potentially via the vascular renin-angiotensin system, which in turn plays a crucial role in the onset of various cardiovascular diseases[16]. Additionally, hyperuricemia is identified as a contributing factor to arteriolar disease in the kidneys by compromising the autoregulatory response, and this impaired autoregulation in cerebral arterioles is closely linked with a heightened risk of stroke[17].

3. Causal exposures and risk factors of gout in nervous system

Although several observational studies have shown that gout is associated with depression symptoms[18], [19], and several previous observational studies have consistently shown lower serum urate levels in people with anxiety and/or depression[20], [21], but MR analysis failed to explain the causal role of anxiety, bipolar disorder, post-traumatic stress disorder, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, schizophrenia, and anorexia nervosa with gout[22], suggested that these observed associations are likely due to confounding or reverse causation. For example, appetite changes seen in depression may alter the intake of purine-rich foods[22]. Genetic proxies for serum UA concentration were related with an increased risk of Alzheimer's Disease (AD), and no reverse causal effects of AD on serum UA levels and gout risk were found[23]. The relation between the nervous system and gout have not been fully studied yet, existing studies have primarily established that the connection between gout and the nervous system occurs through psychiatric pathways. These pathways, influenced by mental status, affect food intake, which in turn impacts serum urate levels.

4. Causal exposures and risk factors of gout in metabolism

With increasing observational studies suggesting the important role that adipokines (cytokines secreted by adipose tissue) play in the attack of gout/hyperuricemia[24], [25], there is a need to discriminate between adipokines features that are causal for disease and those that are a consequence of gout/hyperuricemia. Atwo-sample MR analysis has examined the causality of specific adipokines (like adiponectin (ADP), soluble leptin receptors (sOB-R)), with uric acid (UA)/gout. By extracting summary statistics from large genome-wide association studies, the result showed no causal effect was found

for sOB-R on uric acid (UA), nor was there a causal effect of ADP or sOB-R on gout. This analysis had conclude that these specific adipokines may not play causal roles in UA or gout development[26]. BMI (Body Mass Index), an indicator of health risks associated with obesity and underweight, was also considered to have a causal relation with gout, an MR analysis was performed by analyzing 49 BMI with the risk of 2115 gout cases and 67259 controls, 110347 individuals from the Global Urate Genetics Consortium, the result turned out that genetically higher BMI was positively associated with the risk of gout and serum urate concentrations, each standard deviation (about 4.6 kg/m2) increase in genetically predicted BMI was associated with an odds ratio of gout of 2.24, and with a 0.30 mg/dl increase in serum urate concentrations[27], genetic association of obesity with gout and urate was also investigated in another MR study which agreed with this result, and double-checked by IVW analysis and MR-Egger analysis, but the reverse causal relation was as well done and denied by this analysis[12]. Visceral adipose tissue (VAT) is a type of body fat that's stored within the abdominal cavity, it's located around internal organs such as the liver, pancreas, and intestines. At present, most studies have focused on the association of BMI with the risk of gout[27]–[30], however, little evidence exists investigating the relationships between increased VAT and gout. The causal relationship between VAT and gout had been revealed by a two-sample MR analysis and an observational analysis, which both showed an increase in VAT mass (per standard deviation) was associated with a higher risk of gout. Of note, Sensitivity analyses also performed and showed similar findings, including MR-Egger, weighted median, simple mode, weighted mode, and leave-one-out analyses[31]. Dyslipidemia is often comorbid with gout[32], MR studies have evaluated the causal effect of four lipid traits on gout and serum urate based on publicly available GWAS summary statistics. MR showed that each standard deviation (SD) (~12.26 mg/dL) increase in HDL was associated with an approximately 25% reduction in gout risk, with a 0.09 mg/dL decrease in serum urate, and each SD (~112.33 mg/dL) increase in TG was associated with a 0.10 mg/dL increase in serum urate[33], in the another IVW analysis which the result was consistent, HDL-associated SNPs had a causal effect on decreased serum urate and risk of gout, the result was still deemed suggestive evidence for association between HDL and risk of gout after Bonferroni correction, weighted median and MR-PRESSO analyses performed[12]. MR studies have strengthened the intertwined causal role between the obesity, urate and gout– obesity increased urate and triglycerides, and decreased high-density lipoprotein cholesterol (HDL), higher triglycerides increased urate and higher HDL decreased urate, higher urate and obesity caused gout, the link between obesity and gout, with urate acting as a mediator, suggests that the impact of obesity on gout is entirely channeled through urate levels, and the obesity's impact on urate was exacerbated by its decreasing HDL[34].

Overall, analyses implied that metabolic factors contribute to the development of gout via serum urate, as well as the potential benefit of sound management of increased serum urate in patients with nutrition intake, obesity, dyslipidemia, and liver dysfunction.

5. Causal exposures and risk factors of gout in lifestyle

Lifestyle can greatly affect the development of gout, one of the most significant ways is by beverage intake. An MR analysis found there is no causal association between smoking behavior and gout by MR-Egger analysis, and nor did it supported by weighted median approach. Inverse causal association between smoking behavior and gout was as well none-supported by the analysis[35].

Regarding tea consumption, tea originates from the leaves of the Camellia sinensis plant. It is classified into six primary categories based on the fermentation process of the basic tea leaves, which include green tea, blue tea, black tea, yellow tea, white tea, and dark tea[36]. However, the relationship between specific categories of tea and gout are still lack research. An MR analysis suggested a causal correlation between increased tea intake and a lowered risk of developing gout. Additionally, the analysis found that a low intake of tea was significantly connected to reverse causation of gout. This analysis emphasized the potential benefits of increasing tea consumption as a preventative measure against gout [37].

While the impact of coffee intake on serum uric acid (SUA) levels and the risk of developing gout was disputed. Multivariable MR analysis showed that increased coffee consumption significantly reduced gout risk, and habitual coffee consumption was found to have a significant and inverse association with gout, which may due to the purine-alleviation effect and diuretic action of caffeine. But there was no significance in European database when heterogeneity was considered, and no associations were found between coffee intake and SUA levels in either Japanese and European ancestry when considering pleiotropy in MR analyses[38].

MR studies have been conducted to determine if there is a causal link between alcohol consumption and an increased risk of developing hyperuricemia and gout. It showed that there is no causal relation between genetically predicted drinks consumed per week with risk of gout nor serum uric acid levels, while inverse causation implied a strong association, meaning those with gout are just more likely to consume alcohol more often. So increased alcohol consumption does not

play a causal role in the development of gout[39].

6. Causal exposures and risk factors of gout in intestinal microbiota

With an increasing number of studies showing the cross-talk between intestinal microbiota and gout[40]–[42], it is necessary to discern the relationship between intestinal microbiota characteristics and gout or serum urate (SUA) levels. An MR analysis extracted summary statistics from MiBioGen, Global Biobank Meta-analysis Initiative, CKDGen, and Global Urate Genetics Consortium indicated that Victivallaceae family and the Ruminococcus gnavus had a common causal effect on both gout and urate, and six taxa were commonly affected by both gout and urate, specifically, both gout and urate level commonly had a positive causal effect on the Lachnoclostridium genus and Ruminococcus gnavus group genus, while gout and urate level commonly had a negative causal effect on Coriobacteriia class, Coriobacteriales order, Coriobacteriaceae family, and Lachnospiraceae FCS020 group genus which the causality of which was proved has associated with SUA by another study[43]. Mediation analysis revealed that the Bifidobacteriales order and Bifidobacteriaceae family exerted protective effects on urate levels by increasing docosahexaenoic acid[43]. It can be generally conducted that the causal association between gut microbiota and host urate metabolism is bidirectional[43]. Changes in the gut microbiota not only facilitate the improvement of host urate metabolism but also serve as an indicator of urate metabolic diseases[43]. Another two-sample MR analysis using 196 GM taxa from five levels has identified 5 taxa (Actinobacteria, Family XIII Escherichia Shigella, Lachnospiraceae FCS020 group, Lachnospiraceae NC2004 group) associated with SUA levels and 10 taxa (Actinobacteria, Betaproteobacteria, Melainabacteria, Actinomycetales, Gastranaerophilales, Burkholderiales, Porphyromonadaceae, Actinomycetaceae, RuminococcaceaeUCG011, Anaerotruncus) associated with gout, while in inverse MR implicated that gout affected the composition of five GM taxa, and SUA levels influenced the composition of 30 GM taxa. The study revealed a potential negative loop between phylum Actinobacteria and SUA levels which connects to gout. Additionally, it proposed two new associations between GM taxa (genus Faecalibacterium and genus Prevotella9), SUA levels, and gout[44].

7. Causal exposures and risk factors of gout in respiratory system

There is a paucity of data on outcomes for people with gout and COVID-19. Many observational studies between COVID-19 and gout have been done but few MR studies have been performed[45]. Observational studies suggested that gout was associated with the diagnosis of COVID-19, but not with the risk of COVID-19-related death in the cohort of patients diagnosed with COVID-19. A study conducted by Patel et al. examines the clinical epidemiology of COVID-19-associated acute kidney injury (AKI) across the New York Regional Health system, encompassing cases from intensive care units (ICUs) of patients with severe COVID-19 pneumonia necessitating ventilator support. It is important to note that these findings from the study provide objective and informative information, without subjective evaluations. The analysis revealed rapid increases in serum urea nitrogen (SUN) and serum creatinine levels in all patients, and significant increases in uric acid, phosphorus, and potassium levels, as well as lactic acid-negative ion gap and metabolic acidosis. Furthermore, serum albumin levels showed a rapid drop[46]. Two cohort studies conducted with the Health Improvement Network in the United Kingdom estimated the differences in SARS-CoV-2 infection rates (RD) and hazard ratio (HR) and severe outcomes between patients with and without gout who were vaccinated against SARS-CoV-2 using Cox proportional risk models. 54,576 individuals with gout and 1,336,377 without gout were included in the studies. The results indicated 1,955 infections amongst those with gout and 52,468 infections amongst those without. In addition, gout was associated with an increased risk of hospitalization and death[46][47]. Women with gout are at a heightened risk of hospitalization and mortality. A similar correlation between gout and these outcomes was observed in the unvaccinated cohort. Therefore, appropriate measures must be taken to minimize the associated risks. These findings imply that gout patients, particularly women, maintain an increased susceptibility to SARS-CoV-2 infection and more serious complications even after receiving vaccination.

An MR analysis of individuals with gout shows they had a 4.6% higher risk of developing severe COVID-19. Although gout patients also showed a trend towards higher SARS-CoV-2 infection and hospitalization rates, this association was not statistically significant[48]. A single MR analysis demonstrated that rs141982039 and rs75674432 were independently linked to a greater likelihood of SARS-CoV-2 infection and critically ill COVID-19 in gout patients, respectively. Meanwhile, the reciprocal influences between COVID-19 and gout lacked evidence[48].

The observed affirmative correlation between gout and severe COVID-19 in the current study necessitates further validation in larger datasets, and future research is required to investigate the underlying mechanisms. Ultimately, the investigation determined gout as a genetically linked risk factor for severe COVID-19[48].

8. Assessment of included MR studies and future perspective

The overall quality of all the MR studies that this article mentioned was satisfactory, the selection of genetic instrument was careful and covered relatively large sample, with rigorous protocol to operate through the process of data handling, including a strict and variable, reasonable approach to testing the robustness of the result. Assumption 1 was strictly obeyed by setting P value less than 0.05, which was typically found to be satisfied by using genetic data associated with the exposure factors that selected in the genome-wide significant. By the usage of PhenoScanner, the assumption 2 was strictly obeyed, the independence from other confounding was proved. Due to the horizontal pleiotropy, the most common error in assumption 3, the usage of MR-Egger and MR- PRESSO can detect such pleiotropy. It is worth-noticing that such bias can only be minimized but cannot be fully prevented, only through carefully choosing instrumental variables that were fully understood of biological functions can generate more precise and correct outcomes. Robustness testing in MR studies is crucial to ensure that the results are reliable and not driven by confounding factors or other biases, which were usually conducted by performing a leave-one-out analysis where the MR analysis is repeated multiple times, each time omitting one genetic variant in the studies that this article mentioned. This helps to identify if any single variant is driving the results. Of note, MR studies result is usually hard to interpret, exposures were proxied by genetic variant, so the effect of chronic factors are easy to be neglected, more observational studies and clinical experiment should be conducted to explain the MR result.

The association between the SNPs and the exposure factors are not strong enough, developing more sophisticated methods for selecting and validating genetic tools to ensure they are robust and specific to the exposure of interest is crucial.

MR studies are linear association-friendly, but none-linear association (S-shaped, U-shaped, J-shaped) was not allowed in the analyses which might need to be individually checked in a larger scale of database.

While MR provides a powerful approach for understanding the genetic basis of diseases and traits, it is not universally applicable across all types of exposures such as those traits that without an association with the genetic information, and none-heritable traits, requiring careful consideration of the nature of the exposure being studied.

Several studies this article mentioned have done an inverse MR which flips the direction of investigation in atypical MR analysis, which generally discusses how urate acid/hyperuricemia/gout had an impact on other diseases. Of note, if the genetic variants used as instruments for the outcome have a weak association with the outcome itself, it can lead to biased estimates of the effect of the outcome on the exposure. Inverse MR often assumes linear relationships between the genetic instruments, the outcome, and the exposure. Non-linear relationships can lead to misinterpretation of the results as well.

Pleiotropy occurs when a genetic variant influences more than one trait. This can be problematic in MR studies because the genetic variants used as instruments for exposure are assumed to influence the outcome only through that exposure, not through other pathways. Though many approaches can be used to detect pleiotropy, a new statistical approach should be developed to overcome this issue.

9. Conclusion

This narrative review has integrated data from previously published MR studies, including the effect of various diseases of different systems on hyperuricemia/gout, and has highlighted some that have a casual effect. Reverse causality was also considered and discussed in some studies. Most MR studies have supported the cardiovascular diseases, metabolic diseases, respiratory diseases, intestinal microbiota, mental disorders and lifestyle factors that are casually associated with hyperuricemia/gout. However, some fields still lack research; for instance, the causal relationship between the nervous system and gout, as explored through Mendelian Randomization (MR) analysis, requires further investigation. These findings may help the further studies to illustrate the pathological molecular basis of gout.

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Competing Interests

All authors declare no conflicts of interest.

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