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Gout Does Not Causally Increase the Risk of Endometrial Cancer: Evidence from Mendelian Randomization

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ABSTRACT

Background: Gout is a prevalent condition associated with chronic inflammation and metabolic dysregulation, both of which are known risk factors for various malignancies. However, the potential causal relationship between gout and endometrial cancer has not been systematically explored. Methods: A two-sample Mendelian randomization (MR) analysis was conducted using genome-wide association study (GWAS) summary statistics to evaluate the potential causal effect of genetically predicted gout on the risk of endometrial cancer. Genetic variants strongly associated with gout were selected as instrumental variables. The inverse variance weighted (IVW) method was used for the primary analysis, supplemented by MR-Egger and weighted median approaches. Sensitivity analyses included tests for pleiotropy, heterogeneity, and leave-one-out stability. Results: The MR analysis revealed no significant causal effect of gout on the risk of developing endometrial cancer (IVW OR = 1.015, 95% CI: 0.957–1.077, P = 0.614). Sensitivity analyses indicated no evidence of pleiotropy or heterogeneity, and the leave-one-out analysis confirmed the robustness of the results. Conclusion: This MR analysis found no evidence supporting a causal effect of gout on the risk of endometrial cancer. These results suggest that genetic predisposition to gout does not significantly influence the likelihood of developing endometrial cancer. Further studies in diverse populations are needed to confirm these findings and explore potential shared mechanisms linking metabolic disorders to cancer development.

KEYWORDS

Genetic variants; Gout; Endometrial cancer; Risk factors

1. INTRODUCTION

Gout is a chronic metabolic disorder characterized by the deposition of monosodium urate crystals in joints and soft tissues due to sustained hyperuricemia. It is recognized as the most prevalent form of inflammatory arthritis in adults and is strongly associated with components of metabolic syndrome, including hypertension, insulin resistance, obesity, and dyslipidemia. The clinical manifestations of gout range from acute, intensely painful flares to chronic tophaceous arthritis and renal complications. Beyond its musculoskeletal sequelae, accumulating evidence suggests that gout contributes to systemic inflammation and oxidative stress, both of which are known to influence the pathophysiology of various chronic diseases [1-3]. These systemic effects of gout may extend its impact beyond traditional boundaries and prompt consideration of its role in the etiology of diseases such as malignancies.

Endometrial cancer, one of the most common gynecologic malignancies in developed nations, arises from the epithelial lining of the uterine corpus and is closely associated with unopposed estrogen

exposure, obesity, insulin resistance, and chronic low-grade inflammation. Its incidence has shown a rising trend in parallel with the increasing global prevalence of metabolic disorders, suggesting a possible metabolic etiology. While early-stage endometrial cancer is often detected due to symptomatic presentation, advanced or recurrent disease remains a clinical challenge with significant morbidity and mortality. Moreover, the potential interplay between systemic metabolic dysregulation and endometrial carcinogenesis continues to attract scientific attention [4, 5].

In recent years, the association between gout and cancer risk has emerged as a topic of considerable epidemiologic and clinical interest. Several large-scale cohort studies and meta-analyses have explored whether the chronic inflammatory and metabolic milieu associated with gout may predispose individuals to cancer development. Notably, population-based studies from diverse regions have reported a modest but statistically significant increase in overall cancer incidence among individuals with gout compared to matched controls. These associations have been particularly evident for certain site-specific cancers, such as those of the liver, lung, bladder, and gastrointestinal tract [6-8]. However, while the evidence suggests a potential biological link, the causal direction remains unclear. Existing studies predominantly rely on observational designs, which are inherently vulnerable to residual confounding, reverse causation, and surveillance bias. Furthermore, despite the growing body of literature exploring gout and cancer in general, limited attention has been given to the potential relationship between gout and endometrial cancer specifically. As such, the question of whether gout represents an independent risk factor for endometrial cancer remains unresolved and warrants further investigation using more robust causal inference approaches.

Mendelian randomization (MR) provides an approach to strengthen causal inference by leveraging genetic variants as instrumental proxies for modifiable exposures. Owing to the random assortment of alleles at meiosis, MR mitigates the influence of confounding and eliminates the risk of reverse causality, thereby complementing conventional observational epidemiology [9,10]. In the present study, we employ a two-sample MR framework to investigate the potential causal association between gout and endometrial cancer by integrating summary-level data from genome-wide association studies. By using genetic instruments for gout and evaluating their effects on endometrial cancer risk in an independent dataset, this analysis seeks to determine whether the observed associations may reflect a direct etiological link rather than shared risk factors or biases inherent in traditional study designs. This approach may provide novel insights into the metabolic and inflammatory pathways involved in endometrial carcinogenesis and inform future preventative or therapeutic strategies.

2. MATERIAL AND METHODS

2.1. Summary statistics data for gout and endometrial cancer

The summary-level genome-wide association study (GWAS) data for gout and endometrial cancer were obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/).

The gout dataset (finn-b-M13_GOUT) comprised 3,576 cases and 147,221 controls of European ancestry, with a total of 16,380,152 single-nucleotide polymorphisms (SNPs). The endometrial cancer dataset (ebi-a-GCST006464) included 12,906 cases and 108,979 controls, also of European ancestry, with 9,470,555 SNPs. These datasets were derived from independent samples, thereby minimizing the potential for sample overlap and enhancing the validity of the MR analysis.

2.2. Selection of instrumental variables

In accordance with the core principles of Mendelian randomization, we initially selected SNPs that were strongly associated with gout at genome-wide significance, p less than 5×10^{-8}. To ensure independence between instruments, linkage disequilibrium clumping was applied using an r^2

threshold below 0.001 and a 10,000-kilobase window [11, 12]. The strength of each instrument was assessed using the F-statistic, calculated as $F = \left(\frac{n-1-k}{k}\right) \times \frac{R^2}{1-R^2}$), where n is the total sample size, k is the number of variants, and R^2 denotes the proportion of variance in gout explained by the instruments. The overall F-statistic calculated for the instrumental SNPs exceeded the conventional threshold of 10, indicating sufficient collective strength to minimize the risk of weak instrument bias [13].

2.3. Two-sample Mendelian randomization analysis

A two-sample MR analysis was conducted to explore the potential causal effect of gout on the risk of endometrial cancer. The inverse variance weighted (IVW) method served as the primary analytical approach to estimate odds ratios (ORs) along with 95% confidence intervals (CIs). To assess the consistency and reliability of the findings, additional MR methods were employed, including MR-Egger regression and the weighted median estimator [14, 15]. The objective was to evaluate whether inherited susceptibility to gout causally influences endometrial cancer risk.

2.4. Statistical methods

To evaluate the robustness of the causal estimates between gout and endometrial cancer, multiple sensitivity analyses were conducted. The MR-Egger intercept test and the MR-PRESSO global test were employed to detect potential horizontal pleiotropy, with P-values greater than 0.05 indicating no evidence of directional bias. Instrument heterogeneity was assessed using Cochran's Q statistic, where P-values greater than 0.05 were interpreted as evidence of no substantial heterogeneity among the selected variants [16, 17]. In addition, a leave-one-out analysis was carried out to examine whether any individual SNP exerted an excessive influence on the overall causal inference. All analyses were performed using the TwoSampleMR package in R.

3. RESULTS

The MR analysis suggested that genetic predisposition to gout does not increase the risk of endometrial cancer, as indicated by the inverse variance weighted estimate (IVW OR = 1.015, 95% CI: 0.957–1.077, P = 0.614) (Figure 1). The distribution of SNP-specific associations is illustrated in the scatter plot (Figure 2).

Exposure	Outcome	nSNP	F−statistics	Method	b	OR (95% CI)	P−value
Gout	Endometrial cancer	6	94.045	Inverse variance weighted	0.015	1.015 (0.957 to 1.077)	0.614
				Weighted median	0.030	1.031 (0.975 to 1.090)	0.284
				MR Egger	0.087	1.090 (0.986 to 1.206)	0.169

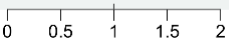

Figure 1. MR estimates of gout on the risk of endometrial cancer

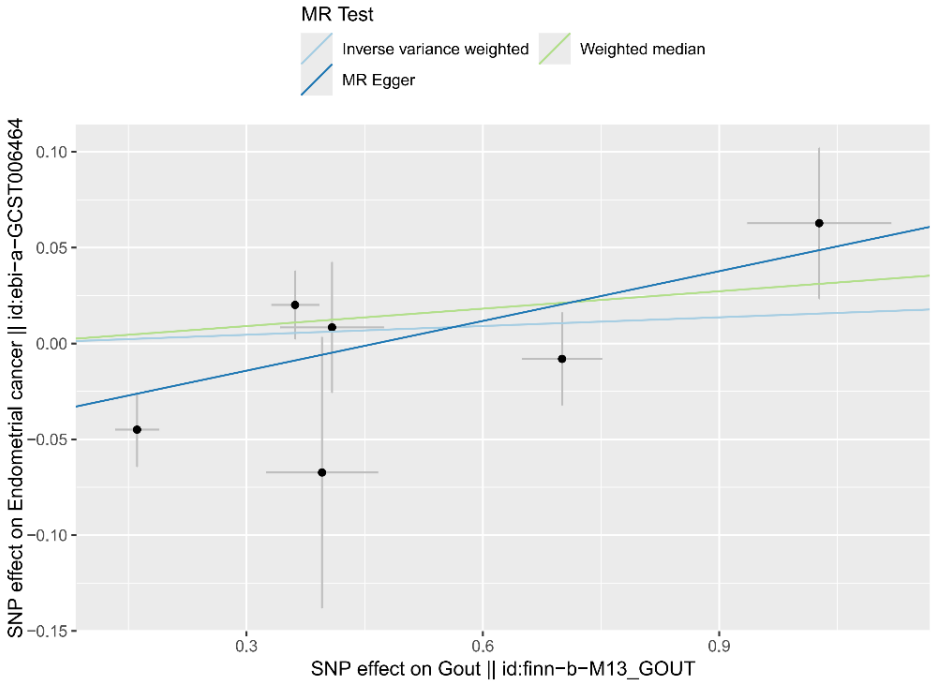

Figure 2. MR scatter plot of the causal effect of gout on endometrial cancer

Sensitivity analyses indicated no notable heterogeneity among the instrumental variables, as suggested by Cochran's Q test (P = 0.079). Additionally, neither the MR-Egger intercept (P = 0.183) nor the MR-PRESSO global test (P = 0.183) provided evidence for horizontal pleiotropy, supporting the validity of the instrumental assumptions.

The leave-one-out analysis revealed that no single SNP had a disproportionate influence on the overall causal estimate, indicating that the results were not driven by any individual instrumental variable. This finding further supports the robustness of the association. The detailed leave-one-out results are presented in Figure 3.

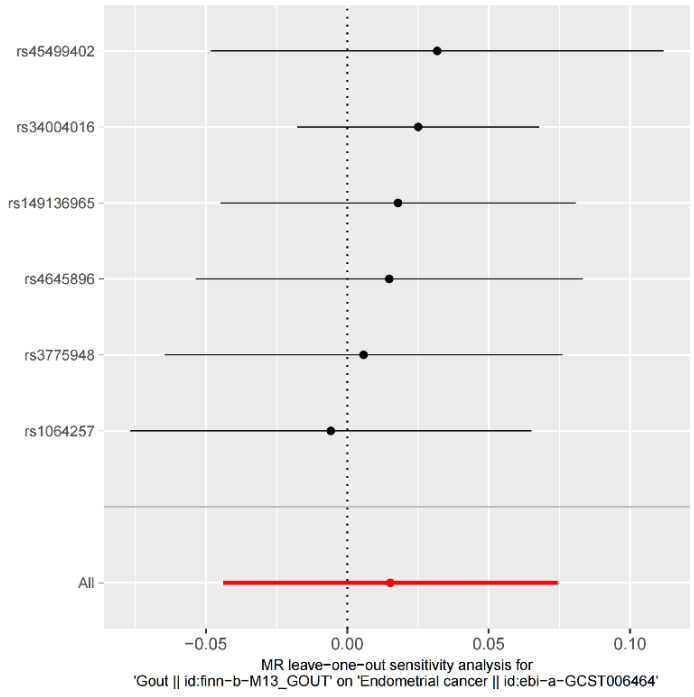

Figure 3. Leave-one-out analysis of the causal effect of gout on endometrial cancer

4. DISCUSSION

In this MR study grounded in genetic evidence, we found no indication that a higher genetic predisposition to gout causally increases the risk of endometrial cancer. The results do not support a positive or risk-promoting relationship between the two conditions, suggesting that gout is unlikely to act as a genetic driver of endometrial carcinogenesis.

Gout is a chronic systemic condition typically associated with prolonged hyperuricemia, often characterized by the deposition of monosodium urate crystals in joints and soft tissues. It is frequently considered a clinical manifestation of metabolic dysregulation and chronic low-grade inflammation and has been observed to co-occur with comorbidities such as obesity, insulin resistance, renal dysfunction, and cardiovascular conditions [18]. In addition to its musculoskeletal manifestations, gout has been speculatively associated with an increased likelihood of developing certain malignancies in some observational contexts, though the underlying nature and consistency of these associations remain uncertain and require further investigation [19]. Endometrial cancer continues to pose a growing public health challenge, with rising incidence trends observed in many regions worldwide. While traditionally considered a hormonally driven malignancy, accumulating evidence suggests that its pathogenesis may be influenced by a broader constellation of factors, particularly those related to metabolic health. Alterations in glucose metabolism, insulin signaling, and chronic low-grade inflammation have been increasingly recognized as relevant components of its biological landscape [20, 21]. Rather than acting in isolation, these metabolic disturbances may interact with hormonal pathways to shape a permissive environment for tumor initiation and progression, highlighting the multifactorial and systemically influenced nature of endometrial carcinogenesis.

The absence of a causal association between genetically predicted gout and endometrial cancer observed in this study may be explained by several underlying biological mechanisms. Although gout is characterized by chronic systemic inflammation and metabolic disturbances, these alterations may not directly influence the endometrial microenvironment in a manner sufficient to initiate or promote malignant transformation. The inflammatory responses associated with gout are largely driven by monosodium urate crystal deposition and activation of innate immune pathways, particularly within joint and periarticular tissues, which may have limited relevance to endometrial epithelial cells. Additionally, the pathogenesis of endometrial cancer is strongly influenced by estrogen exposure, insulin resistance, and adipokine signaling—factors that, although partially overlapping with pathways related to gout, are likely to play dominant roles in tumor development independent of gout-specific mechanisms.

Despite several strengths, this study also has limitations. First, MR analyses rely on core assumptions, and residual pleiotropy cannot be completely excluded. Second, the genetic instruments for gout were derived from GWAS summary data and may not fully reflect clinical heterogeneity such as acute versus chronic forms or asymptomatic hyperuricemia. Third, the endometrial cancer dataset was restricted to individuals of European ancestry, which may limit generalizability. Finally, although large-scale GWAS data were used, the number of instrumental variants available for gout was relatively limited, which may restrict the precision of effect estimates.

5. CONCLUSION

From a genetic perspective, this MR study revealed no evidence that gout contributes causally to the development of endometrial cancer. Further investigations in larger and more diverse populations, integrating genetic, clinical, and mechanistic data, are needed to validate and extend these findings.

DATA SHARING STATEMENT

The analyses were performed using publicly available datasets. Key methodological details and findings are provided in the main text, with additional information available from the corresponding author upon request.

ETHICS APPROVAL

As all data used in this study were obtained from open-access repositories, additional ethical approval and informed consent were not required.

FUNDING

No funding was received for conducting this study.

DISCLOSURE

The authors report no conflicts of interest in this work.

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