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Gout drives metabolic dysfunction-associated steatotic liver disease through gut microbiota and inflammatory mediators

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This study explores the relationship between gout and metabolic dysfunction-associated steatotic liver disease (MASLD), two metabolic conditions linked to worsening health outcomes. While hyperuricemia's association with MASLD is established, the specific connection between gout and MASLD remains less explored. Using data from the UK Biobank, the study employs COX proportional hazard models, multi-state survival analysis, and Mendelian randomization to assess the independent and mutual risks of gout and MASLD. Findings indicate a mutual risk increase: male gout patients, those younger than 60, and those with high BMI are particularly susceptible to MASLD, while female MASLD patients are at heightened risk for gout. Shared risk factors for both conditions include high BMI, hypertension, diabetes, and hyperuricemia. The study further identifies a bidirectional causal link, with gout leading to MASLD, mediated by gut microbiota *Ruminococcaceae* and proteins like IL-2 and GDF11, implicating specific metabolic pathways. The findings highlight a clinical and mechanistic correlation, emphasizing the need for targeted interventions to address these overlapping metabolic pathways in future treatments.

Keywords Gout, MASLD, Hyperuricemia, Multi-state survival model, Mendelian randomization

In recent years, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and gout has significantly increased due to the global rise in obesity and metabolic syndrome[1,2]. These two conditions not only share common pathophysiological mechanisms but also frequently co-occur in clinical presentations[3,4]. Investigating the correlation between gout and MASLD is of significance importance for elucidating their shared pathological mechanisms, guiding clinical diagnosis and treatment, and formulating comprehensive therapeutic strategies. MASLD is a form of steatotic liver disease (SLD) characterized by the presence of at least one cardiovascular metabolic risk factor, such as overweight or obesity, type 2 diabetes, hypertriglyceridemia, hypertension, etc., in the absence of excessive alcohol consumption[5,6]. It affects approximately 30% of the adult population worldwide[2,7] and is the most common cause of chronic liver disease[8]. The pathogenesis of MASLD is complex and closely associated with factors such as lipid metabolism disorders, insulin resistance, oxidative stress, gut microbiota dysbiosis, inflammation, and immune responses[5,9,10]. Due to its complex pathogenesis, there are currently no highly effective treatment options available. Gout is a crystal-associated arthropathy, primarily caused by hyperuricemia leading to monosodium urate (MSU) crystal deposition in joints and other tissues[11]. It commonly manifests as acute arthritis flares, tophi, uric acid nephrolithiasis, and renal impairment, and is frequently associated with metabolic disorders such as hypertension, obesity, and type 2 diabetes[12–14]. Uric acid, a potent antioxidant and pro-inflammatory mediator, is significantly associated with various metabolic diseases, including gout and MASLD. Numerous studies have confirmed a significant correlation between serum uric acid (SUA) levels and both the prevalence and severity of MASLD[15–17]. Hyperuricemia is a critical step in the development of gout[1,18]. Excess uric acid promotes the formation and deposition of MSU crystals, activates the NLRP3 inflammasome, and induces the production of the pro-inflammatory cytokine IL-1β, leading to gout flares[19,20]. Although the association between MASLD and hyperuricemia has been extensively studied[21–25], research on its relationship with gout remains relatively limited. A cross-sectional study has shown that there is an independent association between gout and the risk of MASLD, and that there is a dose–response relationship

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between SUA levels and the occurrence of MASLD[26]. Si et al.[27] also confirmed the increased risk of MASLD in patients with frequent gout attacks in a retrospective cohort study. Moreover, the potential therapeutic effects of febuxostat on MASLD further underscore the relationship between the two conditions[25,28]. Although the above studies have confirmed the association between gout and MASLD, they have certain limitations, including relatively small sample sizes, information bias, and a low level of evidence in terms of evidence-based medicine. Moreover, there are currently no studies on the occurrence of gout in patients with MASLD. Therefore, based on the aforementioned background, this study utilizes a large biobank and summary data from genome-wide association studies to comprehensively investigate the association between gout and MASLD from both clinical and mechanistic perspectives. The study aims to clarify the independent and mutual risk of developing these two conditions under various risk factors, as well as to explore the potential mechanisms underlying their interrelationship. On the one hand, it assists clinicians in more accurately assessing patient risk and formulating screening and preventive measures for high-risk populations; On the other hand, if a correlation between the two is confirmed, treatment strategies for patients could be optimized. For instance, uric acid-lowering therapy (such as allopurinol or febuxostat) could become a potential strategy for treating MASLD, thereby contributing to comprehensive patient management and improving treatment outcomes. Furthermore, understanding the molecular mechanisms between the two conditions could provide potential targets for the development of new drugs. For example, combined therapeutic agents targeting uric acid metabolism and MASLD could hold significant clinical importance.

Results

Baseline characteristics

As shown in Fig. 1, out of the 502,411 participants recruited, 8483 were excluded, resulting in a final cohort of 493,928 participants, with a median follow-up time of 13.1 years. As is shown in Table 1, among 9665 participants diagnosed with gout, 476 cases (4.9%) were recorded in the 6213 participants with MASLD at baseline. Compared to patients without gout, those with gout were more likely to be male ($P<0.001$), had a higher mean age of 60.6 years ($P<0.001$), higher TDI index ($P<0.001$), higher BMI ($P<0.001$), and higher Blood uric acid level ($P<0.001$), with significant racial differences ($P<0.05$). Participants with a history of smoking, past or current alcohol consumption, diabetes, hypertension, hypertriglyceridemia, hyperuricemia, and MASLD were at a higher risk of developing gout compared to those without gout ($P<0.001$). Among the 6213 participants diagnosed with MASLD, the incidence of MASLD in the 9665 participants with gout at baseline was 7.7%. Compared to patients without MASLD, those with MASLD were more likely to be female ($P<0.005$), had a mean age of 57 years ($P<0.001$), higher TDI index ($P<0.001$), and higher BMI ($P<0.001$), with significant racial differences ($P<0.01$). Compared to the control group, the MASLD group had a significantly higher proportion of subjects with a history of or current smoking, never or past alcohol consumption, diabetes, hypertension, hypertriglyceridemia, and hyperuricemia ($P<0.001$).

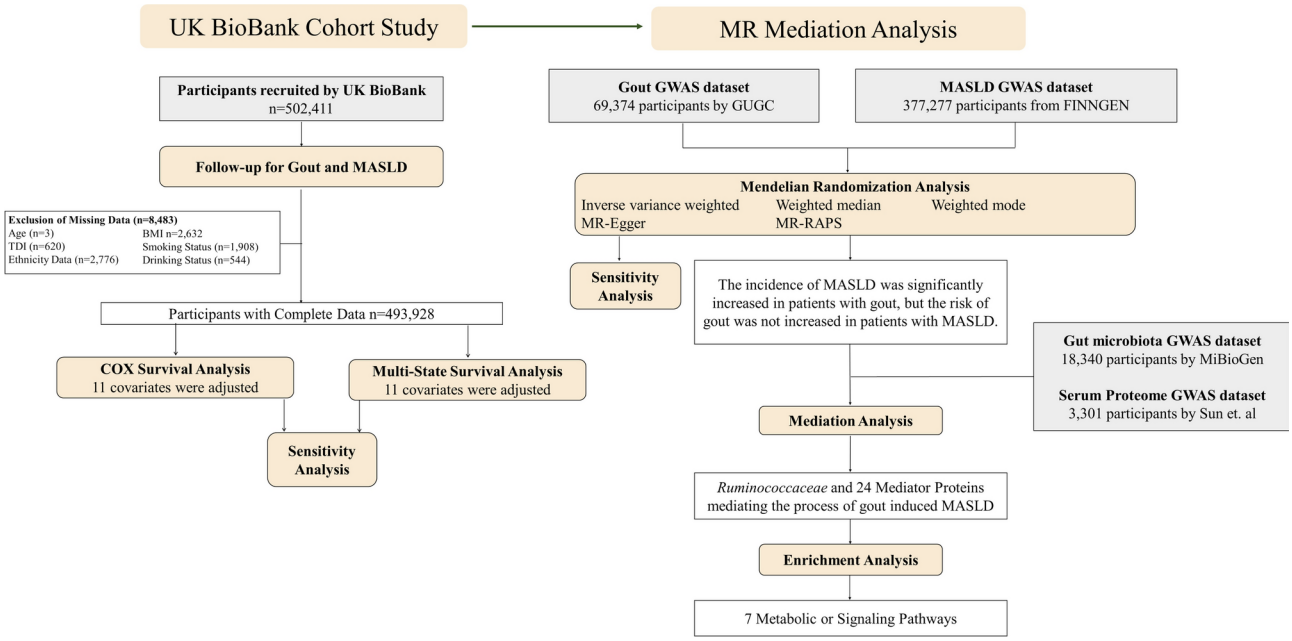

Fig. 1. Flowchart of the study. MASLD: Metabolic dysfunction-associated fatty liver disease, BMI: body mass index, TDI: Townsend deprivation index, MR: Mendelian randomization, GWAS: genome-wide association study.

Characteristic	All (N = 493,928)	Gout		P	MASLD		P
		No (N = 484,263)	Yes (N = 9665)		No (N = 487,715)	Yes (N = 6213)	
Sex, N (%)				< 0.001			0.001
Female	269,202 (55%)	267,627 (55%)	1575 (16%)		265,943 (55%)	3259 (52%)	
Male	224,726 (45%)	216,636 (45%)	8090 (84%)		221,772 (45%)	2954 (48%)	
Age, mean (SD)	56.5 (8.1)	56.4 (8.1)	60.6 (6.8)	< 0.001	56.5 (8.1)	57.0 (7.8)	< 0.001
Ethnic, N (%)				0.030			< 0.001
White	467,879 (95%)	458,727 (95%)	9152 (95%)		462,076 (95%)	5803 (93%)	
Mixed	2909 (0.6%)	2861 (0.6%)	48 (0.5%)		2870 (0.6%)	39 (0.6%)	
Asian or Asian British	9419 (1.9%)	9203 (1.9%)	216 (2.2%)		9257 (1.9%)	162 (2.6%)	
Black or Black British	7793 (1.6%)	7636 (1.6%)	157 (1.6%)		7688 (1.6%)	105 (1.7%)	
Chinese	1541 (0.3%)	1519 (0.3%)	22 (0.2%)		1524 (0.3%)	17 (0.3%)	
Other ethnic group	4387 (0.9%)	4317 (0.9%)	70 (0.7%)		4300 (0.9%)	87 (1.4%)	
TDI, mean (SD)	− 1.3 (3.1)	− 1.3 (3.1)	− 0.9 (3.2)	< 0.001	− 1.3 (3.1)	− 0.3 (3.5)	< 0.001
Smoking status, N (%)				< 0.001			< 0.001
Never	270,562 (55%)	266,620 (55%)	3942 (41%)		267,760 (55%)	2802 (45%)	
Previous	171,322 (35%)	166,550 (34%)	4772 (49%)		168,846 (35%)	2476 (40%)	
Current	52,044 (11%)	51,093 (11%)	951 (9.8%)		51,109 (10%)	935 (15%)	
Drinking status, N (%)				< 0.001			< 0.001
Never	21,714 (4.4%)	21,404 (4.4%)	310 (3.2%)		21,295 (4.4%)	419 (6.7%)	
Previous	17,641 (3.6%)	17,254 (3.6%)	387 (4.0%)		17,185 (3.5%)	456 (7.3%)	
Current	454,573 (92%)	445,605 (92%)	8968 (93%)		449,235 (92%)	5338 (86%)	
BMI, kg/m^2, mean (SD)	27.4 (4.8)	27.4 (4.8)	30.6 (5.1)	< 0.001	27.4 (4.8)	31.3 (5.7)	< 0.001
Blood uric acid level, μmol/L, mean (SD)	309.1 (80.4)	307.0 (78.4)	415.1 (101.8)	< 0.001	308.7 (80.2)	343.0 (84.3)	< 0.001
Diabetes Mellitus, N (%)	39,582 (8.0%)	37,033 (7.6%)	2549 (26%)	< 0.001	37,299 (7.6%)	2283 (37%)	< 0.001
Hypertension, N (%)	147,650 (30%)	140,413 (29%)	7237 (75%)	< 0.001	143,550 (29%)	4100 (66%)	< 0.001
Hypercholesteremia, N (%)	145,875 (32%)	143,900 (32%)	1975 (22%)	< 0.001	144,282 (32%)	1593 (28%)	< 0.001
Hypertriglyceridemia, N (%)	98,403 (21%)	94,608 (21%)	3795 (42%)	< 0.001	96,204 (21%)	2199 (38%)	< 0.001
Hyperuricemia, N (%)	42,500 (9.2%)	37,831 (8.3%)	4669 (52%)	< 0.001	41,505 (9.1%)	995 (17%)	< 0.001
MASLD, N (%)	6213 (1.3%)	5737 (1.2%)	476 (4.9%)	< 0.001	9189 (1.9%)	476 (7.7%)	< 0.001

Table 1. Baseline characteristics. BMI: Body mass index; TDI: Townsend deprivation index, MASLD: Metabolic dysfunction-associated steatotic liver disease.

Investigation of the interaction between gout and MASLD using a COX regression model

In Table 2, a fully adjusted Cox regression model revealed an association between gout and the incidence of MASLD. Specifically, individuals with gout exhibited a 1.261-fold increased risk of developing MASLD compared to non-gout participants (95% CI 1.123–1.416, $P < 0.001$). However, MASLD was not found to independently increase the risk of gout (HR 95% CI 1.063 [0.936–1.207], $P = 0.344$). Further stratified analysis revealed significant differences in the risk of MASLD among gout patients based on age, gender, and BMI: We found that male patients (HR 1.360, 95% CI 1.191–1.554, $P < 0.001$),those under 60 years of age (HR 1.461, 95% CI 1.235–1.727, $P < 0.001$),and patients with a BMI ≥ 30 kg/m^2 (HR 1.281, 95% CI 1.128–1.455, $P < 0.001$) had a significantly increased risk of developing MASLD. The risk of gout was also notably higher in female MASLD patients (HR 1.423, 95% CI 1.130–1.790, $P = 0.003$). In the stratified analysis of metabolic factors, both the risk of MASLD associated with gout and the risk of gout associated with MASLD were significantly present in participants with hypertension, diabetes, and abdominal obesity (Table 3).

Analysis of risk factors for gout and MASLD using a multistate survival model

A multistate survival model was applied to further investigate the risk factors associated with the incidence of these two diseases, as illustrated in Fig. 2. We identified that elevated BMI (HR 1.043, 95% CI 1.037–1.047, $P < 0.001$), hypertension (HR 3.356, 95% CI 3.174–3.556, $P < 0.001$), diabetes (HR 1.241, 95% CI 1.172–1.315, $P < 0.001$), hypercholesterolemia (HR 0.894, 95% CI 0.846–0.946, $P < 0.001$), hypertriglyceridemia (HR 1.381, 95% CI 1.316–1.449, $P < 0.001$), and hyperuricemia (HR 5.464, 95% CI 5.212–5.752, $P < 0.001$) are risk factors for the development of gout. Additionally, increased BMI (HR 1.062, 95% CI 1.057–1.067, $P < 0.001$), hypertension (HR 2.899, 95% CI 2.704–3.105, $P < 0.001$), diabetes (HR 2.915, 95% CI 2.720–3.130, $P < 0.001$), hypercholesterolemia (HR 1.089, 95% CI 1.021–1.163, $P = 0.010$), hypertriglyceridemia (HR 1.439, 95% CI 1.353–1.533, $P < 0.001$), and hyperuricemia (HR 1.093, 95% CI 1.005–1.189, $P < 0.001$) were also identified as risk factors for the development of MASLD. High BMI (HR 1.033, 95% CI 1.003–1.064, $P < 0.001$), hypertension (HR 2.375, 95% CI 1.402–4.016, $P = 0.001$), and diabetes (HR 2.320, 95% CI 1.636–3.286, $P < 0.001$) increased the risk of developing MASLD in patients with gout. High BMI (HR 1.042, 95% CI 1.006–1.079, $P = 0.021$), diabetes (HR 1.536, 95% CI 1.014–

Characteristics	Gout → MASLD		MASLD → Gout		Model
	HR (95% CI)	*P*	HR (95% CI)	*P*	
Total					
	2.840 (2.537–3.179)	< 0.001	2.168 (1.915–2.455)	< 0.001	Model 1
	2.614 (2.330–2.933)	< 0.001	2.057 (1.814–2.332)	< 0.001	Model 2
	1.261 (1.123–1.416)	< 0.001	1.063 (0.936–1.207)	0.344	Model 3
Sex (%)					
Male	2.660 (2.339–3.025)	< 0.001	1.757 (1.512–2.041)	< 0.001	Model 1
	2.531 (2.220–2.886)	< 0.001	1.687 (1.449–1.964)	< 0.001	Model 2
	1.360 (1.191–1.554)	< 0.001	0.932 (0.799–1.086)	0.367	Model 3
Female	3.810 (3.017–4.812)	< 0.001	4.281 (3.423–5.355)	< 0.001	Model 1
	3.074 (2.420–3.903)	< 0.001	3.663 (2.920–4.596)	< 0.001	Model 2
	1.092 (0.858–1.390)	0.476	1.423 (1.130–1.790)	0.003	Model 3
Age (year)					
< 60	3.811 (3.237–4.486)	< 0.001	2.620 (2.163–3.175)	< 0.001	Model 1
	3.526 (2.987–4.163)	< 0.001	2.443 (2.008–2.973)	< 0.001	Model 2
	1.461 (1.235–1.727)	< 0.001	1.113 (0.913–1.358)	0.288	Model 3
≥ 60	2.331 (1.995–2.723)	< 0.001	1.918 (1.629–2.257)	< 0.001	Model 1
	2.147 (1.831–2.517)	< 0.001	1.839 (1.561–2.166)	< 0.001	Model 2
	1.137 (0.968–1.335)	0.118	1.025 (0.868–1.209)	0.774	Model 3
BMI (kg/m^2)					
< 25	3.323 (1.978–5.580)	< 0.001	1.145 (0.476–2.758)	0.762	Model 1
	3.153 (1.876–5.300)	< 0.001	1.090 (0.452–2.627)	0.848	Model 2
	1.682 (0.998–2.836)	0.051	0.651 (0.270–1.571)	0.339	Model 3
≥ 25, < 30	2.025 (1.618–2.533)	< 0.001	1.639 (1.287–2.086)	< 0.001	Model 1
	2.004 (1.599–2.511)	< 0.001	1.627 (1.275–2.076)	< 0.001	Model 2
	1.214 (0.968–1.521)	0.093	1.044 (0.817–1.334)	0.729	Model 3
≥ 30	2.077 (1.811–2.382)	< 0.001	1.599 (1.378–1.854)	< 0.001	Model 1
	1.976 (1.718–2.273)	< 0.001	1.579 (1.359–1.834)	< 0.001	Model 2
	1.294 (1.125–1.489)	< 0.001	1.074 (0.923–1.248)	0.356	Model 3

Table 2. Cox analysis of gout and MASLD as mutual outcome events. Model 1 adjusted for age and gender. Model 2 further adjusted for ethnicity, Townsend deprivation index, smoking status, and alcohol consumption habits based on Model 1. Model 3 additionally adjusted for BMI, diabetes, hypertension, hyperlipidemia, and hyperuricemia on top of Model 2. A *p*-value < 0.05 was considered statistically significant.

Characteristics	Gout → MASLD		MASLD → Gout	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Non-hypertension	2.458 (1.867–3.236)	< 0.001	2.700 (2.055–3.549)	< 0.001
Hypertension	1.277 (1.124–1.450)	< 0.001	1.287 (1.136–1.457)	< 0.001
Non-diabetes	1.477 (1.253–1.742)	< 0.001	1.535 (1.308–1.802)	< 0.001
Diabetes	1.285 (1.093–1.512)	0.002	1.293 (1.102–1.517)	0.002
Non-abdominal obesity	1.356 (1.086–1.694)	0.007	1.474 (1.186–1.832)	< 0.001
Abdominal obesity	1.338 (1.168–1.533)	< 0.001	1.384 (1.212–1.580)	< 0.001

Table 3. Results of metabolic stratification. Model adjusted for age, gender, ethnicity, Townsend deprivation index, smoking status, alcohol consumption habits, BMI, diabetes, hypertension, hyperlipidemia, and hyperuricemia. A *p*-value < 0.05 was considered statistically significant. $P < 0.05$ indicates statistically significant results.

2.325, $P = 0.043$), and hyperuricemia (HR 2.899, 95% CI 1.938–4.337, $P < 0.001$) increased the risk of developing gout in patients with MASLD. The details of the multi-state model are presented in Supplementary Table 1.

Mendelian randomization analysis

Using two-sample Mendelian Randomization (MR) analysis at the genetic level, we identified that gout may contribute to the development of MASLD (OR 95% CI 1.147 [1.075–1.224], $P < 0.001$, Fig. 3A). However, MASLD does not appear to induce gout (OR 95% CI 1.004 [0.907–1.112], $P = 0.94$), with no evidence of heterogeneity

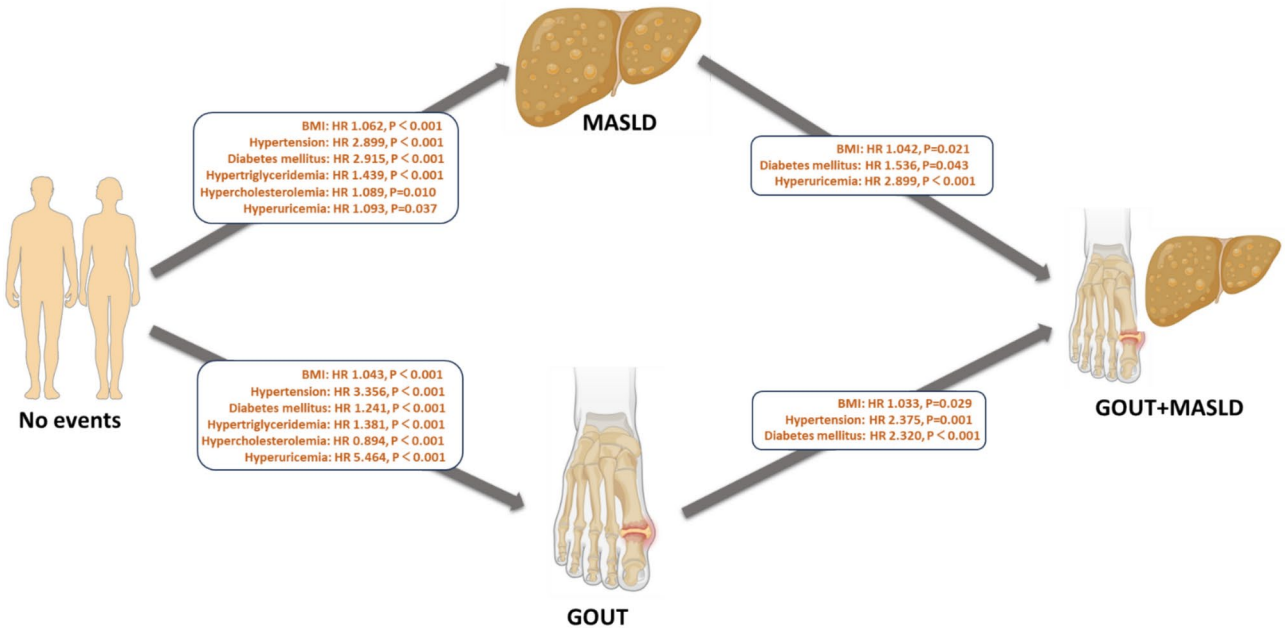

Fig. 2. Schematic diagram of the multi-state model. *Notes*: Results have been adjusted for multiple factors, including age, sex, ethnicity, Townsend deprivation index, smoking status, drinking habits, BMI, diabetes, hypertension, hyperlipidemia, and hyperuricemia. Image source: BioRender.com.

or pleiotropy observed. In the mediation analysis, we identified that the gut microbiota family *Ruminococcaceae* and 24 proteins or metabolites, including the inflammatory cytokine IL-2, the lipid 1-stearoyl-2-arachidonoyl-sn-glycero-3-phosphocholine, and growth differentiation factor 11, contribute to an increased risk of MASLD in gout patients (Supplementary Table 2). A volcano plot illustrating the associations of the mediating proteins in both directions was generated (Fig. 3B,C). Figure 3D and E demonstrate the significant mediating proteins' two-step and total effects. Enrichment analysis of these proteins was conducted using the Reactome database, revealing seven crucial metabolic or signaling pathways. This enrichment analysis identified seven key pathways associated with these proteins (Fig. 3F). Specifically, the pathophysiological processes linking gout to MASLD involve RPIA deficiency (Hit 1/1, ratio 8.53e−05, $P = 0.006$), Pentose phosphate pathway disease (Hit 1/1, ratio 1.71e−04, $P = 0.012$), PTK6 Activates STAT3 (Hit 1/2, ratio 3.41e−04, $P = 0.024$), Interleukin-4 and Interleukin-13 signaling (Hit 3/111, ratio 0.009, $P = 0.029$), RUNX1 regulates transcription of genes involved in differentiation of keratinocytes (Hit 1/8, ratio 6.82e−04, $P = 0.047$), Signaling by Non-Receptor Tyrosine Kinases (Hit 2/58, ratio 0.005, $P = 0.047$), and Signaling by PTK6 (Hit 2/58, ratio 0.005, $P = 0.047$). Detailed enrichment information for mediating metabolic or signaling pathways is provided in Supplementary Table 3.

Discussion

MASLD and gout are two common metabolic diseases that significantly impact individuals' health and quality of life. With their prevalence and incidence increasing annually, they not only impose a heavy economic burden on patients but also exert growing pressure on the healthcare system[2,29]. In this study, we first confirmed the association between gout and MASLD using a COX regression model, which is consistent with previous research[26,27]. Upon further stratified analysis, we observed a significantly increased risk of MASLD development in male gout patients, those under the age of 60, and individuals with a BMI ≥ 30 kg/m^2, while female MASLD patients have a significantly increased risk of developing gout. Although multiple studies have confirmed that hyperuricemia is a key link between gout and MASLD[30,31], we still found an association between the two diseases after adjusting for the effect of hyperuricemia in the model. Therefore, we believe that other factors may influence the interaction between gout and MASLD. Therefore, we further employed a multistate survival model to investigate the risk factors in the development of both diseases. We found that, apart from hyperuricemia, high BMI, hypertension, diabetes, hypercholesterolemia, and hypertriglyceridemia are common risk factors for the onset of both gout and MASLD. For gout patients, high BMI, hypertension, and diabetes increase the risk of developing MASLD, independent of hyperuricemia. And for MASLD patients, high BMI, diabetes, and hyperuricemia elevate the risk of developing gout. These findings have significant clinical implications, as patients with gout, MASLD, or both conditions often present with metabolic abnormalities. This study confirms that maintaining these metabolic parameters within normal ranges can reduce disease risk, facilitating more precise individualized treatment and lowering the incidence of both diseases.

We further validated the causal relationship between the two conditions at the mechanistic level and employed mediation Mendelian randomization analysis to explore the underlying mechanisms from a multi-omics perspective. The results of the study indicate that gout can lead to the development of MASLD, whereas MASLD does not induce the occurrence of gout, which is not entirely consistent with the findings in Section "Baseline

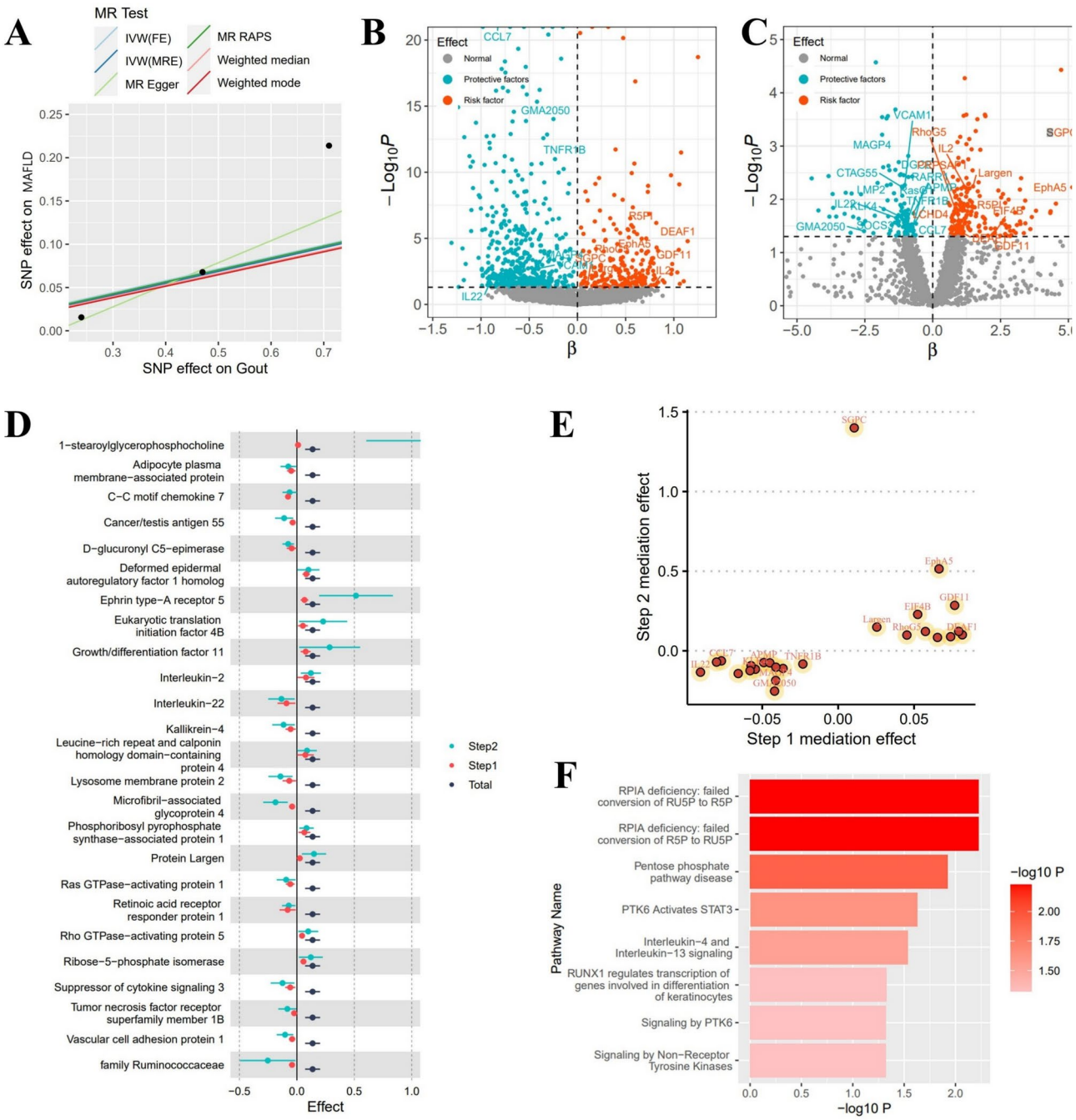

Fig. 3. Results of Mendelian randomization multinomics mediation analysis. *Notes*: (**A**) Scatter and causal effect curve plots for gout influencing MASLD incidence. Points indicate the causal effects of SNPs on gout and MASLD, and the slope of the line represents the overall effect value derived from different MR methods. (**B**) Volcano plot depicting plasma proteomic changes mediated by gout. Points labeled indicate proteins with mediating effects. (**C**) Volcano plot for plasma proteomics influencing MASLD incidence, with labeled points representing proteins showing mediating effects. (**D**) Forest plot of significant direct and two-step mediating effects of plasma proteins, metabolites, gut microbiota, and inflammatory factors in the progression of MASLD among gout patients. Step 1 Mediation: MR analysis between gout and plasma proteomics; Step 2 Mediation: MR analysis between plasma proteomics and MASLD. (**E**) Scatter plot for proteomic mediation effect. Step 1 Mediation: MR analysis between gout and plasma proteomics; Step 2 Mediation: MR analysis between plasma proteomics and MASLD. (**F**) Role of metabolic or signaling pathways with mediating effects in the progression of MASLD in gout patients. The horizontal axis has been log-transformed.

characteristics" (Table 1), where gout and MASLD were shown to promote each other's occurrence. We consider that external environmental factors may play a more significant role in the process by which MASLD triggers the onset of gout, but the specific mechanisms remain unclear and warrant further investigation. Since the pathogenesis of MASLD is complex and driven by multiple factors, involving the interplay of genetic, environmental, and metabolic factors, and is primarily associated with liver lipid metabolism disorders, insulin resistance, oxidative stress, inflammation and immune responses, dysbiosis of the gut microbiota, and impaired gut barrier function[32], the mechanism by which gout leads to MASLD has drawn our attention. Therefore, we conducted mediation analysis across multiple omics layers (including the gut microbiome, proteome, and metabolome) to explore the potential mechanisms underlying the gout-induced development of MASLD. The results suggest that gut microbiota of the *Ruminococcaceae* family, along with 24 proteins or metabolites are responsible for the elevated risk of MASLD in patients with gout. Following enrichment analysis of the significantly altered proteins or metabolites, we identified seven prominent metabolic or signaling pathways. Specifically, these include RPIA deficiency, Pentose Phosphate Pathway Disease, PTK6 Activates STAT3, Interleukin-4 and Interleukin-13 signaling, RUNX1 regulation of transcription of genes involved in keratinocyte differentiation, Signaling by Non-Receptor Tyrosine Kinases, and Signaling by PTK6 in the pathophysiological process of gout-induced MASLD.

The gut-liver axis plays a critical role in the development of MASLD[33–35]. In our study, we found that the gut bacterium *Ruminococcaceae* family is responsible for the elevated risk of MASLD in gout patients. Although previous literature presents conflicting evidence regarding the role of *Ruminococcaceae* in the pathogenesis of MASLD[36–40], the risk factor profile of its representative genus, *Ruminococcus*, is well-established[33,41]. Elevated uric acid levels in patients with gout can increase the abundance of *Ruminococcaceae*[42,43], leading to intestinal barrier damage and increased gut permeability. This allows a large amount of bacterial metabolites, bacterial components, and other harmful substances to enter the liver via the portal vein, exacerbating inflammation, oxidative stress, and lipid accumulation, thereby accelerating hepatic inflammation and fibrosis[44–46]. Additionally, endogenous alcohol produced by this bacterium[47] can be transported to the liver via the portal vein, promoting the production of reactive oxygen species (ROS) and aggravating hepatic inflammation, thereby contributing to the development of MASLD[48].Furthermore, previous studies have demonstrated a positive correlation between *Ruminococcus* and type 2 diabetes (T2D), suggesting that this bacterium may inhibit metabolic pathways related to insulin signaling[49], leading to insulin resistance and further contributing to MASLD.

Among the significantly affected metabolic or signaling pathways, ribose-5-phosphate isomerase (RAIP) is a key enzyme in the pentose phosphate pathway, mediating the interconversion of ribose-5-phosphate (R5P) and ribulose-5-phosphate (Ru5P)[50]. The pentose phosphate pathway enhances the clearance of reactive oxygen species (ROS) by generating NADPH. When this pathway is impaired, the reduction in ROS clearance can disrupt cellular redox balance, leading to damage of biomolecules such as proteins, DNA, and RNA, thereby promoting hepatic steatosis and further contributing to the development of MASLD[51]. Activation of Signal Transducer and Activator of Transcription 3 (STAT3) has been reported in MASLD and MASH, particularly in relation to hepatic inflammation and fibrosis[52,53]. Previous studies have detected STAT3 activation in patients with steatosis[54], MASLD[52], liver fibrosis[55], and in mouse models of NASH[56]. STAT3 activation contributes to the development and growth of hepatocellular carcinoma (HCC) in MASH and obesity-related mouse models. However, specific studies on Protein Tyrosine Kinase 6 (PTK6)-mediated STAT3 activation in MASLD are limited, although this signaling pathway is known as one of the mechanisms regulating inflammation[57]. PTK6 is a non-receptor tyrosine kinase that is known to activate STAT3[57]. STAT3 is closely associated with liver injury, inflammation, regeneration, and the progression of HCC. The activation of STAT3 can enhance inflammatory responses, thereby promoting the development of MASH and liver fibrosis[52,53,56]. Interleukin-4 (IL-4) and Interleukin-13 (IL-13) have been extensively studied in various inflammatory and allergic diseases, and their potential roles in the inflammatory response of MASLD have also been reported[58]. IL-4 and IL-13 are classified as T-helper type 2 (Th2) cytokines[59], and they are typically involved in allergic reactions and immune regulation[60]. In MASLD, IL-4 and IL-13 signaling may influence liver inflammation by modulating macrophage polarization and the hepatic immune environment, thereby promoting the progression of MASLD[61]. Runt-related transcription factor 1 (RUNX1) is a key transcription factor involved in the regulation of embryonic development, hematopoiesis, angiogenesis, and, notably, inflammatory responses[62]. Previous studies have primarily associated RUNX1 with malignancies, particularly those of the hematopoietic system[63,64], while reports on its direct role in MASLD are limited.Although the direct association between RUNX1 and MASLD remains unclear, it is hypothesized that RUNX1 may influence hepatic cell states by regulating genes involved in inflammation and cellular differentiation, thereby indirectly contributing to the pathogenesis of MASLD[65,66]. The target genes of RUNX1 can promote the formation of steatotic vasculature. For instance, eNOS and PI3KCA are involved in endothelial cell proliferation, sprouting, and vascular stabilization in hepatic steatosis and inflammation in high-fat diet mice[67,68]; PRKCE plays a critical role in mediating fat-induced hepatic insulin resistance through the accumulation of diacylglycerol in MASLD[69,70].

Through these exploratory findings, our research provides novel insights into the diagnosis and treatment of gout and MASLD. Firstly, uric acid, as an antioxidant, may serve as a potential therapeutic approach for treating MASLD. Secondly, previous studies have demonstrated that xanthine oxidase inhibitors (XOIs) can ameliorate hepatic steatosis in MASH mice[28,71], providing a theoretical basis for the potential therapeutic effects of XOIs in MASLD by improving hepatic steatosis and reducing serum cholesterol levels. Moreover, specific bacterial strains or microbiota may serve as future biomarkers and therapeutic targets for MASLD screening and treatment. Associated signaling and metabolic pathways, such as the *IL-4/IL-13* pathways and the *JAK/STAT* pathway, offer potential avenues for targeted MASLD therapy. However, extensive high-quality basic and clinical research is required for further exploration and validation.

This study has several strengths: Firstly, it is based on a large sample size from the UK Biobank, incorporating multiple potential covariates into the statistical models to minimize the interference of confounding factors. Secondly, we are the first to utilize multi-state models and Mendelian randomization tools to comprehensively and multi-dimensionally explore the correlation between the two conditions, from clinical cohorts to mechanistic insights, providing robust evidence with significant public health and clinical implications.

However, this study also has certain limitations. Firstly, the UK Biobank database lacks uric acid data at the time of diagnosis for the study population, making the role of uric acid in the development of MASLD not fully understood. Secondly, this study focuses on a European population, which reduces the impact of population stratification; however, the interaction between the two diseases in Asian and other populations requires further investigation. Furthermore, real-time serum uric acid levels at the time of gout diagnosis were not available, limiting the ability to perform further stratified analyses among gout patients. Finally, the Cox proportional hazards model, multistate model, and Mendelian randomization study only address the linear relationships of risk factors, leaving potential nonlinear relationships unexplored.

Methods

Data source

The data for this study were sourced from the UK Biobank, a large-scale prospective cohort study that recruited over 500,000 participants aged 37–73 years in the UK between 2006 and 2010[72]. This database includes participants' genetic information, blood samples, lifestyle, and environmental exposure data, along with follow-up records of their health and medical data for several decades. The UK Biobank has received ethical approval from the North West Multi-center Research Ethics Committee (Ref No. 11/NW/0382). All participants provided informed consent. The application ID for the data used in this study is 84,347. In this study, we excluded 8,483 participants, resulting in a final sample of 493,928 participants for analysis. The detailed flowchart is presented in Fig. 1.

In the two-sample Mendelian randomization (MR) study, we obtained the GWAS dataset for MASLD from FINNGEN, a Finnish database comprising 377,277 individuals, including 2275 MASLD cases and 375,002 controls[73]; the recruitment followed a biobank protocol approved by Fimea. The FinnGen study protocol was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District (HUS) (Ref No. HUS/990/2017). The GWAS dataset for gout was sourced from the Global Urate Genetics Consortium (GUGC), which includes data from over 140,000 individuals of European ancestry, comprising 2115 gout cases and 67,259 controls[74].

In the mediation MR study, we obtained the genome-wide association study (GWAS) data of gut microbiota from the International MiBioGen Consortium[75]. This database harmonized 16S rRNA gene sequencing profiles and genotyping data from 18,340 participants across 24 cohorts from the United States, Canada, Israel, South Korea, Germany, Denmark, the Netherlands, Belgium, Sweden, Finland, and the United Kingdom. A large-scale, multi-ethnic, genome-wide meta-analysis was conducted to investigate the associations between autosomal human genetic variations and the gut microbiome. The GWAS summary data for plasma proteome levels were obtained from the human plasma proteome genetic map published by Suhre et al.[76]. This study employed an expanded version of aptamer-based multiplex protein assays to create and interrogate the genetic map of the human plasma proteome. It quantified 3282 plasma proteins in 3301 healthy participants from 25 centers across England, as part of the INTERVAL study, a genomic biorepository comprising 50,000 blood samples. Genome-wide testing of 10.6 million putative autosomal variants was performed. The study was approved by the UK National Research Ethics Service (11/EE/0538).

Details of the datasets included in the Mendelian randomization analysis are provided in Supplementary Table 4. Ethical approval was obtained from the respective local ethics committees for all studies included in the analysis.

Variables and covariates

Baseline comorbidities and causes of death, along with their occurrence times, were assessed using linked hospital and primary care records. Diseases and causes of death were identified using ICD-10 codes. The outcomes included gout (M100, M109), MASLD (K760), diabetes mellitus (E11), and hypertension (I10). Participants were followed up until the end of June 2022. All consent procedures were completed by the UK Biobank, and detailed information regarding record linkage has been previously published[72]. Our analysis included the following potential confounders: sex, age, ethnicity, Townsend deprivation index (reflecting area-based socioeconomic deprivation), smoking history, alcohol consumption history, BMI, diabetes, hyperlipidemia, hypertension, and hyperuricemia. Hyperlipidemia was defined based on baseline lipid levels as total cholesterol (TC) ≥ 5.2 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/L, high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L, or triglycerides (TG) ≥ 1.7 mmol/L (150 mg/dL). Hyperuricemia was defined as a baseline serum urate level > 420 μmol/L. Abdominal obesity was characterized by a baseline waist circumference > 102 cm in men and > 88 cm in women.

Cohort study design

This study was based on data from the UK Biobank cohort, using a Cox proportional hazards regression model to perform survival analysis, with gout and MASLD as reciprocal outcome events, to clarify the association between gout and MASLD. Specifically, in the exposure group, the observation period commenced at the onset of exposure and ended at either the occurrence of the outcome event or the end of follow-up, whichever occurred first. In the control group, observation started from the recruitment date of participants who did not develop either the exposure or the outcome event and ended at the completion of follow-up. Participants diagnosed with both exposure and outcome events on the same day, as well as those with the outcome event

occurring prior to the exposure, were excluded. Time was measured in days. Subsequently, stratified analyses were conducted based on sex, age, and other factors to explore the association between gout and MASLD in different populations. The model was adjusted for covariates including gender, age, ethnicity, Townsend Deprivation Index, smoking, alcohol consumption, BMI, hypertension, diabetes, and hyperlipidemia. Secondly, we considered four exploratory states: disease-free, gout, MASLD, and comorbid conditions, and used a multi-state survival model to analyze the incidence and disease progression risk of the two conditions under exposure to risk factors such as gender, age, obesity, hyperglycemia, dyslipidemia, hypertension, and hyperuricemia. The model was still adjusted for the aforementioned covariates.

Statistical analysis

In the prospective study based on UK Biobank, we used the Cox proportional hazards model to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of MASLD and gout. In model 1, we established a basic model using age and gender; model 2 further adjusted for ethnicity and additionally corrected for Townsend Deprivation Index, smoking status, and alcohol consumption; model 3 further adjusted for other risk factors, including Body Mass Index (BMI), diabetes, hypertension, hyperlipidemia, and hyperuricemia. Subgroup analyses were conducted based on sex (male, female), age (≥ 60 years, < 60 years), and BMI (< 25 kg/m^2, ≥ 25 and < 30 kg/m^2, ≥ 30 kg/m^2).A multi-state survival model was applied to estimate risk factors for transitions from no event (State 1) to gout (State 2), and then progression to MASLD (State 3), as well as from no event (State 1) to MASLD (State 4), and then progression to gout (State 5), with covariates incorporated into the multi-state model for adjustment[77] (S1 Fig). Both statistical models considered a P-value of < 0.05 as statistically significant, and significance testing was conducted in a two-tailed manner. We conducted a self-assessment using the STROBE checklist (Supplementary Table 5), ensuring that the study adhered to the publication requirements for observational research findings.

Mendelian randomization (MR) study

Study methods

The Mendelian randomization analysis in this study required that the instrumental variables (SNPs) meet three fundamental assumptions: First, the instrumental variables must be significantly associated with the risk factors (relevance assumption). Second, the instrumental variables should be independent of any confounding factors (independence assumption). Third, the instrumental variables must influence the outcome only through the risk factors, without any direct effects (exclusion restriction assumption). A series of selection criteria were applied (P-value < 5 × 10^−8, F-statistic > 10, MR-PRESSO test, MR-Steiger test, PhenoScanner analysis, etc.) to identify eligible SNPs[78,79]. Subsequently, we employed various Mendelian randomization (MR) methods to estimate causal relationships, including inverse variance weighting (IVW), MR-Egger regression, weighted median, weighted mode, and MR-PAPS methods. According to the Mendelian randomization guidelines[80], in the absence of horizontal pleiotropy and heterogeneity, we selected the IVW multiplicative fixed-effects model as the primary analysis. In the presence of heterogeneity, we selected the IVW multiplicative random-effects model as the primary analysis and referenced the results of the weighted median method[80]. When horizontal pleiotropy was present among SNPs, the MR-Egger method was employed as the primary analysis[81]. Additionally, we conducted sensitivity analyses to ensure the robustness of our results, including Cochran's Q test, the MR-Steiger model, and the MR-Egger intercept term[82,83] (Supplementary Tables 6–8). Details of all included SNPs are provided in Supplementary Table 9, SNPs associated with confounding factors are listed in Supplementary Table 10, and information regarding all rounds of MR analyses is available in Supplementary Table 11.

Study design

This study employed a two-step Mendelian randomization approach to investigate the mediating roles of the gut microbiome, metabolome, and plasma proteome in the relationship between gout and the development of MASLD[84]. First, a two-sample Mendelian randomization (MR) analysis was conducted to elucidate the bidirectional causal relationship between gout and MASLD. Subsequently, a mediation analysis was performed. The first step involved MR analysis between gout and each of the gut microbiome, metabolome, and plasma proteome groups. The second step involved MR analysis of the gut microbiome, metabolome, and plasma proteome groups in relation to MASLD. Proteins that were significant in all three analyses exhibited partial mediation effects. Proteins that were significant in both steps of the mediation analysis showed full mediation effects, while those not consistently significant across both steps demonstrated no mediation effects. The indirect effect was calculated using the formula β1*β2, while the direct effect was determined by subtracting the indirect effect from the total effect[85]. We conducted a self-check using the STROBE checklist (Supplementary Table 12), and the study procedures complied with the publication requirements for Mendelian randomization studies.

Reactome enrichment analysis

Reactome is an open-access, peer-reviewed pathway database (https://reactome.org/). The aim is to provide intuitive bioinformatics tools for the visualization, interpretation, and analysis of pathway knowledge, supporting basic and clinical research, genomic analysis, modeling, and more. The names of the identified mediator proteins were input into the Reactome "Analysis Tool" for enrichment, using the human database (Homo sapiens, code 9606) (Supplementary Table 3).

Statistical software and result visualization

All statistical analyses were performed using R software (version 4.1.2), utilizing the 'TwoSampleMR', 'MR PRESSO', and several basic R packages to conduct the analyses and generate corresponding scatter plots, regression curve plots, and forest plots. The P-values from all multiple analyses were adjusted using the False

Discovery Rate (FDR) method to reduce the risk of Type I statistical errors. Causal relationship results were presented as odds ratios (OR) with their 95% CI.

Conclusion

Gout and MASLD are correlated both clinically and mechanistically. Metabolic factors such as BMI and blood glucose play significant roles in the development of both diseases. The gut microbiota *Ruminococcaceae* family and 24 proteins or metabolites, including inflammatory cytokine IL-2 are associated with the high risk of MASLD in gout patients, but the specific mechanisms by which MASLD leads to gout require further investigation. Additionally, this study offers new perspectives on the prevention and treatment of gout and MASLD, such as controlling blood pressure and glucose to reduce the risk of both diseases, and identifying specific bacterial strains as potential biomarkers for MASLD screening and therapeutic targets in the future.

Data availability

For UKB, data and materials are available via UK Biobank upon application at http://www.ukbiobank.ac.uk/. The full GWAS summary statistics are available at the following websites: https://finngen.gitbook.io/documentation/v/r5/data-download, http://www.gwas.eu/gugc, http://www.mbigene.org, http://proteomics.gwas.eu.

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Author contributions

Writing—original draft preparation—SYL. Data calculation—SYL and FL. Data processing—MSY, HJC and YjP. Investigation-YJC. Review and editing—LNR and LS. Supervision—XKG and GXW. Funding acquisition—GXW. All authors read and approved the final version for submission. All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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