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The mediating role of key amino acid and vitamin metabolite ratios in the effects of 5 dietary habits on psoriatic arthritis

A Mendelian randomization study

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Abstract

The causal relationship between dietary habits and psoriatic arthritis (PsA) remains unclear, and the mediating role of human plasma metabolites in this relationship is unexamined. This study aims to elucidate the causal relationship between 80 dietary patterns and PsA using a 2-sample Mendelian randomization (MR) analysis. A 2-step MR approach was employed to investigate whether 1400 human plasma metabolites could serve as potential mediators between dietary habits and PsA. To ensure the reliability of the results, heterogeneity and pleiotropy tests were conducted. Our MR analysis identified 5 dietary factors exhibiting significant inverse causal associations with PsA risk ($P < .05$): red wine intake (odds ratio (OR) = 0.62), total alcohol intake (OR = 0.59), cheese intake (OR = 0.56), monthly alcohol drinks (OR = 0.66), and decaffeinated coffee preference (OR = 0.62). Mediation analysis revealed distinct metabolite pathways underlying these associations. Red wine intake-PsA relationship: Gamma/beta-tocopherol levels mediated 17.8% of the protective effect, followed by citrate (7.2% mediation). Cheese intake-PsA association: Arginine levels accounted for 7.4% of the effect, with phosphate-to-threonine ratio mediating an additional 7.2%. Decaffeinated coffee preference-PsA link: Three amino acid ratios demonstrated significant mediation-glutamate/alanine (12.2%), ornithine/glutamate (10.9%), and arginine/glutamate (8.9%). These results underscore the potential role of plasma metabolites as mediators in the causal relationship between these 5 dietary habits and PsA.

Abbreviations: BWMR = Bayesian weighted Mendelian randomization, GWAS = genome-wide association study, IVs = instrumental variables, IVW = inverse-variance weighted, MR = Mendelian randomization, MR-Egger = The Mendelian randomization-Egger, OR = odds ratio, PsA = psoriatic arthritis, SNP = single-nucleotide polymorphism.

Keywords: diet, genome-wide association study, Mendelian randomization, plasma metabolites, psoriatic arthritis

1. Introduction

Psoriatic arthritis (PsA) is a common, chronic, progressive, immune-mediated rheumatic disease characterized by inflammation of the musculoskeletal system, skin, and nails.[1] The clinical manifestations and progression of PsA can vary significantly; however, many patients experience destructive arthritis that leads to considerable morbidity and disability.[2] Recent studies suggest that over 500,000 individuals in the United States are affected by PsA, with millions more impacted globally.[3] PsA profoundly affects patients' physical and mental health and imposes a substantial economic burden. The functional impairments associated with PsA often result in decreased work productivity, increased absenteeism, and a marked decline in patients' quality of life.[4] The pathogenesis of PsA remains poorly understood and is thought to be influenced by various factors, including genetic predisposition, environmental triggers, metabolic abnormalities, and dietary influences.[5] Therefore, early diagnosis and preventive measures, along with the development of new treatments, have become critical objectives. These efforts not only aim to prevent bone and joint damage and associated disabilities but also to alleviate the economic burden and social impact of the disease.

There is a notable link between diet and PsA. A recent cross-sectional study involving 355 patients demonstrated that adherence to a Mediterranean diet significantly improved treatment outcomes for PsA.[6] Additionally, a ketogenic diet has been shown to yield beneficial effects on disease activity indices and pro-inflammatory markers in individuals with PsA.[7] However, patients diagnosed with PsA often exhibit dietary habits

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

An ethics statement is not applicable because this study is based exclusively on published literature and publicly available databases.

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characterized by high fat intake.[8] Interestingly, both dairy and high dietary fiber diets appear to have no significant impact on the PsA activity index.[9] In the study conducted by Wu et al, it was revealed that women who consumed excessive amounts of alcohol had a markedly increased risk of developing PsA when compared to nondrinkers.[10] Notably, this same study indicated that, when baseline alcohol intake was considered, moderate drinkers had a lower risk of developing PsA than their nondrinking counterparts.[10] Despite these findings, there remains a relative paucity of research on dietary interventions in PsA, and none of the existing studies have conclusively demonstrated that any single diet is distinctly beneficial.[11] Furthermore, the cause-and-effect relationship between dietary habits and PsA remains unclear.

Furthermore, potential pathways connecting diet and PsA remain largely unexplored. Dietary patterns can significantly influence changes in plasma metabolite levels.[12] Studies have demonstrated that dietary habits, including fruit and vegetable intake, as well as coffee and alcohol consumption, are associated with the levels of 163 metabolites, among which 42 associations between metabolite levels and nutritional intake are statistically significant.[13] There exists a correlation between the quantity and type of alcohol consumed and its corresponding metabolites.[14] Diet-related metabolites may have implications for disease processes. Previous research has indicated that certain plasma metabolites linked to coffee consumption, particularly caffeinated coffee, are inversely associated with colorectal cancer.[15] Many plasma metabolites exhibit significant changes in response to dietary composition, and some of these endogenous metabolites may impact pathways related to diabetes, inflammation, and energy metabolism.[16] Additionally, studies have identified connections between metabolites and indicators of PsA disease activity. For instance, serum trimethylamine-N-oxide (TMAO) is a recognized risk factor for cardiovascular disease and obesity, and it is positively associated with cutaneous and peripheral joint mobility in PsA.[17] Therefore, we propose that plasma metabolites could serve as potential mediators between diet and PsA.

Observational studies have inherent limitations, including unmeasured confounders and reverse causation.[18] These limitations render the association between diet and PsA controversial. Mendelian randomization (MR) analysis is an emerging and increasingly popular epidemiological research method.[19] By utilizing randomly distributed single-nucleotide polymorphisms (SNPs) in genetic data as instrumental variables (IVs), MR analysis can effectively investigate the causal relationship between exposure factors and outcomes.[19] By leveraging the mechanism of random assignment of genetic variants during meiosis, MR facilitates causal inference akin to that of randomized controlled trials.[20] This method significantly mitigates the influence of confounding factors and reduces the reverse causality bias that is prevalent in observational studies, thereby enhancing the credibility of research findings.[21] Consequently, we employed the MR analysis method to explore the causal relationship between dietary habits and PsA.

This study employed a MR design to investigate the causal relationships between various dietary habits and PsA, while also evaluating the role of plasma metabolites in mediating the effects of diet on PsA.

2. Methods

2.1. Study design

Figure 1 presents a flow chart illustrating the methodology of this MR analysis study. Initially, a 2-sample MR analysis was performed to investigate the potential causal relationship between various dietary habits and PsA. Subsequently, we examined whether each plasma metabolite mediates the causal relationship between dietary habits and PsA through a 2-step MR analysis. Figure 2 defines the concepts of total, indirect, and direct effects.

2.2. Data source

Genome-wide association studies (GWAS) data on dietary habits were obtained from the GWAS catalog uploaded by Joanne B. Cole, which includes 80 dietary patterns (Table S1, Supplemental Digital Content, https://links.lww.com/MD/O930).[22] Summary statistics for psoriatic arthritis were sourced from the FinnGen biobank, comprising 3897 case subjects and 287,796 controls.[23] Additionally, GWAS data for plasma metabolites were derived from Yiheng Chen study, which encompassed genome-wide association analyses of 1091 blood metabolites and 309 metabolite ratios in 8299 individuals (Table S2, Supplemental Digital content, https://links.lww.com/MD/O930).[24] All data utilized in this study are publicly accessible, and the participants in the GWAS are representative of the European population.

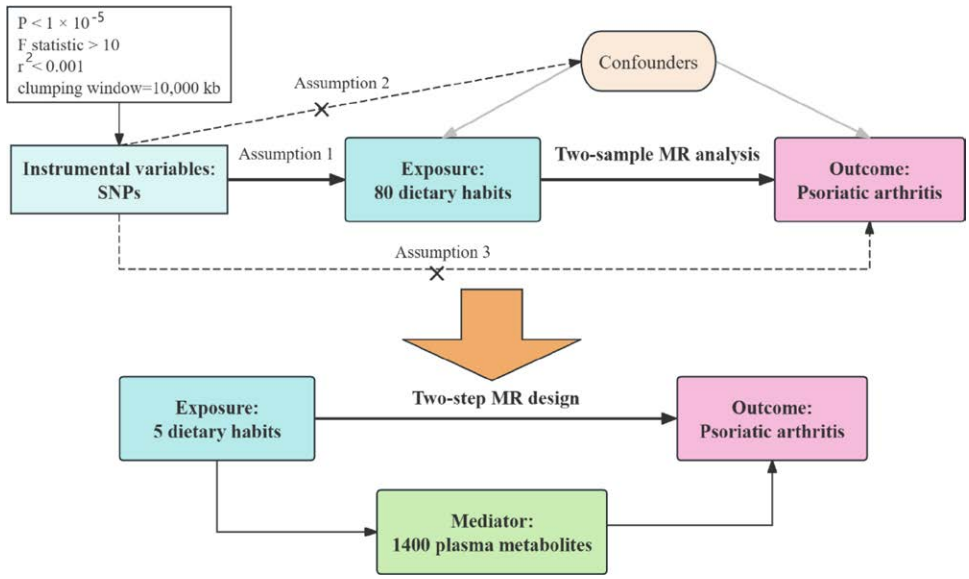

Figure 1. The workflow of this study. SNP = single-nucleotide polymorphism, MR = Mendelian randomization.

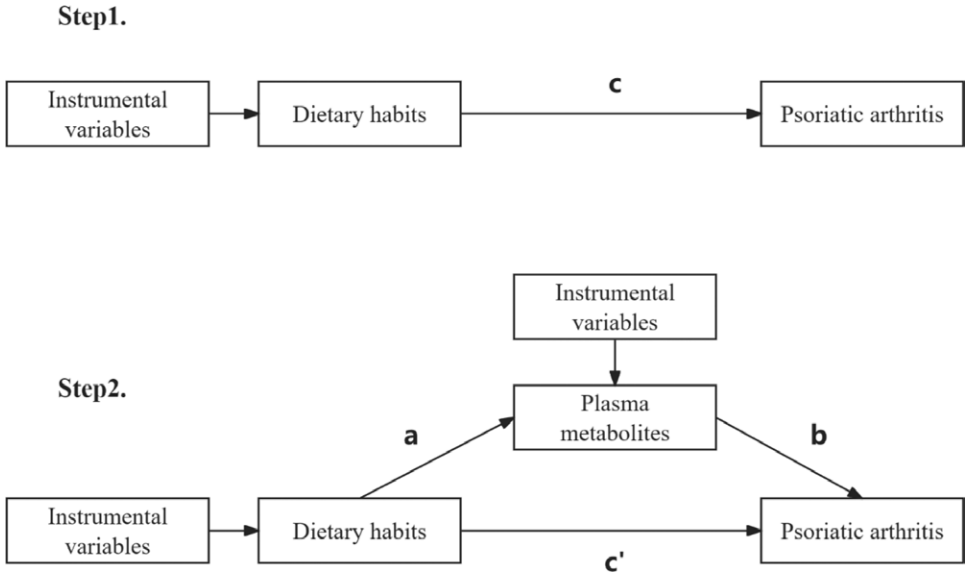

Figure 2. The 2-step Mendelian randomization analysis method. Step 1: The total effect of dietary habits on psoriatic arthritis is denoted as c, with each dietary habit serving as an exposure and psoriatic arthritis as the outcome. Step 2: This total effect is decomposed into 2 components: (1) the indirect effect (a × b), calculated using a 2-step approach, where a represents the total effect of each dietary habit on each plasma metabolite, and b signifies the effect of each plasma metabolite on psoriatic arthritis; and (2) the direct effect, expressed as $c' = c - a \times b$.

2.3. Selection of IVs

The selection of IVs must adhere to 3 key assumptions of MR: Assumption (1) the SNP used as the IV is closely associated with the exposure; Assumption (2) the SNP is not confounded by factors related to both exposure and outcome; and Assumption (3) the SNP influences the outcome exclusively through the exposure, with no direct effect on the outcome.[25]

According to Assumption (1), we extracted the dietary habit database and established a criterion of $P < 1 \times 10^{-5}$ to identify SNPs that are highly correlated with exposure. Simultaneously, we set $r^2 = .001$ and a region width of 10,000 kb to eliminate linkage disequilibrium, thereby ensuring the independence of the IVs. Additionally, we calculated the *F*-statistic to mitigate bias introduced by weak instruments in the study. The formula for the *F*-statistic is $F = (\text{beta/se})^2$, with weak instruments defined as those with $F < 10$ being excluded. Based on Assumption (2) and Assumption (3), the obtained SNPs were entered into the LDlink database to examine the associated phenotypes of each genetic variant (https://ldlink.nih.gov/?tab=home). We explored potential risk factors for PsA and selected BMI, smoking, and psoriasis as confounding factors. We systematically screened and excluded SNPs related to BMI, smoking, and psoriasis. By filtering out SNPs associated with these confounding factors, we aimed to reduce bias. Subsequently, the IVs that passed the aforementioned screening were compared with the psoriasis arthritis outcome data, and palindromic SNPs were removed.

2.4. MR analysis

In this study, a 2-sample MR analysis was conducted, primarily employing the inverse-variance weighted (IVW) method, supplemented by MR-Egger and weighted median approaches, to determine the causal relationship between diet and PsA. IVW, which aggregates ratio estimates for each SNP through meta-analysis under the assumption of a valid IV, serves as the principal method for determining the effect of exposure on outcomes with reliable results.[26] Subsequently, the findings from the 2-sample MR analysis were validated through Bayesian weighted Mendelian randomization (BWMR).[27]

A sensitivity analysis was performed on the aforementioned MR analysis results. The MR-Egger regression test was employed to assess pleiotropy; a significant non-zero intercept at $P < .05$ indicated the presence of pleiotropy. Additionally, Cochran *Q* test was employed to examine discrepancies among the different databases. To further validate the stability of the results, a leave-one-out method was utilized for sensitivity analysis.

In the 2-step MR analysis, the beta value derived from the IVW method in the first step, which performs a 2-sample MR analysis between each dietary habit and PsA, represents the total effect (c) of each exposure on the outcome. In the second step, the beta value obtained from the IVW method in the 2-sample MR analysis between each plasma metabolite and PsA illustrates the effect (b) of the mediator on the outcome. Additionally, the beta value derived from the IVW method in the 2-sample MR analysis between each dietary habit and each plasma metabolite signifies the effect (a) of the exposure on the mediator. The mediation effect is calculated as a * b, while the direct effect of the exposure on the outcome is represented as c' = c—a * b. The proportion of the mediation effect is computed as a * b/ c (Fig. 2). In the aforementioned 2-step MR analysis, if the *P*-values of the IVW method for exposure-outcome, mediator-outcome, and exposure-mediator are all <.05, and the calculated proportion of the mediation effect exceeds 5%, it is concluded that this mediator exhibits a significant mediation effect.[28]

To validate the directionality of the causality in the aforementioned 2-step MR, the MR Steiger method was employed.[29] In cases where SNPs suggested reverse causality, these SNPs were excluded, and the 2-step, 2-sample MR analysis was conducted again.

3. Results

3.1. Association of dietary habits with PsA

Two-sample MR analyses were conducted to explore the relationship between dietary intake and PsA. The analysis identified 5 dietary factors—red wine intake (measured in glasses per month), overall alcohol intake, overall cheese intake, total drinks of alcohol per month, and coffee type (decaffeinated)—that exhibited statistically significant causal relationships with PsA (Fig. 3). For these 5 dietary factors, 123, 226, 164, 208, and 120 SNPs were extracted as IVs, respectively. The circular heatmap plot provides a comprehensive visualization of the

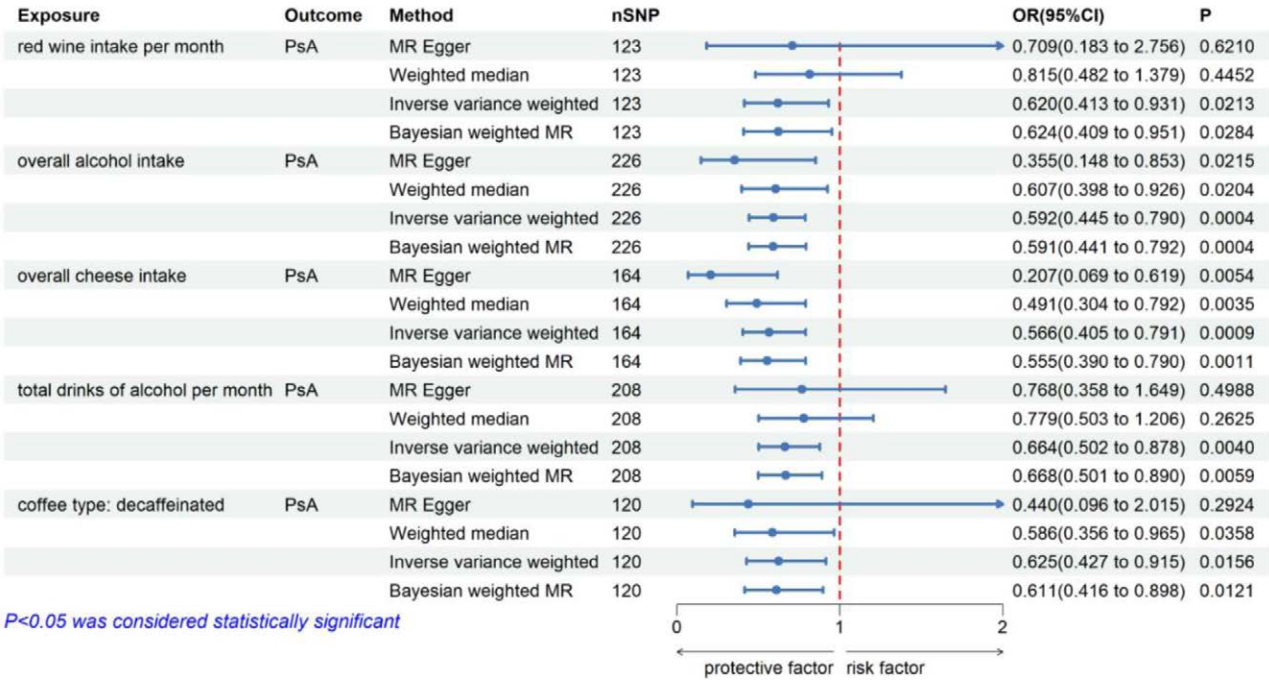

Figure 3. Forest plot showing the impact of significant dietary habits on psoriatic arthritis. PsA = psoriatic arthritis, MR-Egger = The Mendelian randomization-Egger, Bayesian weighted MR = Bayesian weighted Mendelian randomization, nSNP = the number of single-nucleotide polymorphism, OR = odds ratio.

relationship between all 80 dietary habits and PsA (Fig. 4). The IVW method revealed significant causal relationships between diet and reduced risk of PsA, with the following odds ratio (OR) and 95% confidence intervals (CI): red wine intake (measured in glasses per month) (OR = 0.6203, 95% CI: 0.4131–0.9314), overall alcohol intake (OR = 0.5924, 95% CI: 0.4445–0.7895), overall cheese intake (OR = 0.5657, 95% CI: 0.4045–0.7913), total drinks of alcohol per month (OR = 0.6641, 95% CI: 0.5024–0.8778), and coffee type (decaffeinated) (OR = 0.6253, 95% CI: 0.4274–0.9149). Subsequent verification using BWMR corroborated that these 5 dietary habits maintain a consistent negative causal relationship with PsA (Table S3, Supplemental Digital Content, https://links.lww.com/MD/O930). In addition, there was no significant causal relationship between 75 dietary factors, including cups of tea per day (OR = 1.1453, 95% CI: 0.8098–1.6196), fresh fruit intake per day (OR = 1.3397, 95% CI: 0.9783–1.8346), overall beef intake (OR = 1.0572, 95% CI: 0.6759–1.6537), milk type (any milk vs never) (OR = 0.4475, 95% CI: 0.0672–2.9787), and psoriatic arthritis (IVW: *P*-value > .05) (Table S3, Supplemental Digital Content, https://links.lww.com/MD/O930).

We also conducted the sensitivity analysis. The leave-one-out analysis further demonstrated the sensitivity of these findings (Fig. S1, Supplemental Digital Content, https://links.lww.com/MD/O932). In the pleiotropy test, MR-Egger regression was performed on 5 significant dietary habits (Table 1). The results indicated the following: red wine intake (measured in glasses per month) (Intercept = −0.002, *P*-value = .839), overall alcohol intake (Intercept = 0.008, *P*-value = .226), overall cheese intake (Intercept = 0.015, *P*-value = .061), total drinks of alcohol per month (Intercept = −0.002, *P*-value = .689), and coffee type (decaffeinated) (Intercept = 0.005, *P*-value = .641). These findings suggest that the aforementioned results do not demonstrate horizontal pleiotropy. Furthermore, the MR-Egger regression tests for the remaining 75 dietary habits also fail to exhibit horizontal pleiotropy (Table S4, Supplemental Digital Content, https://links.lww.com/MD/O930). Given that the random effects IVW was employed as the primary analysis, Cochran *Q* test indicated that heterogeneity was acceptable (Table S4, Supplemental Digital Content, https://links.lww.com/MD/O930).[30] Finally, the MR Steiger test confirmed that the direction of causality is unidirectional, flowing from diet to PsA (Table S5, Supplemental Digital Content, https://links.lww.com/MD/O930).

3.2. Association of plasma metabolites with PsA

MR analysis identified 132 plasma metabolites significantly associated with PsA (Table S6, Supplemental Digital Content, https://links.lww.com/MD/O930). Of these, 65 metabolites exhibited positive correlations with outcomes, while 67 metabolites showed negative correlations. The volcano plot was generated to visually illustrate these results (Fig. 5). In the MR-Egger regression tests conducted on the 132 significant plasma metabolites, all *P*-values exceeded .05. This finding indicates that the observed causal relationships are not confounded by pleiotropy. Details of pleiotropy tests for the remaining plasma metabolites are presented in Table S7, Supplemental Digital Content, https://links.lww.com/MD/O930. Cochran *Q* test was conducted, with detailed results provided in Table S7, Supplemental Digital Content, https://links.lww.com/MD/O930. Additionally, the MR Steiger test further confirmed that the causal relationship between plasma metabolites and PsA is unidirectional (Table S8, Supplemental Digital Content, https://links.lww.com/MD/O930).

3.3. Association of dietary habits with plasma metabolites

Conduct a 2-sample MR analysis on red wine intake per month, overall alcohol intake, overall cheese intake, total drinks of alcohol per month, and coffee type (decaffeinated), respectively with the 132 significant plasma metabolites. Through MR analysis, it was found that red wine intake (measured in glasses per month) is causally related to 6 plasma metabolites (Table S9, Supplemental Digital Content,

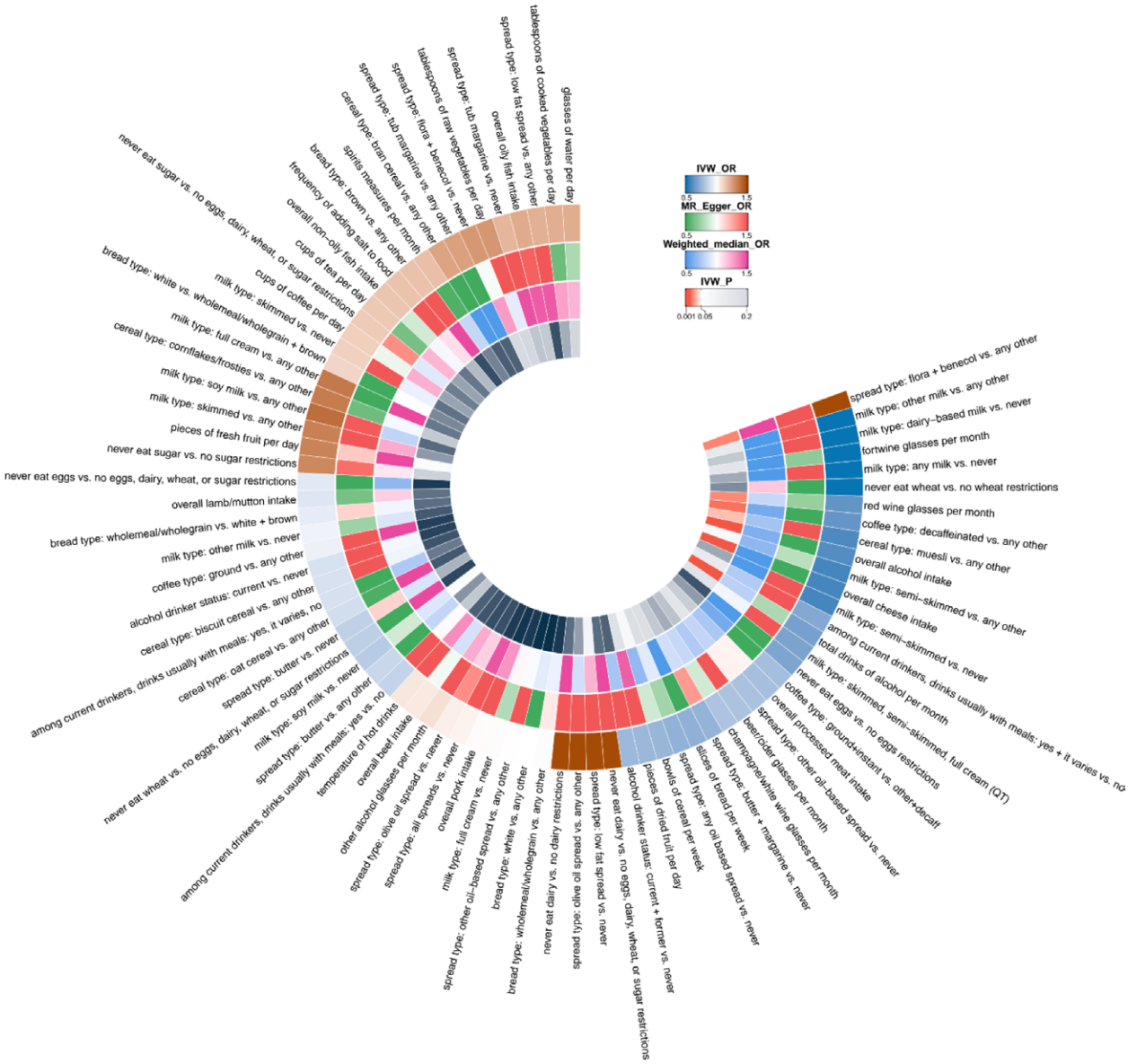

Figure 4. The circular heatmap plot comprehensively depicts the causal analysis of dietary habits and psoriatic arthritis. IVW = inverse-variance weighted, MR-Egger = The Mendelian randomization-Egger, OR = odds ratio.

Table 1

Sensitivity analysis of the associations between 5 significant dietary habits on psoriatic arthritis.

		Heterogeneity test				Pleiotropy test		
		MR-Egger		IVW		MR-Egger intercept		
Exposure	Outcome	*Q*	pval	*Q*	pval	Intercept	SE	pval
Red wine intake per month	PsA	168.7	.003	168.8	.003	−0.002	0.009	.839
Overall alcohol intake	PsA	281.6	.005	283.5	.005	0.008	0.006	.226
Overall cheese intake	PsA	184.6	.107	188.7	.082	0.015	0.007	.061
Total drinks of alcohol per month	PsA	232.3	.101	232.5	.108	−0.002	0.005	.689
Coffee type (decaffeinated)	PsA	156.5	.010	156.8	.012	0.005	0.011	.641

IVW = inverse-variance weighted, MR-Egger = The Mendelian randomization-Egger, PsA = psoriatic arthritis, *Q* = The *Q* statistic of Cochran *Q* test, SE = standard error.

https://links.lww.com/MD/O931). Overall alcohol intake is causally associated with 12 plasma metabolites, while overall cheese intake is also causally associated with 12 plasma metabolites. Additionally, total drinks of alcohol per month is causally associated with 4 plasma metabolites. The analysis of coffee type (decaffeinated) reveals a causal association with 19 plasma metabolites. No evidence of pleiotropy was observed in the MR-Egger regression test, and Cochran *Q* test

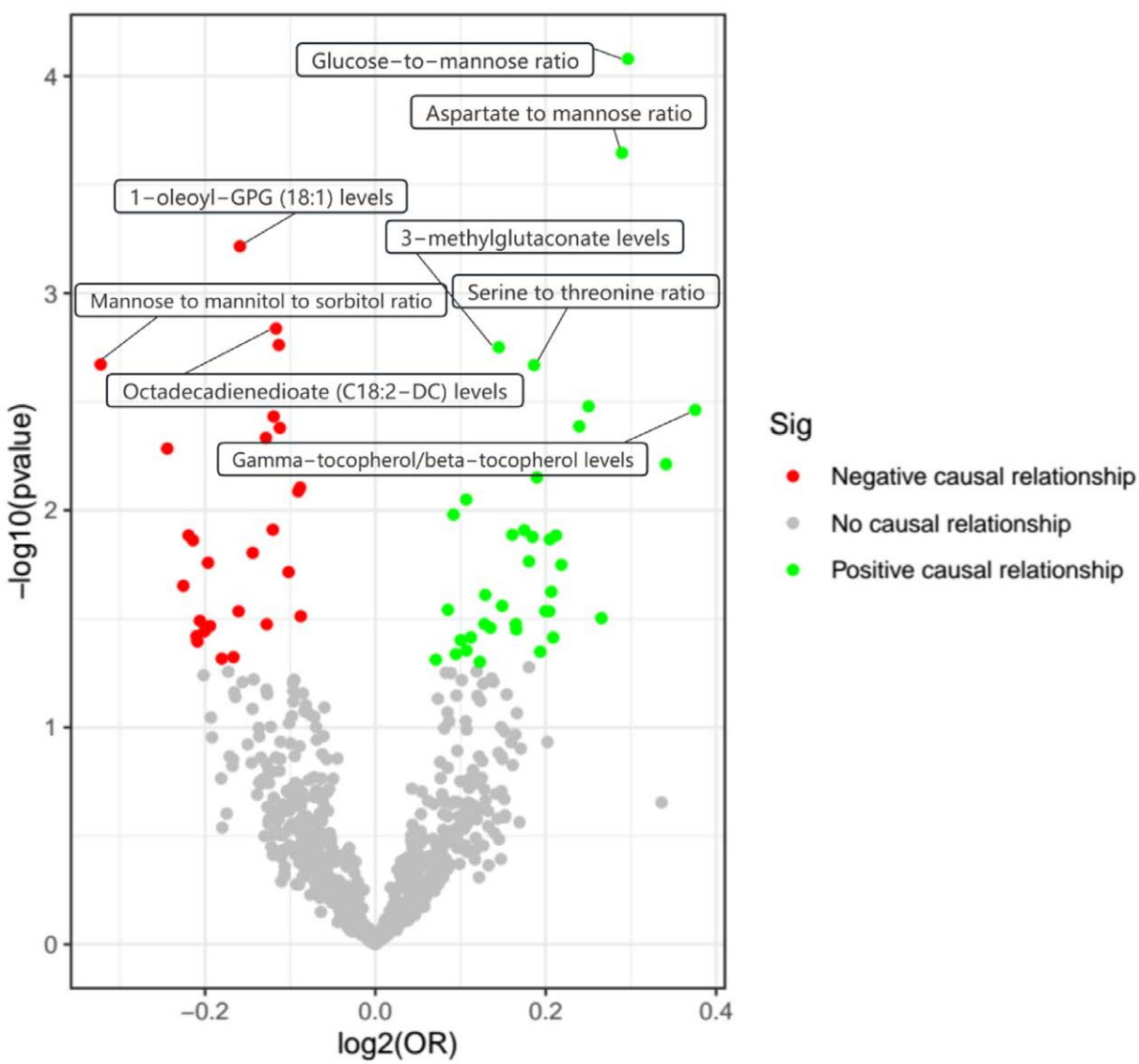

Figure 5. The volcano plot was generated to illustrate the associations between serum metabolites and psoriatic arthritis. The figure displays OR on a log2 scale, with *P* values converted to −log10 (*P* value) using the IVW method. Metabolites that are causally associated with psoriatic arthritis at a nominal significance level (*P*-IVW < 0.05) are highlighted with red circles, indicating negative causality, and green circles, indicating positive causality. OR = odds ratio, IVW = inverse-variance weighted.

indicated no heterogeneity (Table S10, Supplemental Digital Content, https://links.lww.com/MD/O931). Furthermore, the causal relationship between diet and plasma metabolites was found to be unidirectional, as evidenced by the MR Steiger test (Table S11, Supplemental Digital Content, https://links.lww.com/MD/O931).

3.4. Mediation effect of plasma metabolites between dietary habits with PsA

Through a 2-step MR design analysis, Gamma-tocopherol/beta-tocopherol levels and citrate levels were identified as mediators of the causal relationship between red wine intake (measured in glasses per month) and PsA (Table 2). The indirect effect values are −0.0850 and −0.0343, respectively. The proportions of the mediating effect relative to the total effect are 17.8% and 7.2%, respectively. Additionally, arginine levels and the phosphate-to-threonine ratio are considered mediators in the causal relationship between overall cheese intake and PsA, with indirect effect values of −0.0420 and −0.0412, respectively. The proportions of the mediating effect to the total effect for these variables are 7.4% and 7.2%, respectively. Furthermore, the glutamate-to-alanine ratio, ornithine-to-glutamate ratio, and arginine to glutamate ratio are regarded as mediators of the causal relationship between coffee type (decaffeinated) and PsA, with indirect effect values of −0.0574, −0.0511, and −0.0419, respectively. The proportions of the mediating effect to the total effect for these ratios are 12.2%, 10.9%, and 8.9%, respectively.

4. Discussion

This study provides genetic evidence supporting a causal relationship between 5 dietary habits and PsA, revealing a negative correlation. Furthermore, plasma metabolites may mediate this causal association between diet and PsA. This research is believed to be the first to investigate the causal relationship among dietary habits, plasma metabolites, and PsA through MR analysis, while emphasizing the role of plasma metabolites as mediators.

Table 2

Two-step MR analysis results.

Exposure	Mediator	Outcome	Total effect	Indirect effect	Direct effect	Proportion
Red wine intake per month	Gamma-tocopherol/beta-tocopherol levels	PsA	-0.477	-0.085	-0.392	17.80%
Red wine intake per month	Citrate levels	PsA	-0.477	-0.034	-0.443	7.20%
Overall cheese intake	Arginine levels	PsA	-0.569	-0.042	-0.527	7.40%
Overall cheese intake	Phosphate-to-threonine ratio	PsA	-0.569	-0.041	-0.528	7.20%
Coffee type decaffeinated)	Glutamate-to-alanine ratio	PsA	-0.469	-0.041	-0.427	12.20%
Coffee type (decaffeinated)	Ornithine-to-glutamate ratio	PsA	-0.469	-0.051	-0.418	10.90%
Coffee type (decaffeinated)	Arginine -to-glutamate ratio	PsA	-0.469	-0.057	-0.412	8.90%

MR = Mendelian randomization, PsA = psoriatic arthritis.

Our results demonstrate a negative causal relationship between the intake of red wine, cheese, and decaffeinated coffee and PsA, corroborating findings from previous studies.[6,10] The Mediterranean diet is characterized by the traditional eating habits of the Mediterranean region, encompassing fresh fruits and vegetables, cereals, high-quality dairy products, including cheese, and moderate amounts of red wine.[31] One study examining the relationship between diet and PsA found that among patients with PsA, higher levels of disease activity, as measured by the Disease Activity Index for PsA (DAPSA), were associated with lower adherence to the Mediterranean diet.[32] This suggests that this dietary pattern may offer potential anti-inflammatory benefits. Additionally, findings indicate that adherence to the Mediterranean diet is linked to lower levels of biomarkers such as C-reactive protein, interleukin-6, and fibrinogen.[33] The Mediterranean diet is recognized as a low-inflammatory diet.[33] A recent meta-analysis reported that a low-inflammatory diet was not only significantly associated with greater weight loss but also demonstrated positive effects in reducing inflammatory biomarkers in PsA and psoriasis compared to a conventional diet.[34] Furthermore, it effectively improves joint pain and overall body function.[34] Moderate alcohol intake may confer benefits to the bone health of men and postmenopausal women.[35] Individuals who consume moderate amounts of alcohol exhibit a lower risk of developing PsA compared to those who abstain from alcohol altogether.[10] Resveratrol, a stilbene compound found in red wine, possesses antioxidant and anti-inflammatory properties through related molecular pathways and has shown protective effects against osteoarthritis by reducing inflammatory markers.[36] The aforementioned research indicates that moderate alcohol intake may reduce joint inflammation and potentially lower the risk of PsA to some extent. Our MR analysis yielded similar findings, suggesting a significant association between both alcohol intake and red wine intake with PsA, indicating that these factors may serve as protective elements against the disease. Furthermore, our study identified coffee and cheese intake as protective factors for PsA. Coffee contains various compounds, such as caffeic acid and flavonoids, which possess anti-inflammatory properties and may contribute to mitigating inflammation within the joints.[37] Numerous studies have demonstrated that dairy products supply essential nutrients, including protein and minerals, which are beneficial for bone health.[38,39] Additionally, full-fat dairy products and milk fat exhibit neutral or negative effects on circulating levels of inflammatory biomarkers.[40,41] Based on these findings, it is hypothesized that coffee and cheese intake may confer certain anti-inflammatory benefits. However, there is a scarcity of clinical studies directly examining the relationship between decaffeinated coffee intake and cheese intake and PsA, indicating that future clinical research should aim to increase the number of studies exploring these correlations.

In addition, our findings reveal no significant causal relationship between the remaining 75 dietary habits and PsA. Currently, there is a lack of research investigating the association between tea consumption and PsA. Interleukin-1 beta (IL-1β) plays a crucial role in the inflammatory processes associated with various inflammatory diseases. Studies have demonstrated that green tea polyphenols can effectively reduce IL-1β-induced inflammatory cytokines, thereby potentially delaying the progression of inflammatory diseases.[42] Our study indicates that there is no significant causal relationship between green tea intake and PsA. Fruits, which are rich in antioxidants and anti-inflammatory components, may effectively alleviate arthritis symptoms and play a beneficial role in preventing arthritis.[43] However, our results do not support a causal effect of fruit consumption on PsA. Further exploration in this area may be warranted. Beef, classified as red meat, is believed to potentially increase inflammatory responses within the body, thereby exacerbating arthritis symptoms.[44] The prospective cohort study conducted in Denmark found no significant association between low meat intake and the risk of developing psoriatic arthritis.[9] Additionally, studies have shown that dairy products do not elevate the concentration of biomarkers for chronic systemic inflammation.[45] Research by Denissen et al indicates a significant negative correlation between the intake of full-fat dairy products and osteoarthritis.[46] In light of the negative results obtained in this study, further clinical research is necessary to explore this topic in greater depth.

Plasma metabolites refer to the biochemical substances present in the blood, including amino acids, lipids, and other small molecule metabolites, which are involved in various physiological processes such as energy metabolism, cell signaling, and immune responses.[47] Additionally, they can reflect the metabolic status of the body.[48] Recent studies have indicated that plasma metabolites play a crucial role in the regulation of the immune system.[49] They are associated with a variety of immune-related inflammatory diseases, including systemic lupus erythematosus, psoriasis, and PsA.[50–52] Gamma-tocopherol and beta-tocopherol are significant members of the vitamin E family.[53] Some studies have suggested that gamma-tocopherol has a pro-inflammatory effect, increasing lung inflammation and exacerbating the severity of related diseases, while beta-tocopherol exhibits anti-inflammatory effects in humans.[54,55] The absorption of vitamin E primarily occurs in the small intestine, where it is absorbed with fats into the lymphatic system.[56] Given that lipid metabolism may be altered in patients with PsA, this could affect the distribution and utilization of vitamin E.[56] Furthermore, oxidative stress induced by long-term alcohol consumption may lead to the depletion of antioxidants, such as tocopherols, in the body, thereby affecting their levels.[57] A small sample size study found that red wine consumption was directly related to plasma tocopherol concentrations, with moderate consumption of red wine having a counteractive effect on plasma antioxidant content.[58] Our study demonstrates that the levels of gamma-tocopherol/beta-tocopherol mediate the negative causal relationship between red wine intake and PsA. These findings provide new insights into the association between red wine intake and PsA.

Citrate, an intermediate product in the citrate tricarboxylic acid (TCA) cycle, is crucial for cellular energy production

and various metabolic processes.[59] Changes in citrate metabolism are linked to cytokine levels in T cell subsets, particularly T helper 17 (Th17) cells.54 Th17 cells are integral to the pathogenesis of PsA, and alterations in citrate metabolism may modulate the inflammatory response by influencing the production of these cytokines.[60] Additionally, chronic alcohol consumption leads to increased production of acetaldehyde, a toxic metabolite.[61] Elevated levels of acetaldehyde are closely associated with disorders of citric acid metabolism, which can disrupt mitochondrial function and consequently affect citrate levels and the normal progression of the citric acid cycle.[61] Our study demonstrates that citrate serves a mediating role in the negative causal relationship between red wine consumption and PsA.

Caffeine, as an adenosine receptor antagonist, influences the activity of various neurotransmitters, including glutamate.[62] Caffeine intake can stimulate the brain to release increased amounts of glutamate, which contributes to its stimulant effect.[63] Due to its very low caffeine content, decaffeinated coffee does not significantly elevate glutamate levels compared to regular coffee. Clinical studies have demonstrated that glutamate levels are associated with inflammatory skin diseases, with psoriasis patients exhibiting significantly higher glutamate levels than healthy individuals.[64] Furthermore, enzymes involved in glutamate metabolism show increased expression in psoriasis patients.[65] This suggests that the utilization and conversion of glutamate may be altered in the metabolic processes of these patients, potentially impacting disease progression and symptom expression. Alanine aminotransferase plays a role in regulating the body's alanine levels. One study involving 5944 adults found that coffee and caffeine consumption may help reduce the risk of elevated alanine aminotransferase levels in high-risk individuals.[65] Additionally, another study indicated that patients with PsA were 2 to 3 times more likely to have elevated alanine aminotransferase and aspartate aminotransferase levels compared to patients with rheumatoid arthritis.[66] Ornithine has been found to be overexpressed in the serum of patients with PsA.[67] It is believed that ornithine promotes inflammation by regulating immune responses, which may play a significant role in the pathological processes associated with PsA.[68] Research indicates that caffeine significantly influences arginine metabolism.[69] Furthermore, decaffeinated coffee may affect arginine metabolism differently compared to regular coffee. Asymmetric dimethylarginine (ADMA), a metabolite of arginine, serves as an endogenous inhibitor of nitric oxide synthesis.[70] Studies have demonstrated that patients with PsA exhibit a reduced L-arginine to ADMA (L-arginine/ADMA) ratio, which may correlate with their inflammatory state.[70] These findings offer insights into potential mechanisms underlying the mediating role of 3 plasma metabolite ratios (glutamate to alanine ratio, ornithine to glutamate ratio, and arginine to glutamate ratio) in the causal relationship between decaffeinated coffee intake and PsA.

As a nutrient-rich dairy product, cheese positively influences human health and metabolism.[38] In a randomized parallel group intervention trial, cheese consumption was found to affect arginine metabolism by regulating blood sugar and fat metabolism; these changes may be linked to variations in its nutritional composition and pH value.[71] In patients with PsA, elevated arginase activity may lead to increased consumption of arginine, resulting in reduced nitric oxide production.[70] This alteration may trigger vascular dysfunction and exacerbate the inflammatory response in the joints. Moreover, cheese consumption has been associated with sustained increases in blood amino acid levels, including threonine, which is beneficial for muscle repair, growth, and overall metabolic health.[72] Elevated threonine levels in humans may also correlate with inflammatory responses.[73] Notably, threonine, citrulline, and ornithine exhibit strong positive correlations with Psoriasis Area and Severity Index scores.[73] Additionally, in patients with PsA, levels of certain metabolites, such as ethanolamine phosphate, have been found to be significantly higher than in healthy controls.[51] Our results suggest that the levels of arginine and the phosphate-to-threonine ratio may mediate the causal association between cheese intake and PsA. These findings complement the aforementioned mechanistic studies.

Dietary intervention has a significant impact on PsA.[11] Our findings indicate that 5 dietary habits exhibit a causal relationship with PsA, serving as protective factors against the condition. These results may assist in clinical diagnosis and treatment strategies. Moderate consumption of red wine and decaffeinated coffee, along with increased cheese intake, may reduce the risk of developing PsA. In managing patients with a family history of psoriatic arthritis, monitoring alcohol intake could be integrated into the disease prevention recommendation system. In the context of PsA diagnosis, approximately 25% of patients test positive for human leukocyte antigen-B27 (HLA-B27); however, elevated serum C-reactive protein levels or erythrocyte sedimentation rates are observed in only 40% of cases.[2] Notably, this study reveals that Gamma-tocopherol/beta-tocopherol levels have a significant mediating effect (accounting for 17.8%) on the relationship between red wine consumption and PsA. The ratio of these metabolite levels serves as a potential biomarker, providing a theoretical foundation for the development of new blood test indicators that may facilitate the early identification of individuals at high risk for developing PsA. Regarding treatment, clinicians should recognize that for immune-mediated inflammatory diseases, including PsA, anti-inflammatory diets complement pharmacotherapy.[74] Our findings suggest that adopting a dietary habits perspective for PsA patients, combined with dietary log monitoring, can contribute to the formulation of personalized treatment plans.

The significance of this study lies in its use of MR analysis, which provides robust evidence for the causal relationship between various dietary habits and PsA, effectively mitigating the influences of confounding factors and reverse causality. Furthermore, the MR analysis identified direct links between 5 specific dietary intakes and PsA. These findings offer valuable insights for dietary interventions and treatment strategies for PsA. Additionally, the study revealed that multiple plasma metabolites serve as mediators in the association between dietary habits and PsA, as demonstrated through a 2-step MR design analysis. This discovery lays the groundwork for further investigation into the pathological mechanisms underlying PsA.

This study has several limitations. Firstly, the GWAS data for the exposures (dietary factors), mediators (plasma metabolites), and outcomes (PsA) included in this study were derived exclusively from individuals of European ancestry. While utilizing a homogeneous population can mitigate bias stemming from population stratification, the generalizability of the causal inferences to non-European populations (such as those of Asian or African descent) necessitates cautious validation.[75] The IVs for exposures, mediators, and outcomes may be influenced by variations in dietary culture, gene-environment interactions, and differences in the genetic architecture of diseases.[76] These factors limit the applicability of our findings beyond European populations. Future research should aim to include a broader range of population cohorts (such as Latin American groups and the East Asian Japan Biobank), employing cross-ancestry GWAS meta-analyses to develop genetic tools that are effective across ethnicities, thereby validating and enhancing the relevance of our observed findings.[77] Secondly, the timeliness and rationality of data selection are crucial factors. It is important to conduct a systematic evaluation in subsequent research, tracking updates to the GWAS database and deepening existing studies. Additionally, bidirectional 2-sample MR analysis can systematically assess reverse causality. In the next phase of this research, it is crucial to explore the bidirectional analysis of plasma metabolites and PsA. Furthermore, conducting

longitudinal clinical cohort studies or randomized controlled trials focused on dietary interventions will help verify the temporal sequence of this bidirectional causality. Lastly, further experimental studies are essential, particularly those utilizing cell and animal models, to thoroughly investigate the specific mechanisms by which plasma metabolites interact with dietary habits in relation to PsA.

5. Conclusion

In summary, our study demonstrates a causal relationship between 5 dietary habits and PsA. Multiple plasma metabolites significantly mediate the effects of diet on PsA. These findings provide valuable insights into the underlying mechanisms linking diet and PsA, as well as the potential for preventing and managing PsA through dietary modifications.

Author contributions

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