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Impact of habitual intake of glucosamine, fresh fruit, and tea on the risk of urolithiasis

A two-sample Mendelian randomization study

Yongdong Pan[a], Jingyi Su[a], Subo Qian[b], Guofeng Xu[a,*]

Abstract

Dietary patterns have a significant impact on the occurrence of urolithiasis. This study aimed to investigate the causal relationships between the consumption of glucosamine, fresh fruits, and tea, and the predisposition to urinary stones using a Mendelian randomization (MR) approach. Genetic proxies for these dietary factors were obtained from the UK Biobank, while the summary data for urolithiasis genome-wide association analyses were sourced from the FinnGen consortium. Five MR methodologies, namely inverse variance weighted (IVW), MR-Egger regression, weighted median, weighted mode, and simple mode, were employed in the analysis. To validate the findings, sensitivity evaluations such as the MR-PRESSO disruption test and Cochran Q test for heterogeneity were performed. The IVW method showed that glucosamine consumption had a strong inverse association with urolithiasis risk (Odds Ratio [OR] = 0.006, 95% Confidence Interval [CI] 0.0001–0.287, P = .009), surpassing the associations of fresh fruits (OR = 0.464, 95% CI 0.219–0.983, P = .045) and tea (OR = 0.550, 95% CI 0.345–0.878, P = .012). These findings were consistent when verified using alternative MR techniques, and the sensitivity analyses further supported their credibility. The results of this MR analysis demonstrate that regular consumption of glucosamine, fresh fruits, and tea is inversely correlated with the risk of developing urolithiasis.

Abbreviations: CRP = C-reactive protein, GWASs = genome-wide association studies, IV = genetic variation, IVW = inverse variance weighted, MR = Mendelian randomization, OR = odds ratio, SNPs = single nucleotide polymorphisms.

Keywords: fresh fruit, glucosamine, Mendelian randomization, tea, urolithiasis

1. Introduction

The incidence of urolithiasis has been on the rise on a global scale, with varying prevalence rates observed across different continents: North America reports 7% to 13%, Europe has rates between 5% to 9%, and Asian countries note 1% to 5%.[1] Moreover, longitudinal observations post-initial urolithiasis episode reveal a staggering recurrence rate of 50% within a decade.[2] This high frequency and repeat occurrence of urolithiasis impose a significant financial burden on healthcare systems. Projections indicate that by the year 2030, the costs associated with the prevention and management of urolithiasis in the United States may escalate by as much as 33%, equating to an extra $1.24 billion annually.[3] There is accumulating evidence that suggests a correlation between urolithiasis and dietary habits that may be considered detrimental to health.[4,5] Factors such as the composition and the pH of urine are instrumental in the formation of crystals, which could initiate the development of stones within the urinary tract. Given that both dietary intake and pharmacotherapy have the potential to modulate the metabolic byproducts in urine, a thorough investigation into the connection between the ingestion of food substances and medications in regular diets and the incidence of urolithiasis is of paramount significance. Such research is not only essential for the prevention of urolithiasis but also plays a crucial role in its medical nutritional management.

Glucosamine, an amino monosaccharide that naturally occurs in cartilage and synovial fluid as well as in the exoskeletons of marine crustaceans and some fungal species, is extensively utilized as a nutritional adjunct in the United States and Australia,[6,7] and is sanctioned as a medicinal agent for managing osteoarthritis across the majority of European

YP, JS, and SQ contributed equally to this work.

All subjects received informed consent in the original study.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

No additional ethical approval is required as this is a re-analysis of data that is already publicly available.

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[a] Department of Pediatric Urology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China, [b] Department of Urology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China.

**Correspondence: Guofeng Xu, Department of Pediatric Urology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200092, China (e-mail: 18556355759@163.com).*

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nations.[8] Glucosamine is renowned not solely for its ameliorative influences on osteoarthritis and joint malaise but also epidemiologic investigations have revealed its potential role in forestalling cardiovascular pathologies,[9] metabolic disorders such as diabetes,[10] and malignancies of the colorectal[11] and pulmonary regions,[12] with supplemental usage of glucosamine correlated with reductions in overall mortality rates.[13] Advances in both animal and human studies have discerned alterations in gut microbial populations post-glucosamine supplementation,[14,15] culminating in mitigatory effects on inflammatory gastrointestinal conditions.[16,17] Recent scholarly endeavors have corroborated the efficacy of glucosamine oral application in conferring expansive defense against human coronaviruses.[18] Pertaining to its plausible pathways of action, prior analyses have postulated that glucosamine participates in synthesizing anti-inflammatory agents.[19] The etiology and progression of urolithiasis are intertwined with numerous inflammatory processes.[20] Nonetheless, contemporary literature is deficient in examinations pertaining to the correlation of glucosamine consumption and the hazard of urolithiasis.

Abundant in essential micronutrients and dietary fiber, fresh fruits are integral to fulfilling the nutritional requisites of the human body.[21] Concurrently, tea offers a rich source of polyphenols and a diversity of phytochemicals.[22] The regular consumption of fresh fruits and tea provides a plethora of benefits, encapsulating antioxidative capacities, cardiovascular fortification, immune system enhancement, digestive health support, along with anti-inflammatory effects.[23,24] Protective correlations between the intake of fruits and tea against urolithiasis have been manifest in prior investigations,[25] yet substantiating their causal influence demands additional empirical substantiation.

Employing Mendelian randomization (MR), a methodological paradigm for inferring causality, this research leverages single nucleotide polymorphisms (SNPs) as implements for genetic variation (IV) to approximate the rigor of randomized controlled trials.[26] This approach capitalizes on the random allocation of genetic variants during meiosis, which are then ostensibly unaffected by disease states in subsequent stages of life, thereby diminishing the impact of confounders and nullifying reverse causation concerns when probing gene-disease associations in a population of adequate scale. For the scope of this work, MR was utilized, harnessing genetic variants identified to be related to the intake of glucosamine, fresh fruits, and tea, aiming to interrogate the putative causal connections between these dietary factors and the risk of developing urolithiasis.

2. Materials and methods

Our study design and methodology adhered stringently to the stipulations of the "Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization" (STROBE-MR) checklist.[27] The core of Mendelian Randomization (MR) analysis hinges on using genetic variants as instrumental variables (IVs) to establish putative causal relationships between an exposure and an outcome. These analyses rest on 3 primary hypotheses: the Relevance Criterion: a robust association must exist between the single nucleotide polymorphism (SNP) and the exposure of interest; the Independence Criterion: the SNP must maintain independence from all confounding variables; the Exclusion Criterion: the SNP impact on the outcome is exclusively mediated through the exposure. This investigation synthesizes summary-level data extant in extensive genome-wide association studies (GWASs) and various consortia, ensuring prior patient consent and ethical clearance from pertinent institutional review boards.

2.1. Data sources

The genetic correlates of glucosamine intake, fresh fruit consumption, and tea drinking habits were sourced from a comprehensive GWAS implemented by the UK Biobank, canvasing upwards of 500,000 individuals aged 40 to 70 years.[28] The baseline assessment of these dietary elements was gathered via food frequency questionnaires administered during visits spanning 2006 to 2010,[29] querying: Do you regularly take any of the following? (1: Fish oil; 2: Glucosamine;3: Calcium;4: Zinc; 5: Iron; 6: Selenium; 7: None of the above); About how many pieces of FRESH fruit would you eat per DAY? (Count 1 apple, 1 banana, 10 grapes etc as 1 piece; put '0' if you do not eat any); How many cups of tea do you drink each DAY? (Include black and green tea). Complementary information is accessible at https://biobank.ndph.ox.ac.uk/showcase.

The GWAS summary statistics pertinent to urolithiasis were procured from the FinnGen consortium latest release (URL: https://r8.finngen.fi/pheno/N14_UROLITHIASIS), with case delineation grounded in ICD-10 codification (N20-N23).[30] The analytical cohort comprised 309,154 participants—8060 individuals with urolithiasis and 301,094 controls—all with European genetic lineage. A compendium of this data is systematically itemized in Table 1.

2.2. Genetic instrument selection

Instrumental variable (IV) selection was predicated on GWAS datasets corresponding to specific traits, which were extracted from the IEU OPEN GWAS database (https://gwas.mrcieu.ac.uk/datasets). The SNP filtration ensued in sequential phases: SNPs concomitant with glucosamine, fresh fruit, and tea intake as IVs were initially earmarked at a genome-wide significance threshold of $P < 5 \times 10^{-8}$. Ensuring the autarky of the chosen IVs via imposition of stringent criteria, with linkage disequilibrium at an r^2 threshold <0.001 and a maximal distance interval restrained within 10,000 kilobases. The SNP-exposure associations were quantified employing F-statistics, dismissing any SNPs with F < 10 to preclude the inclusion of weak instruments. This rigorous screening culminated in the identification of 5, 55, and 41 SNPs as IVs for glucosamine, fresh fruit, and tea intake, respectively. An elaborative tabulation of these SNPs is accessible in Supplementary Table S1, http://links.lww.com/MD/L702.

2.3. Statistical analysis

Our initial Mendelian Randomization (MR) approach incorporated the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test, using a 10,000-simulation cohort.[31] Upon the detection and exclusion of outliers via MR-PRESSO, the residual IVs were employed in the principal MR inquiries. To deduce the causal connections between glucosamine, fresh fruit, and tea intake on the predisposition to urolithiasis, we deployed a 2-sample MR analysis featuring an assortment of 5 established methodologies: Inverse Variance Weighted (IVW), MR-Egger regression, Weighted Median,

Table 1

Detailed information about data sources of glucosamine, fresh fruit and tea intakes, and urolithiasis.

Traits	GWAS ID	Consortium	Yr	Sample
Glucosamine intake	ukb-b-11535	UKBB	2018	461,384
Fresh fruit intake	ukb-b-3881	UKBB	2018	446,462
Tea intake	ukb-b-6066	UKBB	2018	447,485
Urolithiasis	N14_UROLITHIASIS	FinnGen	2022	309,154

GWASs = genome-wide association studies.

Weighted Mode, and Simple Mode. The IVW result was appointed as the mainstay MR estimate, with corroborative consistency scrutinized through the alternative MR avenues.[32] All p-values were expressed in a 2-tailed manner with a significance level affixed at $P < .05$.

Cochran Q test was initiated to probe the heterogeneity of MR outcomes; a P value < .05 indicated significant heterogeneity in SNP effectual estimations.[33] Meanwhile, the MR-Egger regression intercept served as a diagnostic measure of potential horizontal pleiotropy—assuming the presence of such pleiotropy was negated when the intercept neared zero, aligning with the IVW results.[34] Additionally, leave-one-out sensitivity assessments pinpointed outliers altering causality. An intercept P value < .05 in MR Egger implied directional pleiotropy, with MR-PRESSO also detecting and amending pleiotropic outliers.[31]

Our MR analyses were executed utilizing R software (version 4.2.1), encompassing the "TwoSampleMR," "mr-raps," and "MR-PRESSO" packages.

3. Results

The F-values associated with the set of 101 SNPs uniformly surpassed a threshold of 25, signifying a robust association between the application of our analytic instrument and the consumption patterns of glucosamine, fresh fruits, and tea. Additionally, our examination utilizing the MR-PRESSO tests for these dietary elements identified no anomalous SNPs.

Figurative representation of the MR findings appears in Figure 1. Predictive genetic models linking the consumption of glucosamine, fresh fruits, and tea with urolithiasis incidence infer a converse relationship. Notably, the predicted causal influence of glucosamine consumption on urinary calculi formation exhibited paramount significance (Inverse Variance Weighted Odds Ratio (IVW OR) = 0.006, 95% Confidence Interval (CI) 0.0001–0.287, P = .009), exceeding the effects from fresh fruit consumption (IVW OR = 0.464, 95% CI 0.219–0.983, P = .045), and tea (IVW OR = 0.550, 95% CI 0.345–0.878, P = .012). Analogous effect measures were observed consistently for the trio of dietary consumptions within quintuple MR analytical methods (demonstrated in Figs. 1 and 2).

To minimize the impact of confounding biases, exhaustive sensitivity checks were carried out to determine the robustness of the MR analytical framework and assess any potential pleiotropic influences of the dietary intake instrument variables. No variants demonstrating potential causative connections with urolithiasis were identified. The statistical outcomes, detailed in Table 2, via Cochrane Q test applied to both MR-Egger and IVW modalities, presented no substantial heterogeneity ($P > .05$). The funnel plot corresponding to glucosamine intake, limited by the quantifiable SNP count, disallowed conclusive symmetry. In contrast, those for fresh fruit and tea intake were characteristically symmetrical (Fig. 2). Intercept values calculated in MR-Egger regression approximated the null value, suggesting an absence of horizontal pleiotropy. Complementary leave-one-out sensitivity analyses substantiated that no single SNP exclusion significantly modified the overarching results (Fig. 2). These comprehensive sensitivity evaluations thus affirm the integrity of the MR analytical construct deployed in this study.

4. Discussion

Up until the present, while numerous MR studies have scrutinized the correlation between dietary patterns and disease vulnerability, our research constitutes the inaugural MR exploration to elucidate the causative influence of glucosamine and fresh fruit consumption on the susceptibility to urolithiasis. The MR inquiry utilized data extracted from the UK Biobank GWAS repository, thus unraveling the direct causality linking augmented intake of glucosamine, fresh fruits, and tea with a diminished incidence of urolithiasis (OR < 1). The regular intake of glucosamine demonstrated the most profound

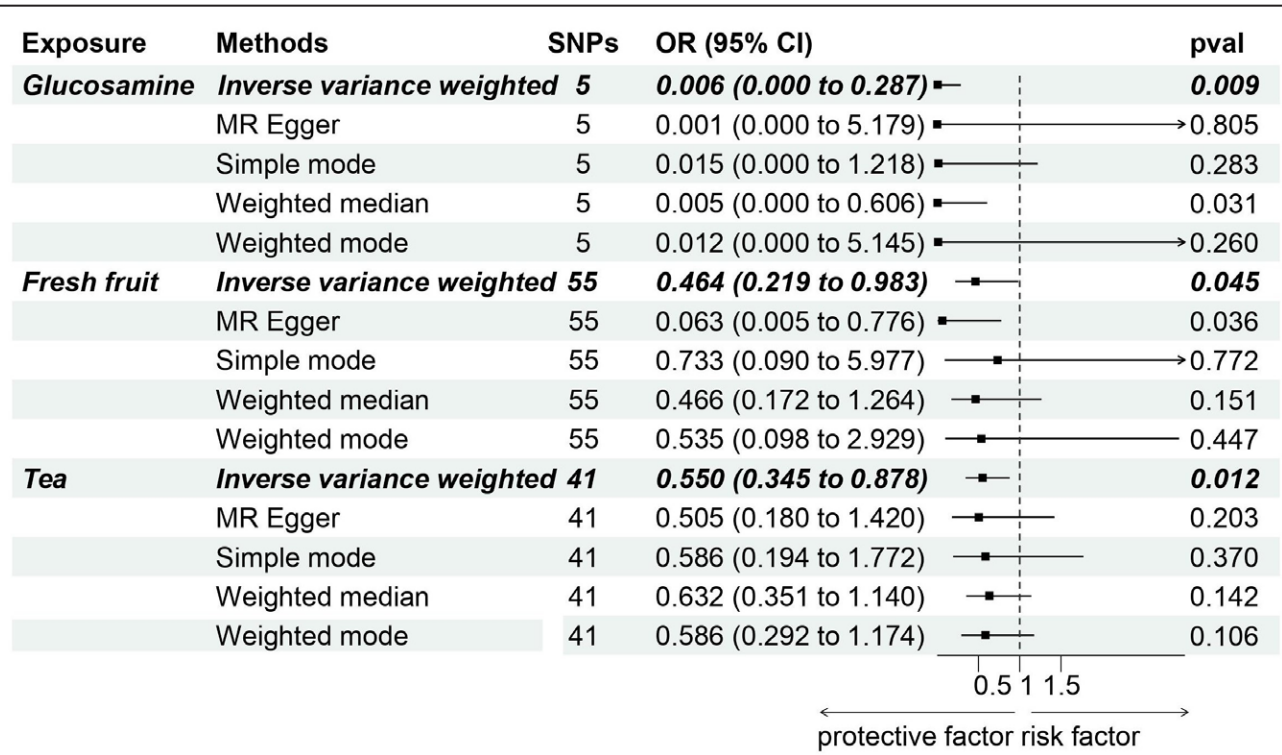

Figure 1. Mendelian randomization estimates of glucosamine, fresh fruit, and tea intake and the risk of urolithiasis using 5 different mendelian randomization methods. OR = odds ratio, SNP = single-nucleotide polymorphism.

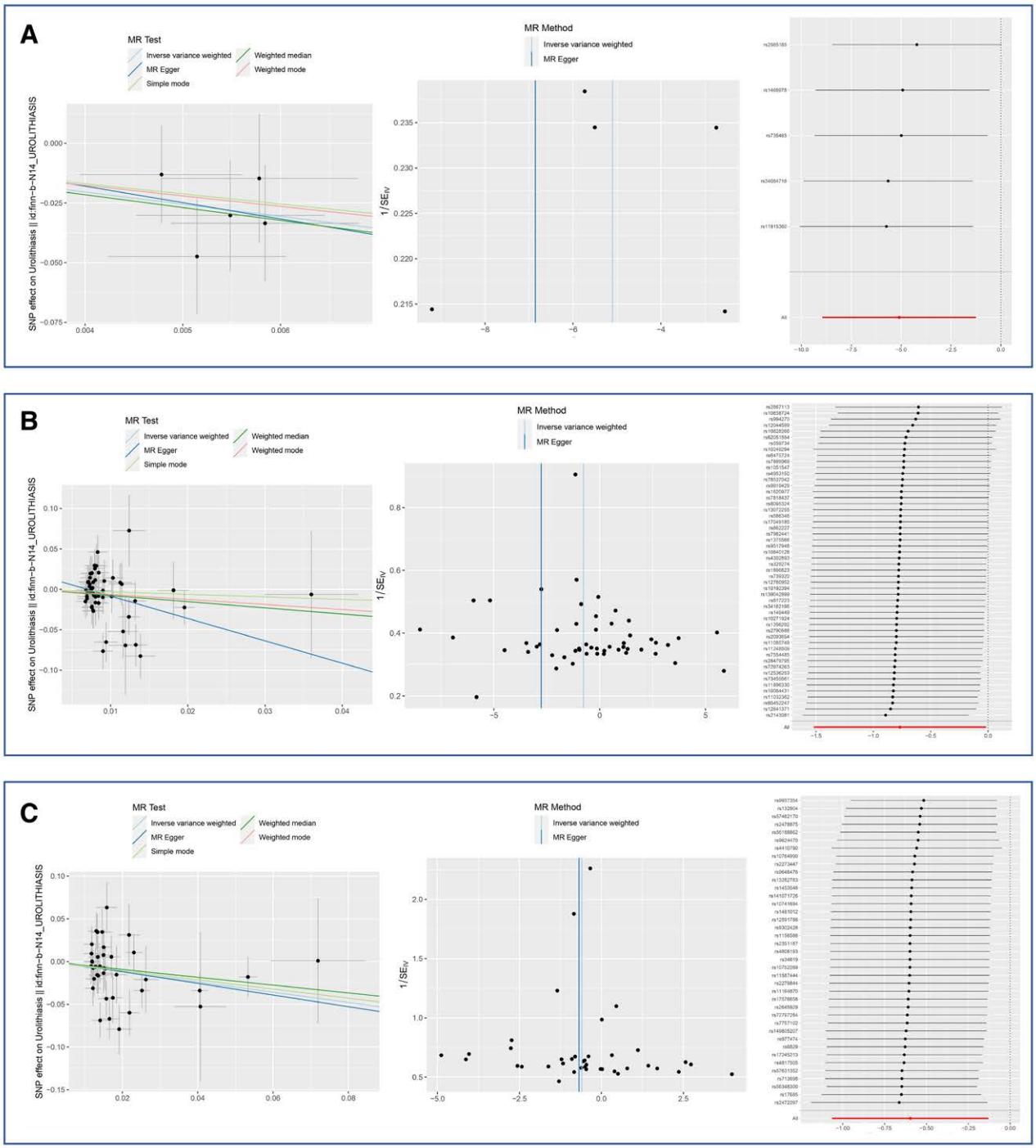

Figure 2. A, B, and C represent the collection of scatter plots, funnel plots, and leave-one-out analysis of MR analysis on the association between the intake of glucosamine, fresh fruit, tea and the risk of urolithiasis, respectively. SNP = single-nucleotide polymorphism.

Table 2

Sensitivity analysis for MR.

Exposure	Q-Egger	*P* value	Q-IVW	*P* value	Egger-Intercept	*P* value
Glucosamine	1.41	.70	1.41	.84	0.009	.95
Fresh fruits	59.60	.17	62.77	.12	0.012	.11
Tea	54.58	.31	54.63	.39	0.002	.86

IVW = inverse variance weighted.

impact in curtailing the risk of developing urinary stones (IVW OR = 0.006, 95% CI 0.0001–0.287, $P = .009$), amidst a paucity of studies previously probing into this specific association. These results emphasize the vital significance of daily dietary consumption in the etiology of urolithiasis and offer imperative insights for subsequent investigative endeavors.

Glucosamine sulfate, commonly referred to as glucosamine, is a naturally-occurring amino sugar with widespread prevalence. The protective influence of glucosamine against urolithiasis can be attributed to several potential biological mechanisms. Kantor et al[35] have previously reported a noteworthy association between habitual glucosamine consumption and attenuated levels of C-reactive protein (CRP), a marker of inflammation. Following research by the same team[36] delineated lower concentrations of systemic inflammatory markers, such as high-sensitivity CRP and urinary prostaglandin E2 metabolites, among glucosamine users compared to non-users. The inhibitory effect of glucosamine on nuclear factor κB activity, a pivotal transcription factor in the inflammatory response, was observed in an in vitro study by Largo et al[37] Furthermore, glucosamine administration in animal models has been linked to a decrease in nuclear factor κB-associated inflammatory markers.[38,39] The connection between glucosamine utilization and mitigated inflammatory response aligns with emerging evidence tying inflammation to urolithiasis pathogenesis, particularly in calcium-based kidney stone disease. For instance, the activation of M1 macrophages is intimately involved in the formation of initial Randall plaques, the substrate supporting the adhesion and growth of calcium oxalate crystals.[40] Additionally, renal crystal deposits have been correlated with the production of reactive oxygen species and inflammasome activation.[41] Historical research dating to 1990 by demonstrated that glycosaminoglycans, metabolic byproducts of glucosamine, could alter erythrocyte oxalate transport, thereby reducing renal clearance of oxalate and hindering calcium oxalate stone formation.[42] Moreover, glucosamine has been shown to imitate the metabolic profile of a low-carbohydrate regimen by decreasing glycolysis and heightening amino acid catabolism in murine models.[43] Diets low in carbohydrates offer protection against obesity, diabetes, and cardiovascular ailments—conditions recognized as urolithiasis risk factors.[44–46] Observations indicate heightened carbohydrate consumption in individuals prone to stone formation compared with non-stone formers, with increased carbohydrate intake potentially augmenting both intestinal calcium absorption and urinary calcium excretion via diminished renal tubular reabsorption.[47] Glucosamine intake has also been correlated with an improved composition of gut microbiota.[14,16] The significance of the gut microbiome in modulating renal physiology through the gut-kidney axis, and its implied role in urolithiasis pathogenesis, has been well documented in recent literature.[48,49] Consequently, the impact of glucosamine on urolithiasis may extend to modulation of gut microbial ecology. Acknowledging the prospect of additional interrelated pathways, the need for extensive exploration of the mechanisms mentioned above remains pressing.

Consumption of fresh fruits provides a dietary avenue for alkaline and citrate enrichment, a position substantiated by numerous studies illustrating the fruit protective role against urolithiasis, a finding consistent with our own data. Citrus varieties, namely lemons, limes, and oranges, stand as rich natural sources of citric acid.[50] Recorded meta-analytic evidence indicates that high citrus consumption correlates with elevated urinary pH and citrate concentrations in comparison to control subjects.[51] Furthermore, among individuals afflicted with urolithiasis, those consuming citrus fruits demonstrate a reduction in urinary calcium discharge. Plants synthesize phytochemicals, such as polyphenols and flavonoids, which are powerful antioxidants found abundantly in a myriad of vegetables and fruits. Augmenting fresh fruit consumption bolsters the body antioxidative defense, mitigating renal oxidative damage wrought by an excess of free radicals, thus thwarting urinary calculi formation.[52,53] In parallel, tea—a beverage laden with polyphenols and various phytochemicals—provides similar antioxidative benefits.[54] Comprehensive investigation within vast cohort studies predominantly endorses tea intake as a potential prophylactic measure against the crystallization of renal stones.[55] Additionally, the caffeine present in tea imparts a diuretic action and diminishes the likelihood of nephrolith adherence onto the renal tubular epithelial surfaces.[56]

Our investigation boasts several methodological strengths. To commence, we sourced our dietary data from the expansive UK Biobank study, incorporating a considerable cohort size that reflects a vast array of dietary habits. This sizable data pool enables meticulous longitudinal monitoring of health trajectories while conforming to rigorous ethical and regulatory standards.[57] In addition, the adoption of a Mendelian randomization (MR) framework enhances the robustness of our cause-effect deductions by curtailing latent confounders and biases, a conclusion corroborated by our sensitivity analysis substantiating the dependability of the causal linkage. Moreover, our inquiry is circumscribed to a European descent cohort, which consolidates the analysis by narrowing confounders due to population stratification. Nevertheless, our study is subject to limitations. Predominantly, the applicability of our conclusions to populations beyond European lineage necessitates further corroboration, as this research was confined to participants of European heritage. Moreover, despite the uniformity displayed across the quintuple MR estimations, the specter of horizontal pleiotropy cannot be completely dismissed in MR explorations. Additionally, the UK Biobank survey lacks precision in its data capture concerning the specifics of glucosamine supplementation, including brand, dosage, and duration, as well as lacking detail regarding types of fresh fruits and teas consumed, which may undercut result validity and complicate subgroup assessments. The assortment of genetic probes associated with glucosamine-related SNPs is somewhat constrained, potentially neglecting the full genetic influence on the studied traits and hence impacting result preciseness. Our focus on urinary stone pathology as a prime outcome does not extend to differentiating stone location or composition. Conversely, a possible convergence of the exposure and outcome cohorts invites the risk of analytic overfitting, potentially skewing causal estimates towards correlations noted in observational studies.[58] Yet, the deployment of an F-statistic >25 in our analytics suggests that any induction of bias due to sample overlap is likely inconsequential.

5. Conclusions

In summary, the current MR analysis offers empirical support for the hypothesis that regular consumption of glucosamine, alongside fresh fruits and tea, is associated with a reduced risk of urolithiasis.

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Author contributions

Conceptualization: Yongdong Pan.
Data curation: Yongdong Pan, Jingyi Su.
Formal analysis: Yongdong Pan.
Investigation: Guofeng Xu.
Methodology: Yongdong Pan, Subo Qian.

Software: Yongdong Pan, Jingyi Su, Subo Qian.
Supervision: Subo Qian.
Validation: Guofeng Xu.
Writing – original draft: Yongdong Pan, Subo Qian.
Writing – review & editing: Guofeng Xu.

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