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ORIGINAL RESEARCH

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Can micronutrient supplementation prevent erectile dysfunction? A bidirectional two-sample Mendelian randomization study

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Abstract

Background: Although previous studies have reported associations between various vitamins, trace elements, and erectile dysfunction (ED), it remains unclear whether deficiencies in these micronutrients are associated with ED risk or whether their use as dietary supplements can prevent ED. This study aims to investigate the bidirectional causal relationship between ED and the use of various micronutrients supplements, including vitamins and trace elements. **Methods**: This study employed a bidirectional two-sample Mendelian randomization (MR) framework. Exposure and outcome data were derived from genome-wide association study (GWAS) datasets. The MR analysis incorporated inverse variance weighted (IVW) regression as the primary method, supplemented by the weighted median method and MR-Egger regression, to evaluate causal relationships between ED and vitamin and mineral supplements use. **Results**: Among various micronutrients analyzed, the supplementation of glucosamine chondroitin ($p = 0.030$, odds ratio (OR) = 1.168, 95% confidence interval (CI) = 1.015–1.344), chromium ($p = 0.005$, OR = 1.041, 95% CI = 1.012–1.070) and selenium ($p < 0.001$, OR = 1.084, 95% CI = 1.033–1.137) was associated with an increased risk of erectile dysfunction. However, no vitamins or trace elements were found to protect against ED. **Conclusions**: Vitamins and trace elements demonstrated no protective effect against erectile dysfunction (ED). Conversely, dietary supplementation with glucosamine, chondroitin, chromium, and selenium was associated with an increased risk of ED. These findings provide new suggestions for future prevention and treatment intervention of ED.

Keywords

Micronutrients; Erectile dysfunction; Mendelian randomization analysis; Genome-wide association study

1. Introduction

Erectile dysfunction (ED), recognized as the most prevalent form of sexual dysfunction, is defined as the persistent inability to achieve and maintain an erection sufficient for satisfactory sexual performance [1]. Approximately half of men over the age of 40 experience varying degrees of ED [2], imposing substantial burdens on healthcare systems, economic resources, and societal well-being. It is not only confined to sexual intercourse, but also poses a serious threat to patients' quality of life, psychological well-being, and partner relationships. The etiology of ED is complex and multifactorial [3], including chronic disease (metabolic and cardiovascular disease), lifestyle factors (smoking, alcoholism, and chronic psychological stress), and use of certain medications [4–8]. However, the factors mentioned above cannot fully explain ED onset in many cases, highlighting an imperative to discover additional risks.

Micronutrients, composed of trace elements and vitamins, are increasingly attracting the interest of researchers in their relationship with human health. Trace elements (*e.g.*, zinc, iron, and selenium) and vitamins (*e.g.*, Vitamins D, B, and E), serving as crucial cofactors for numerous enzymes and biochemical reactions, play indispensable roles in vital physiological processes, including maintaining vascular endothelial function, antioxidant defense, and hormone synthesis [9]. Numerous observational epidemiological studies have suggested an association between the levels of certain trace elements and vitamins and the risk of ED. For instance, low serum vitamin D levels and low zinc concentrations have been reported to be associated with a higher prevalence of ED [9, 10]. However, uncertainty persists regarding a potential causal link between micronutrient deficiencies and the development of ED. An equally critical and unresolved question is the therapeutic or

preventive potential of dietary micronutrient supplementation in modulating ED occurrence.

While substantial evidence supports associations between micronutrient status and ED, a systematic investigation into the relationships between specific micronutrients and ED remains lacking. However, traditional observational studies are highly susceptible to confounding factors (*e.g.*, age, obesity, smoking, and comorbidities) and reverse causality. This significantly complicates establishing conclusive causal relationships between micronutrients and ED. Although randomized controlled trials (RCTs) represent the gold standard for inferring causality, large-scale, long-term nutritional intervention RCTs are often prohibitively costly and logistically challenging to implement, and may also face ethical considerations.

To address this predicament, we employed Mendelian randomization (MR) to investigate the causal effects of micronutrients on ED. This approach utilizes genetic variants that robustly predict exposure levels as instrumental variables (IVs), thereby strengthening causal inference regarding specific outcomes [11]. Given that genotypes are randomly assigned at conception and typically independent of environmental factors, lifestyle influences, and disease progression, MR studies effectively mitigate the confounding biases inherent in observational research while substantially alleviating reverse causation. These findings are expected to provide higher-level genetic evidence for the nutritional etiology of ED, offering a scientific basis for developing targeted nutritional interventions or precision prevention strategies in the future.

While previous studies have established associations between micronutrients and ED, the causal relationship between them remains unclear. To address this knowledge gap, we proposed the following hypotheses: Does a causal relationship exist between micronutrients and ED? Can Micronutrient supplementation prevent erectile dysfunction? This study aimed to test these hypotheses through multivariable MR analysis.

2. Methods

2.1 MR sources and selection of IVs

Mendelian randomization relies on three cardinal assumptions that collectively ensure the validity of causal inference: relevance, independence, and exclusivity. The relevance assumption necessitates that instrumental variables (IVs) exhibit a strong association with the exposure of interest, serving as the foundational requirement for their utility in causal estimation. The independence assumption mandates that IVs must be devoid of any association with potential confounders. The exclusivity assumption requires that IVs exert their effects on outcomes exclusively through the specified exposure variable, precluding alternative biological pathways that could compromise causal interpretation [11]. Additionally, to verify the reliability of the results, all positive findings were tested for heterogeneity and pleiotropy, with results demonstrating heterogeneity ultimately excluded [12] (Fig. 1).

2.2 Data sources

Several genome-wide association study (GWAS) datasets related to vitamin and mineral supplements were used in this study, including "Multivitamin", "Multivitamin with iron", "Multivitamin with calcium", "Multivitamin with multimineral", "Glucosamine chondroitin", "Evening primrose", "Vitamin A", "Vitamin B6", "Vitamin B12", "Vitamin C", "Vitamin D", "Vitamin E", "Folic acid", "Chromium", "Magnesium", "Selenium", "Calcium", "Iron", "Zinc", "Other vitamin". These datasets were sourced from GWAS Catalog (GCST90042585–GCST90042588, GCST90042590–GCST90042605), accessible at https://www.ebi.ac.uk/gwas/. It should be particularly noted that although glucosamine and chondroitin are not classified as micronutrients, they were still included in this analysis due to their widespread use as over-the-counter dietary supplements and their availability in GWAS exposure data. The GWAS summary data for ED were extracted from

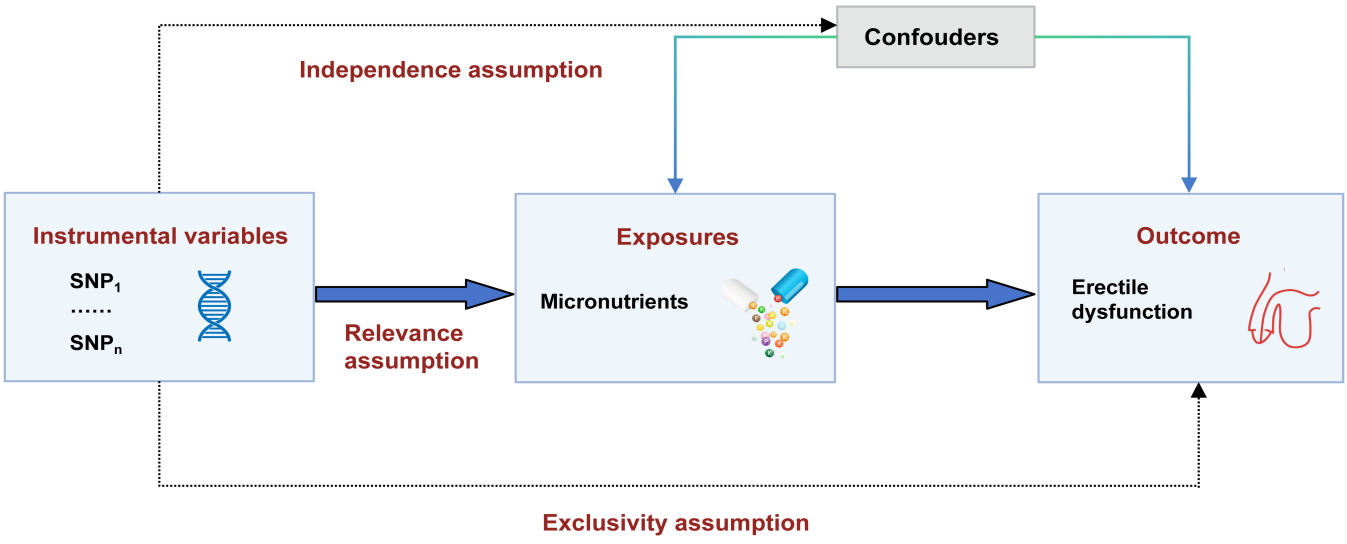

FIGURE 1. Illustration of the Mendelian randomization between micronutrients and erectile dysfunction. SNP: Single nucleotide polymorphism.

FinnGen (https://r12.finngen.fi/), including 2886 patients and 215,272 controls of European ancestry.

2.3 Selection of instrumental variables

First, we screened all IVs associated with the ED phenotype from GWAS data, setting the significance threshold at $p < 5 \times 10^{-6}$. Subsequently, leveraging the European 1000 Genomes Project reference panel, we estimated linkage disequilibrium (LD) among these variants. Single nucleotide polymorphisms (SNPs) exhibiting high LD ($R^2 > 0.001$, 10 Mb) were excluded. To ensure consistency in allele effect direction, we harmonized SNP information between exposure and outcome datasets. Finally, we calculated the F-statistic for each SNP, with instruments exceeding $F > 10$ considered statistically robust.

2.4 Statistical analyses

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guidelines [13]. Weighted median (WM), inverse variance weighting (IVW), maximum likelihood, and MR-Egger (ME) methods are employed to evaluate the causality between vitamin and mineral supplements and ED. The main approach with the highest statistical power is IVW which considers all genetic variants to be valid IVs [14]. At the same time, during the evaluation of causal effects by the ME method, the regression intercept of ME can also be used as a basis for testing horizontal pleiotropy [15]. Pleiotropy RESidual Sum and Outlier (MR-PRESSO) was also used to identify horizontal pleiotropy and improve potential pleiotropy via the removal of outliers [16]. The heterogeneity of IVs can be detected by using the Cochrane Q statistic [17]. We assessed the overall stability with a leave-one-out approach to our research findings. When the IVW showed statistical significance ($p < 0.05$), despite the ME and WM methods showing no statistical significance, it was still seen as favorable if the β were consistently in the same direction [18]. The "forestploter" package was used to draw forest plots, the "TwoSampleMR" package and "MR-PRESSO" package were used to perform MR analysis and to detect horizontal pleiotropy. All analyses in this study were performed using R 4.4.2 software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Causality between various micronutrients and ED

Our findings indicate that among the 20 micronutrients analyzed, supplementation with glucosamine chondroitin, chromium, and selenium was associated with an increased risk of ED. However, no vitamin or trace element was found to prevent ED (Figs. 2,3). The forest plot in Fig. 3 demonstrates the causal relationships between the various micronutrients and ED, revealing that supplementation with glucosamine chondroitin ($p = 0.030$; odds ratio (OR) = 1.168, 95% confidence interval (CI) = 1.015–1.344), chromium ($p = 0.005$; OR = 1.041, 95% CI = 1.012–1.070), and selenium ($p < 0.001$; OR = 1.084, 95% CI = 1.033–1.137) increased the risk of ED. To verify the robustness of the results, we performed sensitivity analysis using Cochran's Q test, which showed no evidence of heterogeneity ($p = 0.345$ for glucosamine chondroitin, $p = 0.455$ for chromium, $p = 0.835$ for selenium) (Fig. 4). Additionally, the MR-PRESSO analysis was employed to assess horizontal pleiotropy, with glucosamine chondroitin ($p = 0.450$), chromium ($p = 0.376$), and selenium ($p = 0.487$) all yielding negative results, indicating that the observed associations were not confounded by pleiotropic effects. Furthermore, MR-PRESSO analysis confirmed the absence of outliers among the SNPs related to financial difficulties and absence of psychological stressors.

3.2 Reverse MR between various micronutrients and ED

To investigate potential reverse causation, we employed SNPs associated with ED as exposure variables and utilized SNPs related to glucosamine chondroitin, chromium, and selenium supplements as outcome variables, respectively. Reverse Mendelian randomization analysis revealed no significant causal relationship between glucosamine chondroitin supplementation and ED ($p = 0.828$) or between selenium supplementation ($p = 0.574$) and ED, while a significant causal relationship was observed between chromium supplementation ($p = 0.024$) and ED (Table 1).

4. Discussion

Whereas prior research have typically focused on a single nutrient in isolation, our study's strength lies in its systematic investigation of multiple micronutrients simultaneously within the same genetic framework. Our findings substantiated that no protective effect of vitamin or trace element on ED. On the contrary, dietary supplementation with glucosamine chondroitin, chromium or selenium may act as potential risks of ED.

The association between glucosamine chondroitin and ED risk is a novel finding. Despite its widespread use as a dietary supplement for osteoarticular diseases, the relationship between glucosamine and erectile dysfunction has received limited research attention, and its systematic effects remain poorly characterized. For instance, previous study has suggested glucosamine might induce insulin resistance *in vivo* by impairing glucose transporter 4 (GLUT4) translocation in skeletal muscle at high doses [19]. Since insulin resistance is a key risk factor for endothelial dysfunction [6], it seems we can directly conclude that glucosamine increases the risk of erectile dysfunction. Conversely, recent research suggests that glucosamine administration at standard doses has no significant effect on glucose metabolism as well as insulin resistance [20], and may reduce the incidence of type 2 diabetes [21]. Regarding the seemingly contradictory conclusions, we propose the following possible reasons. The effects of glucosamine may exhibit heterogeneity across populations depending on their baseline health conditions. In patients with diabetes or insulin resistance, glucosamine may exert adverse metabolic

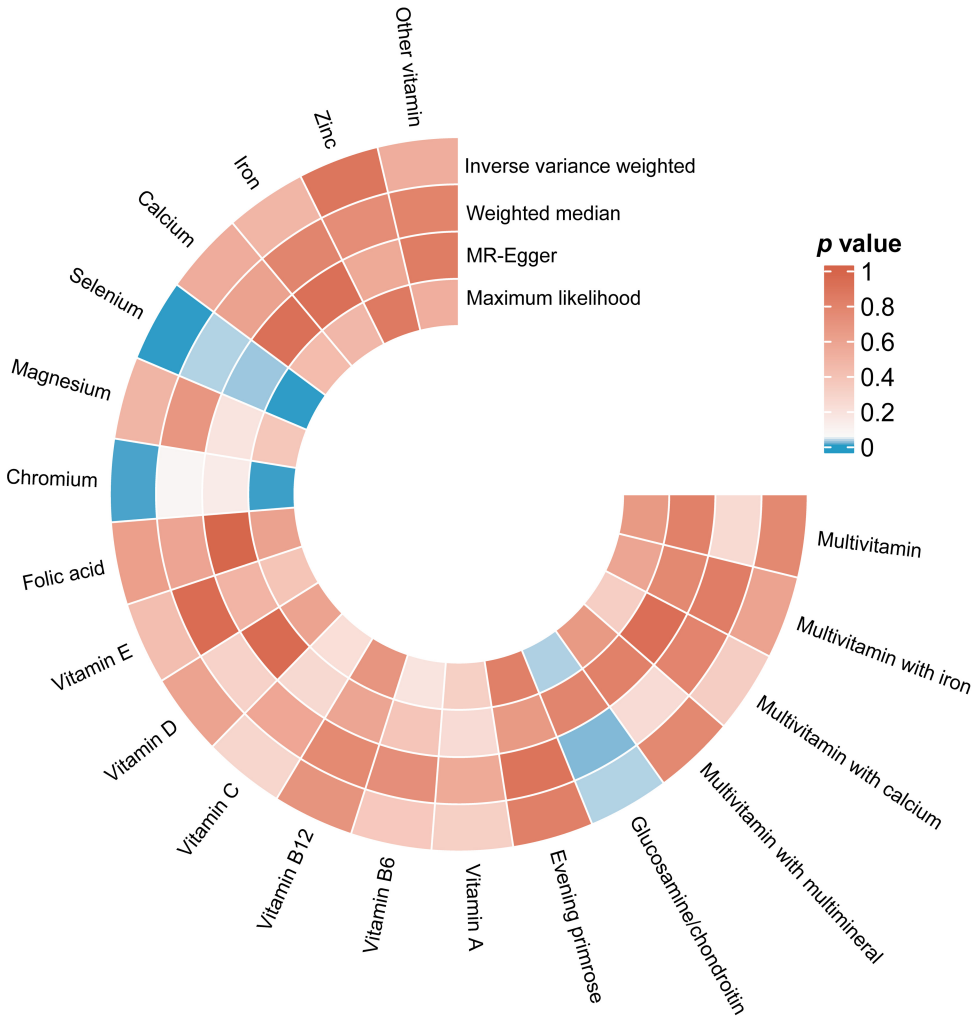

FIGURE 2. Circular heatmap illustrating the impact of different micronutrients on ED. Each colored tile represents the *p*-value for the causal relationship between an individual micronutrient and ED, with blue tiles denoting *p*-values < 0.05 and orange tiles indicating *p*-values > 0.05. MR: Mendelian randomization.

Exposure	SNP	OR (95%CI)	*p* value
Multivitamin	8	1.029 (0.852−1.242)	0.768
Multivitamin with iron	13	0.983 (0.922−1.048)	0.602
Multivitamin with calcium	9	1.017 (0.983−1.052)	0.327
Multivitamin with multimineral	8	0.988 (0.888−1.100)	0.768
Glucosamine/chondroitin	13	1.168 (1.015−1.344)	0.030
Evening primrose	7	0.988 (0.887−1.101)	0.827
Vitamin A	7	1.028 (0.974−1.085)	0.319
Vitamin B6	11	1.042 (0.954−1.138)	0.357
Vitamin B12	9	0.986 (0.920−1.057)	0.698
Vitamin C	12	1.072 (0.946−1.215)	0.275
Vitamin D	10	1.022 (0.942−1.108)	0.600
Vitamin E	13	1.026 (0.964−1.091)	0.426
Folic acid	12	1.012 (0.964−1.063)	0.628
Chromium	10	1.041 (1.012−1.070)	0.005
Magnesium	10	1.025 (0.956−1.099)	0.487
Selenium	14	1.084 (1.033−1.137)	0.001
Calcium	11	1.038 (0.920−1.172)	0.543
Iron	7	0.978 (0.922−1.039)	0.475
Zinc	8	0.992 (0.891−1.105)	0.888
Other vitamin	10	1.028 (0.942−1.122)	0.537

FIGURE 3. Forest plot demonstrating the casual effects of various micronutrients on ED. SNP: Single nucleotide polymorphism; OR: odds ratio; CI: confidential interval.

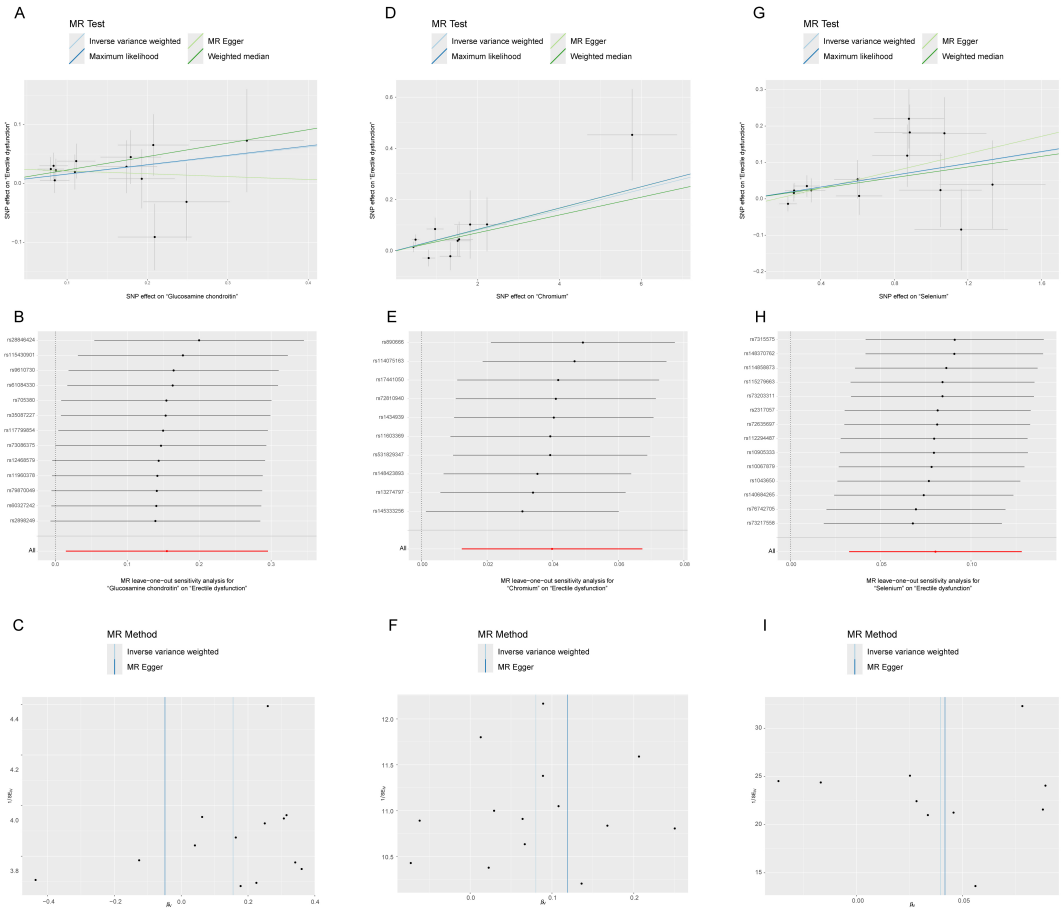

FIGURE 4. Scatter plots, forest plots, and funnel plots represent the corresponding risk relationships between SNPs of glucosamine chondroitin (A–C), chromium (D–F), selenium (G–I) and ED. SNP: single nucleotide polymorphism; ED: erectile dysfunction; MR: Mendelian randomization; SE: standard error.

TABLE 1. Reverse Mendelian randomization analysis between erectile dysfunction and glucosamine chondroitin, chromium, and selenium supplementation.

Micronutrients	Methods	IVs	Beta	Standard Deviation	*p* value
Glucosamine_chondroitin					
	Inverse variance weighted	10	0.010	0.045	0.828
	Weighted median	10	0.026	0.057	0.643
	MR-Egger	10	0.016	0.100	0.874
	Maximum likelihood	10	0.010	0.045	0.828
Chromium					
	Inverse variance weighted	10	−0.583	0.258	0.024
	Weighted median	10	−0.401	0.346	0.246
	MR-Egger	10	0.269	0.552	0.639
	Maximum likelihood	10	−0.604	0.258	0.019
Selenium					
	Inverse variance weighted	10	0.080	0.142	0.574
	Weighted median	10	−0.074	0.168	0.660
	MR-Egger	10	0.240	0.332	0.490
	Maximum likelihood	10	0.083	0.129	0.522

IVs: instrumental variables; MR: Mendelian randomization.

effects; by contrast, in normoglycemic individuals, it could confer beneficial outcomes through alternative mechanisms, such as anti-inflammatory pathway [15]. Our MR analysis reflects the average effect on the entire population and may capture the negative pathways for the risk of ED. Besides, prior studies focusing on metabolism were mostly based on self-reported users, which may have involved confounding factors. Moreover, these studies used diabetes onset as the endpoint, while our study used ED as the endpoint. It is probable that while glucosamine has only a negligible effect on glucose metabolism, which is insufficient to precipitate diabetes, it may still exert a significant impact on the more sensitive endpoint of erectile function. Therefore, although our results indicate that glucosamine chondroitin is a potential risk factor for ED, the underlying biological mechanism still needs to be further elucidated. But this discovery still holds clinical implication. In particular, for those patients who are suffering from osteoarticular diseases, they should be aware of the increased risk of ED due to the long-term use of glucosamine.

Another risk factor we discovered was chromium (Cr). However, unlike the consistent findings for glucosamine and selenium, the causal relationship between chromium supplementation and ED should be interpreted with caution. In our bidirectional MR analysis, the effect of chromium on ED was not consistently supported across all sensitivity MR methods, indicating that this finding is less robust than the primary results. As an essential trace element, Cr plays an important role in the glucose metabolism in human body [16] and exerts multiple impacts on erection [10]. Its two isotopes are hexavalent (Cr(VI)) and trivalent chromium (Cr(III)). Its trivalent compound, chromium picolinate (tris(picolinate) chromium (III)) ($CrPic_3$) has been utilized as a nutritional supplement to lose weight or lower blood glucose levels. Moreira R *et al*. [22] have pointed out that $CrPic_3$ may diminish testosterone levels by reducing the expression of a receptor and enzymes involved in steroidogenesis in leydig cells. Given that previous studies have demonstrated that erectile dysfunction is associated with low testosterone levels [23], we can infer that chromium compound is indeed a risk factor for ED, which is consistent with the conclusion of our study. Except for Cr(III), Cr(VI) is a potent oxidative stress inducer and has been shown to be reproductive-toxic to both animals and humans [24, 25]. Given that endothelial dysfunction, driven by oxidative damage, is a cornerstone of vasculogenic ED, a pro-oxidant effect of high chromium levels could detrimentally affect penile blood flow and vascular relaxation.

As for selenium, our MR analysis revealed a genetically predicted positive association between the supplementation of selenium and an increased risk of ED. This finding appears to contradict the prior observational research suggesting a beneficial or protective role of selenium intake against ED development [26]. The relationship between selenium and health outcomes is notoriously non-linear, often following a U-shaped curve [27]. Deficiency is detrimental, sufficiency is protective, but excess can become toxic. Previous observational studies, often conducted in populations with moderate or suboptimal selenium status, may have primarily captured the contrast between deficiency and sufficiency, thus observing a protective effect. Conversely, our MR estimates, which reflect life-long genetic exposure, might capture the consequences of higher, potentially supra-nutritional selenium levels that push into the adverse end of the U-shaped curve, leading to increased ED risk. At physiological levels, selenium is involved in spermatogenesis and maturation, as well as testosterone synthesis. It is also a key component of various antioxidant enzymes, such as glutathione peroxidase 1 (GPX1), GPX3, and GPX4, which can reduce the oxidative damage of sperm caused by reactive oxygen species (ROS), and protect against environmental toxin-induced testicular damage and sperm quality decline [27, 28]. However, pro-oxidant effects of selenium have been observed at high concentrations [29], where it may promote oxidative stress and inflammation, ultimately contributing to endothelial dysfunction—the hallmark of vasculogenic ED. This dual role depending on dosage offers a plausible biological mechanism for our findings. Therefore, our study does not necessarily invalidate previous findings, but rather highlights that the relationship between selenium and ED is more complex than a simple linear association. Our result suggests that there may be an optimal range of selenium for sexual health, beyond which the benefits cease and potential harms emerge.

Our research provides novel genetic evidence suggesting a potential causal role of chromium, selenium, and glucosamine/chondroitin in increasing the risk of ED. The findings suggest that blanket recommendations for micronutrient supplementation for general health may not be universally appropriate and could have adverse impact on sexual health in men. However, given that MR reflects lifelong genetic predisposition, these findings may not be directly generalizable to short-term or low-dose supplementation regimens. Future research, including randomized controlled trials, is needed to determine the clinical relevance of these associations and to guide precise prevention and treatment interventions for ED. Therefore, clinicians need to carefully evaluate whether patients need long-term or high-dose use of drugs containing chromium, selenium or glucosamine chondroitin. In addition, men with long-term exposure to chromium or selenium should also be alert to the increased risk of ED. Notably, no micronutrient supplement has been proven to mitigate ED risk, necessitating mechanistic studies to establish a potential causal link.

Conversely, dietary supplementation with glucosamine, chondroitin, chromium, and selenium was associated with an increased risk of ED from a genetic perspective. However, given that MR reflects lifelong genetic predisposition, these findings may not be directly generalizable to short-term or low-dose supplementation regimens. Future research, including randomized controlled trials, is needed to determine the clinical relevance of these associations and to guide precise prevention and treatment interventions for ED.

There still exists several limitations in our study. First, MR employs genetic instruments to infer causality, though it may not fully capture the influence of non-genetic factors such as lifestyle and environmental exposures. Second, our findings are based on European-ancestry populations, and their generalizability to other ethnic groups requires further investigation. Third, the absence of dosage information in

the source GWAS data precludes any dose–response analysis, meaning our conclusions are limited to the presence or absence of supplement use. Further research with detailed nutritional assessments, such as 24-hour dietary recalls or circulating micronutrient measurements, will be essential to confirm and refine our findings.

5. Conclusions

This bidirectional two-sample Mendelian randomization study provides genetic evidence regarding the causal relationships between micronutrient supplementation and erectile dysfunction. Our analysis identified that the use of glucosamine chondroitin, chromium, and selenium supplements was associated with an increased risk of ED. Notably, no vitamins or trace elements were found to have a protective effect against ED. The reverse MR analysis suggested a potential causal effect of ED on chromium supplement use, warranting further investigation. These findings highlight that supplementation with specific, commonly used over-the-counter minerals and compounds may be a potential risk factor for ED, rather than a preventive measure.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

JC and WW—designed the research study. SY—performed the research. TQ and YS—provided help and advice on the interpretation of the results. HL and BT—analyzed the data. SY, TQ and YS—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. This study utilized publicly available summary-level data from genome-wide association studies (GWAS). Since the analysis was based on aggregated, de-identified data, no additional ethical approval or informed consent was required for the present Mendelian randomization analyses. All original GWAS included in our study had obtained ethical approval and participant consent, as detailed in their respective publications.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Jun Chen is serving as one of the Editorial Board members of this journal. We declare that Jun Chen had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to LR.

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