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ORIGINAL RESEARCH

Genetic Association Between Serum Calcium, Potassium Levels, and Rosacea: Evidence from a Two-Sample Mendelian Randomization Study

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Purpose: Recent advances in epidemiological and genetic studies have provided some insights regarding the pathophysiology of rosacea, but the majority of its underlying mechanisms are still poorly understood. In particular, more data are needed to fully understand the role of micronutrients in rosacea development. This study aimed to explore the causality of associations between Calcium, Copper, Selenium, Zinc, Iron, Potassium and Magnesium with the risk of rosacea.

Patients and Methods: This was a two-sample Mendelian Randomization (MR) study that used data from genome-wide association studies (GWAS) on serum levels of selected micronutrients as exposure and rosacea as the outcome. The analysis primarily employed the Inverse Variance Weighted (IVW) method. Additional methods included weighted median, weighted mode, and MR-Egger regression. Sensitivity analysis included MR-Egger, MR-PRESSO, Cochran's Q, and leave-one-out methods. A total of 301 Instrumental Variables were selected for analysis.

Results: The genetic prediction indicated a statistically significant association between serum Calcium levels and higher rosacea risk (Odds Ratio (OR) = 2.27, 95% Confidence Interval (CI): 2.02–2.55, P < 0.001), further confirmed by all supplementary MR methods. Significant association was also found between serum Potassium levels and lower rosacea risk (OR = 0.36, 95% CI: 0.14–0.93, P = 0.0354), further confirmed by the weighted-median method. Sensitivity analyses showed that the results were robust and not driven by any single factor, with low probability of horizontal pleiotropy.

Conclusion: This study found an evidence of a causal association between genetically predicted serum levels of Calcium and Potassium with the risk of rosacea. The roles of these micronutrients should be further studied in rosacea, especially as a link to neurovascular dysregulation and oxidative stress.

Keywords: rosacea, micronutrients, Mendelian randomization analysis, calcium, potassium

Introduction

Rosacea is a chronic dermatosis primarily affecting the face, characterized by flushing, persistent redness, papules, pustules, and telangiectasia.[1] Manifestations of rosacea include itching, burning or stinging in the affected areas, for the prolonged periods of time, including exacerbations and remissions.[2,3] Rosacea affects about 3.5% to 5.5% of the population globally – and, although not considered life-threatening, has a high impact on the quality of life.[4,5] Ocular changes are found in up to 50% of rosacea patients and range from dryness and irritation to sight-threatening keratitis.[2] Moreover, since the highly visible area of the facial skin is affected, rosacea has profound negative psychological and social effects including anxiety, stigmatization, loss of self-esteem, depression and social phobia.[2,6] Recent advances in epidemiological and genetic studies helped to achieve some insights into the pathophysiology of rosacea, but majority of its underlying mechanisms are still poorly understood.

In addition to therapeutic and cosmetic factors, many dietary and environmental triggers have been found to be associated with the development and exacerbation of rosacea. In particular, the intestine-skin axis theory highlights the importance of

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maintaining a healthy diet for rosacea patients with balanced intestinal microbiome.[7,8] Patients with rosacea often experience micronutrient deficiencies, which can significantly impact the effectiveness of treatment and overall quality of life.[9] Supplementation with micronutrients, such as vitamins C and E, iron, copper, manganese and selenium has been shown to improve the quality of life for rosacea patients.[10] Additionally, zinc and vitamin D supplementation has been helpful in treating rosacea symptoms in deficient patients.[11] Optimizing the use of these micronutrients, whether through topical or oral supplementation, has the potential to reduce exacerbations and enhance quality of life in affected patients. However, more robust data are needed to fully understand the role of certain micronutrients in alleviating rosacea symptoms.

Epidemiological studies cannot completely rule out distortions and confounders, especially in the field of dietary supplementation and micronutrients use. In order to limit confounding bias, Mendelian randomization (MR) method was proposed; by utilizing genetic variants from genome-wide association studies (GWAS) that are substantially correlated with exposure as instrumental variables, MR could determine the causation between two factors with the minimal impact of other confounders.[12] In the last few years, once GWAS data on rosacea become publicly available, a number of MR studies were performed: smoking (but not alcohol consumption)[13] and caffeine[14] were confirmed to be causally related to a lower risk of rosacea, while no association was found between obesity and rosacea, despite previous observational evidence.[15] Recent MR study on gut microbiota provided compelling evidence of intestine-skin axis involvement, offering potential directions for therapeutic interventions in rosacea management.[16] Regarding micronutrients, only one study was published at the moment, discussing inverse correlation of serum vitamin D levels with the risk of incident rosacea.[17] Further research is warranted to explore the effects of micronutrient deficiency on rosacea, as well as their role in the complex pathogenesis of this condition.

This study used MR methodology to investigate the causality between selected micronutrients, including Calcium, Copper, Selenium, Zinc, Iron, Potassium and Magnesium, with the risk of rosacea.

Materials and Methods

Study Design

This was a two-sample MR study that used data from GWAS on serum levels of selected micronutrients to model the exposure, and data on Single Nucleotide Polymorphisms (SNPs) associated with rosacea to model outcomes. Inclusion of Instrumental Variables (IVs) was based on the three main assumptions of MR,[18] namely: 1) IVs are strongly associated with exposure; 2) IVs are associated with outcome only through exposure and not directly; 3) IVs are not associated with any known confounders that influence exposure and outcome. The MR design of this article and research roadmap are described in Figure 1.

Ethics committee of the research institution waived the demand for informed consent based on the public nature of the GWAS data.

Data Source

Disease Outcome Data

GWAS data for rosacea were obtained from the genome sequencing data of FINN cohort (finngen.fi/en) and included 1195 cases and 211,139 controls, all of European ancestry.

Exposure Data

GWAS data for Calcium serum levels were obtained from study by Mbatchou et al[19] published in 2021; GWAS data for Copper, Selenium, Zinc, and Iron were obtained from study by Evans et al[20] published in 2013 and GWAS data for Potassium and Magnesium were obtained from the MRC-IEU database (gwas.mrcieu.ac.uk). All GWAS data were obtained from individuals of European ancestry, and identification information for utilized datasets is presented in Supplementary Table 1.

Instrumental Variable Selection

The IVs included in this study must meet the following criteria: 1) Initially, SNPs significantly associated with micronutrients, with a threshold of $P < 5 * 10^{-6}$, were screened; 2) SNPs with a minimum minor allele frequency

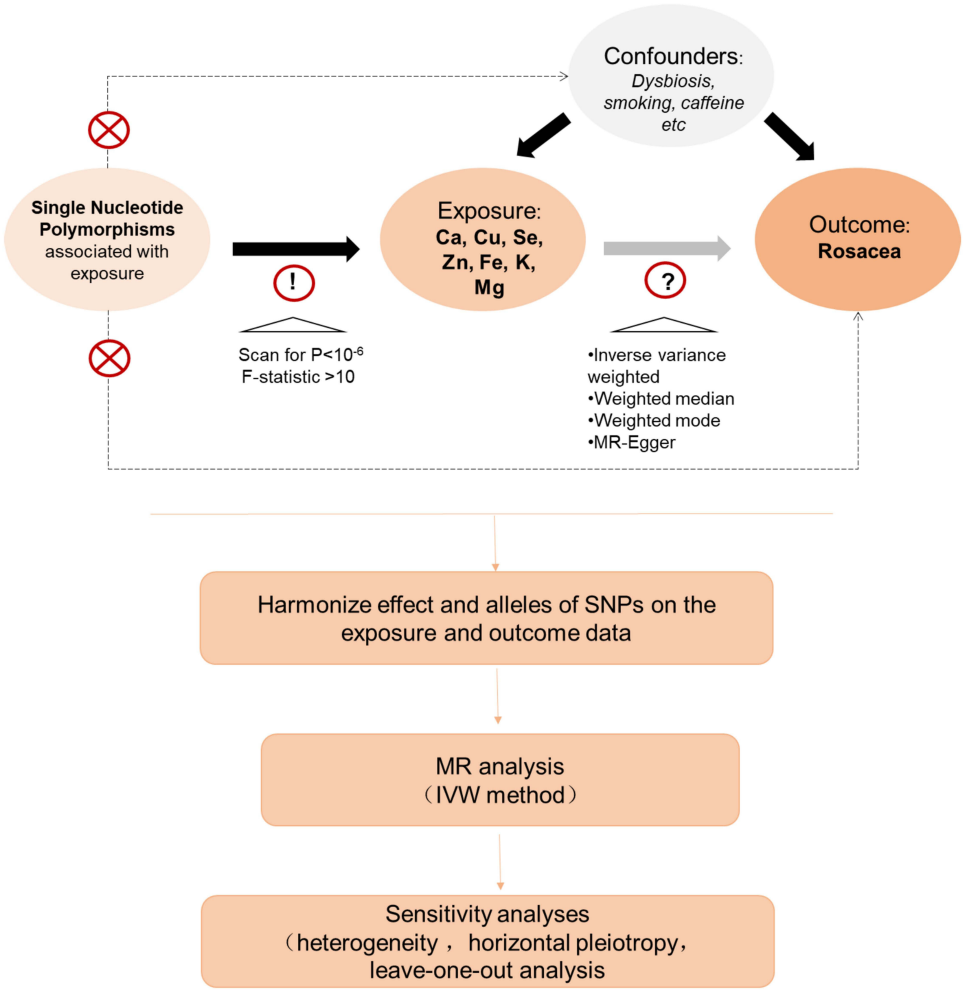

Figure 1 The MR design of this study and inclusion of Instrumental Variables (IVs), based on the three main assumptions of Mendelian Randomization, namely: 1) IVs are strongly associated with exposure; 2) IVs are associated with outcome only through exposure and not directly; 3) IVs are not associated with any known confounders that influence exposure and outcome.

(MAF) > 0.01 were selected;[21] 3) SNPs were filtered out by linkage disequilibrium (LD) based on the standard of $R^2 < 0.001$ and a window size of 10,000 kb;[22] 4) In cases where the selected IV was not present in the outcome summary data, SNPs with high LD ($R^2 > 0.8$) were sought as proxy SNPs for replacement; 5) The F value for each SNP in the IV was calculated to assess IV strength, aiming to mitigate potential weak instrument bias between IVs and exposure factors. The calculation formula is as follows: $F = R^2*(N-2)/(1-R^2)$, where R^2 represents the proportion of exposure variance explained by SNPs in the IV, and the requirement for F value was >10[23].

MR Analysis

This study used "Two-sample MR" package in R version 4.0.5 for statistical analyses, including random-effects inverse variance weighted method (IVW), MR-Egger, weighted-median and weighted-mode methods; odds ratio (OR) and 95% confidence interval (CI) were calculated. The IVW was the main method for interpreting MR results, and the other three methods were used to test the robustness of the results.[18,21] Visualization of the results was performed using scatter plots and sensitivity analysis plots.

Sensitivity Analysis

Sensitivity tests were performed to identify potential heterogeneity in MR studies. Cochran's Q test assessed heterogeneity among IVs, with a P > 0.05 indicating low heterogeneity.[23] To account for the possible effect of genetic variation

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on association estimates, the study utilized the MR-Egger regression method to investigate horizontal pleiotropy. An intercept of MR-Egger regression close to zero or not statistically significant was adopted as a sign of pleiotropy absence.[24] Furthermore, the MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to identify potential outliers (ie, SNPs with $P < 0.05$) and re-estimate causal associations after removing them to correct for horizontal pleiotropy.[25] Leave-one-out analysis was also conducted to evaluate the robustness and consistency of the results.[26]

Results

Instrument Variables Selection

After thoughtful selection and quality control measures, a total of 301 IVs were selected. Of them, 235 relevant IVs were screened for the MR analysis with Calcium as the exposure, 6 IVs were identified for Copper serum levels, 6 IVs for Selenium, 8 IVs for Zinc, 19 IVs for Magnesium, 16 IVs for Potassium, and 11 IVs for Iron exposure. Information for 3 SNPs in Calcium dataset, two SNPs in Potassium and one SNP in Iron datasets were not matched in the summary data for rosacea; among these, in Calcium dataset rs4937122 was used as a proxy for rs73632745, and rs202039560 for rs139231513, all others were excluded. The F-statistics of IVs ranged from 14.15 to 1353.94, all >10 indicating the absence of instrumental bias. Detailed list of all SNPs used as IVs in this MR analysis is presented in Supplementary Table 2.

MR Analysis Results

A statistically significant association was found between serum Calcium levels and higher rosacea risk by the IVW analysis (OR = 2.27, 95% CI: 2.02–2.55, $P < 0.001$) and confirmed by all supplementary MR methods (Figure 2A). Another significant association was found between serum Potassium levels and lower rosacea risk (OR = 0.36, 95% CI: 0.14–0.93, $P = 0.0354$), confirmed by the weighted-median method (Figure 2B). No statistically significant associations with rosacea were found for other micronutrients or with other methods (all $P > 0.05$), as detailed in Table 1. Forest plots demonstrating the effect sizes for all associations are presented in Figure 3.

Sensitivity Analysis Results

The MR-Egger pleiotropy analysis suggested a possibility of horizontal pleiotropy for Calcium as the exposure and rosacea as the outcome, but neither the leave-one-out nor the MR-PRESSO tests identified outliers, necessitating no further adjustments. Other exposure-outcome analyses were unaffected by pleiotropy (Table 2). The MR-PRESSO results confirmed the absence of outliers in the analysis (Table 3). The funnel plots of the MR-Egger regression are demonstrated on Figure 4 for significant associations and Supplementary Figure S1. Results of leave-one-out analysis are presented on Figure 5 and Supplementary Figure S2.

Discussion

This study applied a two-sample MR approach to statistically investigate the effect of selected micronutrients on rosacea, and found that genetically predicted moderate hypercalcaemia was causally associated with the higher risk or rosacea, while moderate hyperkalemia was associated with the lower risk or rosacea. A series of sensitivity tests confirmed that results are robust and not affected by horizontal pleiotropy, thus suggesting that serum levels of Calcium and Potassium may play a notable role in the development of rosacea.

The published evidence on the relationship between serum Calcium and rosacea is not conclusive, with one recent study reporting that total and ionized Calcium levels did not differ significantly between rosacea cases and controls,[23] while another presenting evidence that serum Calcium levels in rosacea patients were lower than the controls.[27] Although pathogenesis of rosacea is mostly unknown, some assumptions can be made, based on the current findings on cathelicidin and neurovascular dysregulation. Firstly, trigger factors in the development of rosacea are linked to the release of various mediators in keratinocytes, most studied of which is cathelicidin, with the hypothesis that an abnormal cathelicidin levels play a role in the inflammatory response of the innate immune system.[28] Previous rosacea study showed significantly higher serum cathelicidin,[29] and increased proteolytic processing of cathelicidin is believed to regulate the inflammatory

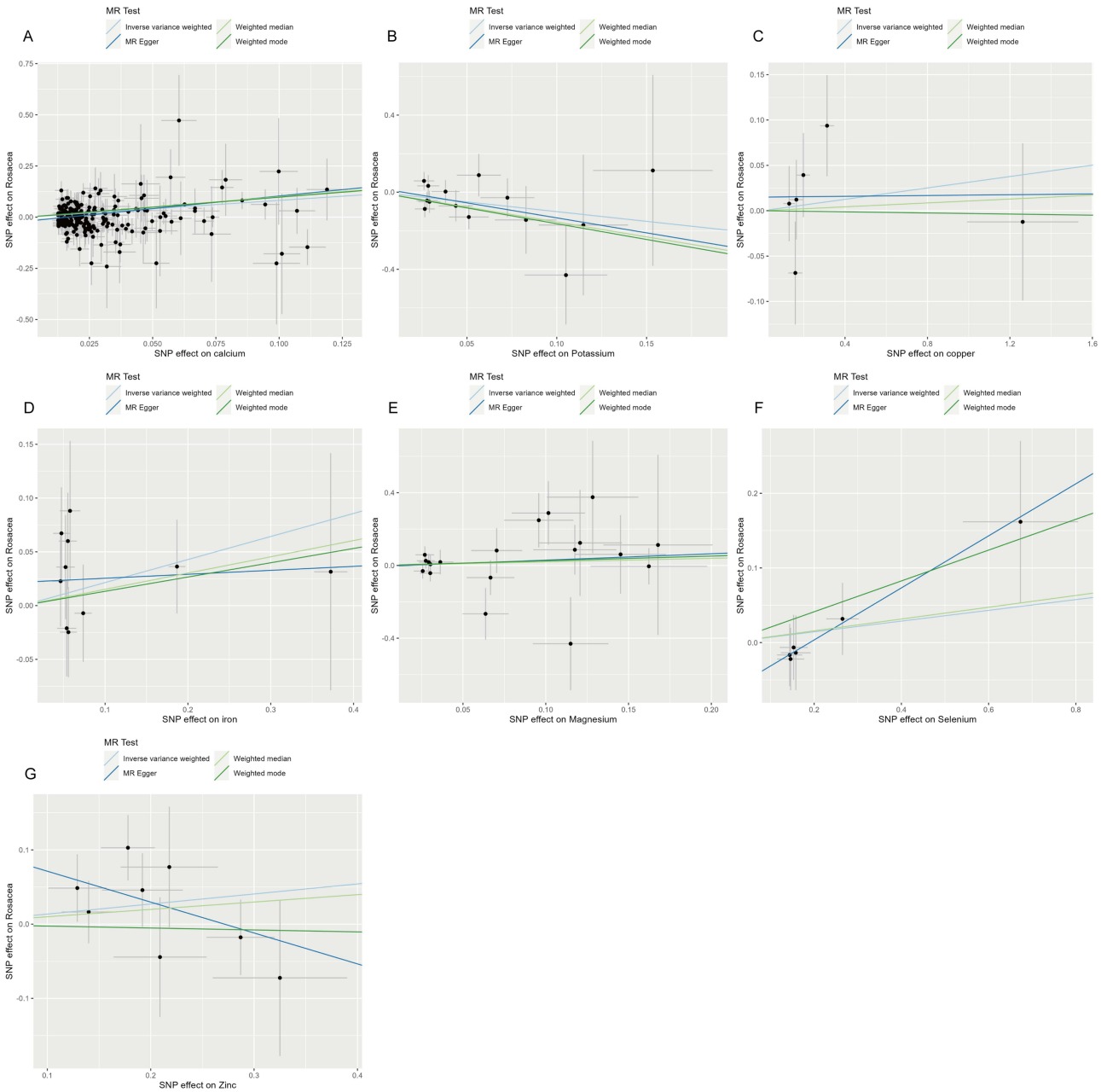

Figure 2 Scatter plot demonstrating statistically significant association between serum Calcium levels and higher rosacea risk (**A**), confirmed by all methods; between serum Potassium levels and lower rosacea risk (**B**), confirmed by inverse variance weighted (IVW) and weighted-median methods. Remaining plots are demonstrating results for Copper (**C**), Iron (**D**), Magnesium (**E**), Selenium (**F**), Zinc (**G**) and rosacea risk.

process possibly via mTORC1 pathway,[30] which is heavily dependent on Calcium. It has been therefore suggested that downregulating cathelicidin may have benefit to rosacea patients.[31] Secondly, trigger factors can directly communicate to the cutaneous nervous system by neurovascular and neuroimmune active neuropeptides, leading to the manifestation of rosacea lesions,[28] while Calcium influx and efflux are essential for releasing neurotransmitters and regulating synaptic transmission.[32] Finally, rosacea may be associated with high thyroid autoantibodies, suggesting possible immune–endocrine interactions and drawing attention to hypercalcemia in hyperparathyroidism.[33] In the present study, all applied MR methods demonstrated statistically significant results, with the minimal odds ratio as high as 2.27, which suggests a high probability of elevated serum Calcium to increase the risk of rosacea. To the best of our knowledge, this study presents evidence that the role of Calcium (and probably cathelicidin) in rosacea should be further discussed and

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Table 1 Results of Mendelian Randomization Methods Application, Assessing the Causal Associations Between Micronutrients and the Risk of Rosacea

Exposure	Methods	OR (95% CI)	P
Calcium	Inverse variance weighted	2.27 (2.02 – 2.55)	<0.00000001
	MR Egger	3.43 (2.68 – 4.39)	<0.00000001
	Weighted median	2.72 (2.28 – 3.25)	<0.00000001
	Weighted mode	2.65 (2.24 – 3.13)	<0.00000001
Copper	Inverse variance weighted	1.03 (0.92–1.16)	0.05841751
	MR Egger	1(0.85–1.19)	0.08623122
	Weighted median	1.01 (0.88–1.16)	0.07150279
	Weighted mode	1(0.87–1.14)	0.06946231
Selenium	Inverse variance weighted	1.07 (0.9–1.29)	0.4394
	MR Egger	1.42 (0.96–2.09)	0.1517
	Weighted median	1.08 (0.85–1.38)	0.5199
	Weighted mode	1.23 (0.91–1.66)	0.2383
Zinc	Inverse variance weighted	1.14 (0.94–1.39)	0.1771
	MR Egger	0.66 (0.34–1.28)	0.2648
	Weighted median	1.1 (0.86–1.43)	0.4469
	Weighted mode	0.97 (0.69–1.38)	0.8873
Potassium	Inverse variance weighted	0.36 (0.14–0.93)	0.0354
	MR Egger	0.21 (0.02–2.61)	0.249
	Weighted median	0.21 (0.05–0.85)	0.0283
	Weighted mode	0.19 (0.02–1.94)	0.186
Magnesium	Inverse variance weighted	1.29 (0.67 – 2.48)	0.448
	MR Egger	1.42 (0.46 – 4.35)	0.5474
	Weighted median	1.22 (0.46 – 3.2)	0.6908
	Weighted mode	1.29 (0.46 – 3.64)	0.63
Iron	Inverse variance weighted	1.24 (0.91–1.68)	0.1675
	MR Egger	1.04 (0.63–1.7)	0.8876
	Weighted median	1.16 (0.8–1.69)	0.4278
	Weighted mode	1.14 (0.81–1.62)	0.4749

Abbreviations: OR, odds ratio; CI, confidence interval.

researched. Moreover, Calcium supplements appear to have a negative risk-benefit effect,[34] and should be used with caution in rosacea patients.

Another finding of this study is a relationship between higher serum Potassium and lower risk of rosacea. There are notable knowledge gaps in our understanding of Potassium homeostasis,[35] but it was previously found to be associated with vascular function[36] and oxidative stress.[37] It is important to note that only weak association was proven between dietary potassium intake and serum potassium level,[38] thus notable changes in serum potassium could be a sign of impaired renal function or other health conditions. In a recent study that included 56602 cases of chronic kidney disease (CKD) and 268305 controls, CKD patients were less likely to have been diagnosed with rosacea (OR = 0.92, 99% CI: 0.87–0.97),[39] which – alone with other factors – might be a sign of potential influence of serum potassium, as suggested in our study. In another study serum potassium, along with albumin and B12, were potential oxidative stress markers,[37] and oxidative stress is thought to be an important contributory factor in the pathogenesis of rosacea.[40] The MR approach used in the present study model only moderate exposure, not extreme cases of hyper- or hypokalemia, but even within the physiological range increases in potassium concentration showed the ability to inhibit the formation of ROS in vascular cells.[36] Still, increasing dietary potassium intake may increase the risk of hyperkalemia in unhealthy individuals, which have important health concerns.

However, we did not observe a causal link between serum zinc levels and rosacea.[9] Previous studies have considered zinc as part of broader anti-oxidant system, which plays a role in various skin conditions, including rosacea. Despite this,

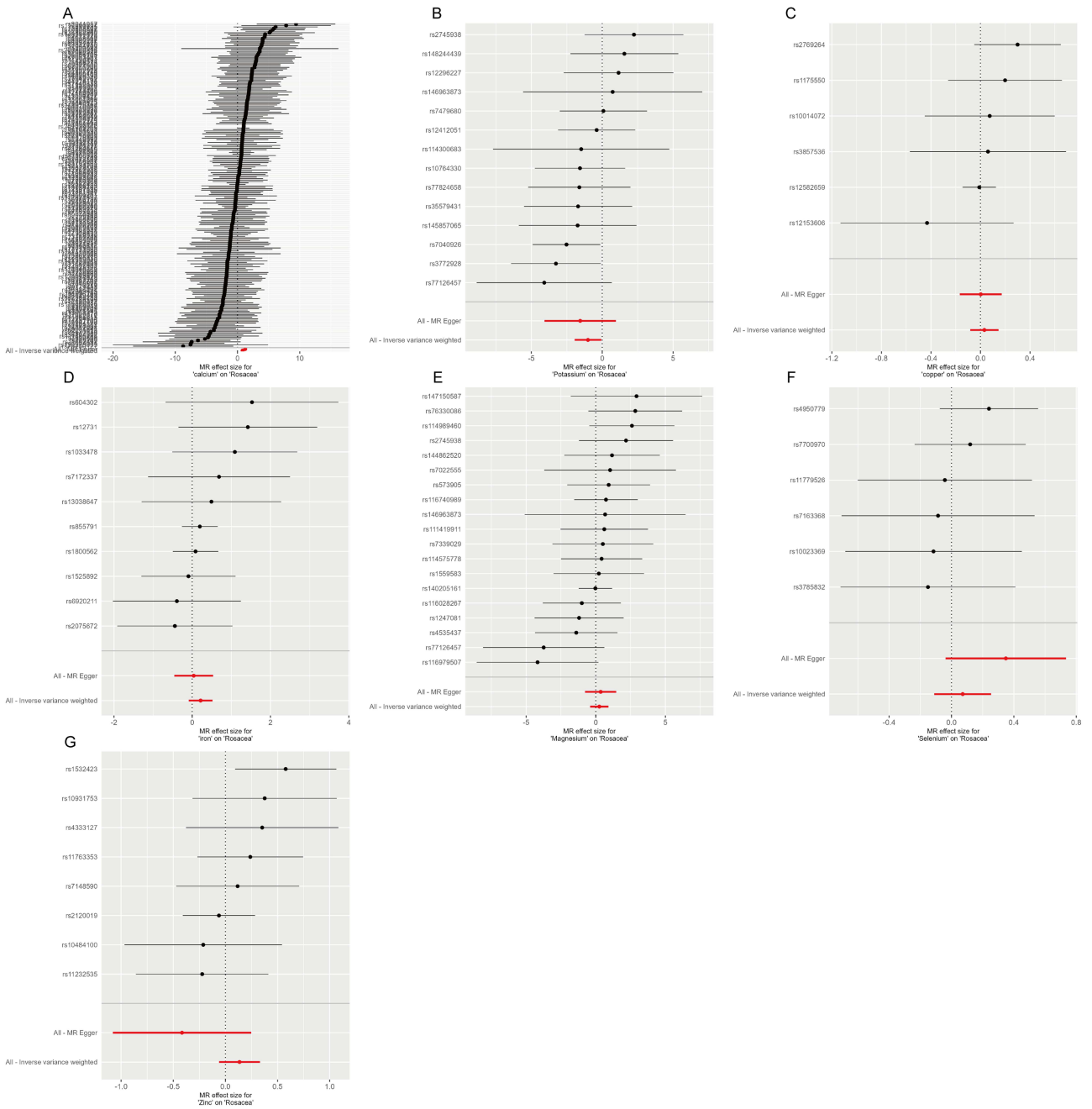

Figure 3 Forest plot demonstrating the effect sizes for associations between Calcium (**A**), Potassium (**B**), Copper (**C**), Iron (**D**), Magnesium (**E**), Selenium (**F**), Zinc (**G**) and rosacea risk.

recent studies on zinc supplementation have mainly focused on improving the quality of life of rosacea patients, rather than addressing its clinical characteristics.[10] Moreover, one of the older oral zinc clinical trials is already discontinued due to the lack of efficacy in rosacea.[41] This study did not find conclusive evidence on the causal role of other micronutrients, besides Calcium and Potassium, in the rosacea. The absence of an association in our MR study does not necessarily conflict with previous findings but rather highlights the complex nature of rosacea, where causal relationships may differ depending on the research design and study population.

The relationship between rosacea and vitamin D has been more extensively documented, although the results across studies have been limited and inconsistent.[29] A recent Mendelian randomization study found a significant association between higher serum vitamin D levels and a decreased risk of rosacea.[17] Our study, however, focused on micronutrients

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Table 2 Assessment of Pleiotropy in the Mendelian Randomization Study Results

Exposure	Outcome	Heterogeneity		Pleiotropy	
		Q statistic (IVW)	*P* value	MR-Egger Intercept	*P* value
Calcium	Rosacea	247.148	0.128	−0.02	<0.001
Copper		4.845	0.435	0.015	0.649
Selenium		2.602	0.761	−0.066	0.187
Zinc		7.443	0.384	0.113	0.14
Potassium		12.861	0.459	0.022	0.653
Magnesium		17.984	0.393	−0.006	0.835
Iron		6.391	0.7	0.022	0.4

Abbreviations: OR, odds ratio; CI, confidence interval; IVW, Inverse variance weighted.

Table 3 Assessment of Outliers by MR-PRESSO Method When Considering the Micronutrients Exposure

Exposure	Outcome	RAW		Outlier-Corrected		Global P	Number of Outliers	Distortion P
		OR (CI%)	*P* Value	OR (CI%)	*P* Value			
Calcium	Rosacea	2.25 (2–2.53)	0	NA	NA	0.095	NA	NA
Copper		1.03 (0.92–1.15)	0.61	NA	NA	0.486	NA	NA
Selenium		1.07 (0.94–1.23)	0.33	NA	NA	0.713	NA	NA
Zinc		1.14 (0.94–1.39)	0.22	NA	NA	0.37	NA	NA
Potassium		0.4 (0.17–0.96)	0.06	NA	NA	0.43	NA	NA
Magnesium		1.29 (0.67–2.48)	0.46	NA	NA	0.5	NA	NA
Iron		1.23 (0.96–1.56)	0.13	NA	NA	0.828	NA	NA

Abbreviations: OR, odds ratio; CI, confidence interval.

that have not been as thoroughly investigated in the context of rosacea. By expanding the analysis to include elements like calcium, potassium, copper, and others, our findings help fill a gap in the literature and provide new insights into the potential roles these micronutrients might play in rosacea's pathogenesis. By using a notably large sample size and data sources derived from a number of highly validated GWAS, our Mendelian randomization approach minimizes confounding factors and provides a direct assessment of causality.

Some limitations should also be taken into account. Firstly, measurements of serum micronutrients in healthy individuals do not always reflect dietary intake and supplementation, thus clinical application of the findings needs further research. Moreover, the focus on a select group of minerals with available GWAS data may lead to overlooking the potential relevance of other important micronutrients. Secondly, study participants were predominantly white and of European ancestry, while metabolism of micronutrients vary by race and ethnicity, limiting the generalizability of the findings. In addition, the GWAS data used for rosacea was not stratified by clinical subtypes, which might give additional insight into the pathogenesis. Thirdly, although additional methods were applied to avoid horizontal pleiotropy, initial analysis still showed signs of it in the Calcium dataset; some factors, such as Vitamin D, have a close relationship with serum calcium that might influence the distribution of genetic variants impossible to exclude with current methodology. Finally, due to the comparatively large number of participants, there may be a possibility of a missing rosacea diagnosis among the FinnGen cohort, limiting the reliability of the MR model to some degree.

Conclusion

In conclusion, this study found an evidence of a causal association between genetically predicted serum levels of Calcium and Potassium with the risk of rosacea. The roles of these micronutrients should be further studied in rosacea, especially as a link to neurovascular dysregulation and oxidative stress.

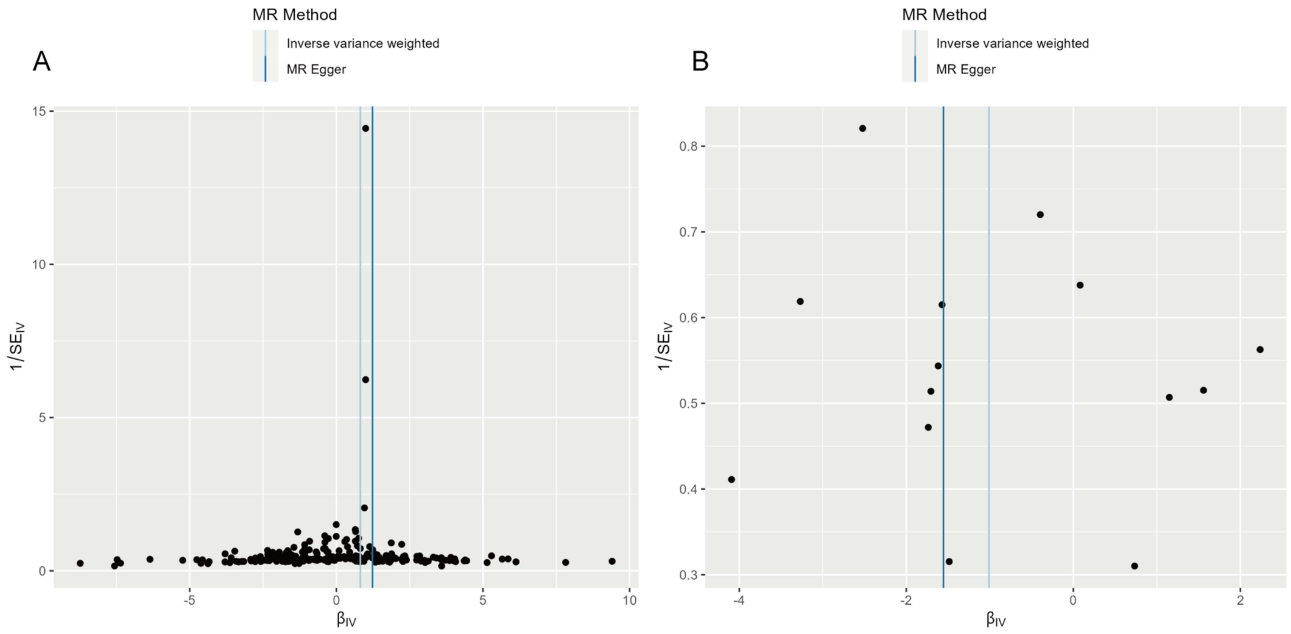

Figure 4 Funnel plot demonstrating MR Egger assessing the possible pleiotropy in the associations between Calcium (**A**), Potassium (**B**) and rosacea risk; pleiotropy assessment for other micronutrients is presented in Supplementary Figure S1.

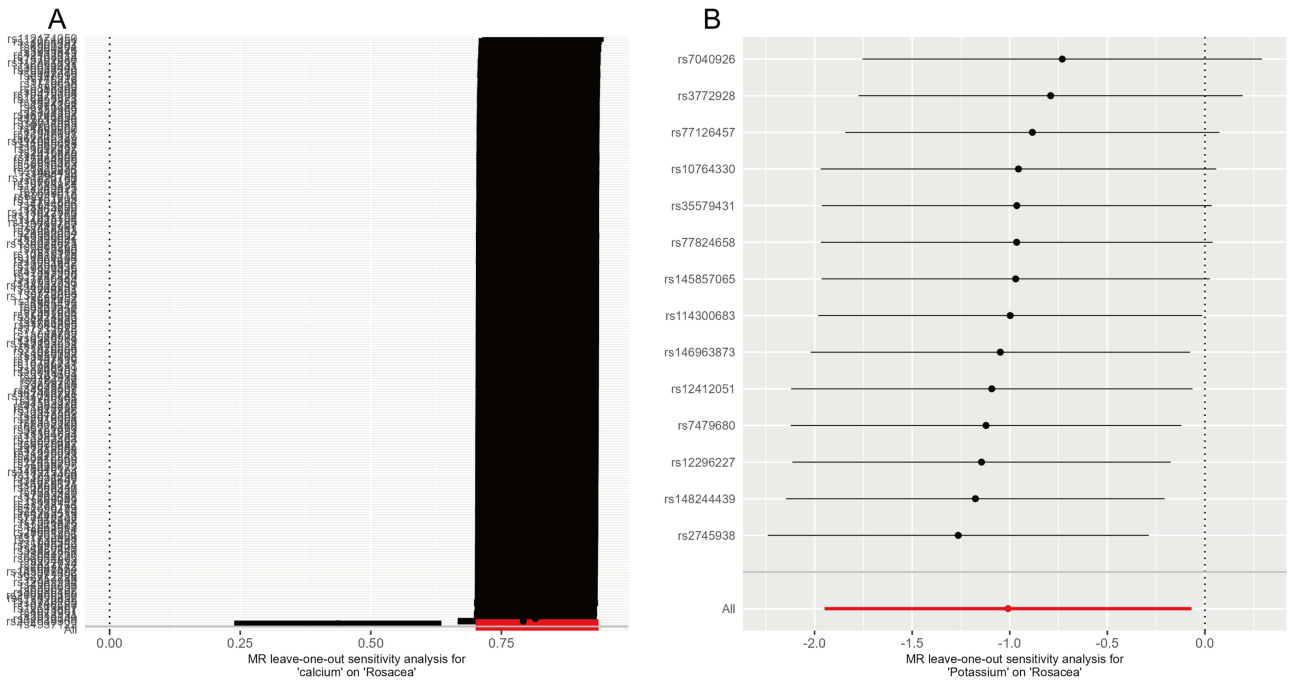

Figure 5 Leave-one-out plot demonstrating the robustness of associations between Calcium (**A**), Potassium (**B**) and rosacea risk; similar assessment for other micronutrients is presented in Supplementary Figure S2.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

According to Article 32 of the Ethical Review Measures for Life Science and Medical Research Involving Human Beings of the People's Republic of China, the data used in this study will not cause any form of harm to human beings, nor will

it touch sensitive personal privacy or trade secrets, so the ethical review can be exempted. In addition, the database used in this study was publicly available and legally available.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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