Diao *et al. Nutrition & Metabolism* (2025) 22:49
https://doi.org/10.1186/s12986-025-00940-1

Nutrition & Metabolism

RESEARCH Open Access

Deciphering the causality between micronutrients and esophageal cancer via Mendelian randomization

Zhuo Diao[1], Guangyin Peng[2], Yige Chen[2], Jun Wang[2], Jianjun Liu[2], Zhaopeng Zhang[2] and Wei Zhang[2*]

Abstract

Background There is an ongoing debate about how micronutrients influence the risk of developing esophageal cancer (EC), requiring more definitive proof to ascertain their causal relationship.

Objective The current study seeks to identify the causal relationship between 14 micronutrients and EC through Mendelian randomization (MR) methods.

Methods We performed a two-sample MR analysis of micronutrients in relation to EC, using five different MR methodologies, chief among them the Inverse Variance Weighted method. To ascertain the direction of causal links, Steiger filtering was applied. The study culminated in a sensitivity analysis to test the robustness of the results.

Results In the European population, iron (OR = 0.231, 95% CI: 0.073–0.727, $P = 0.012$) and magnesium (OR = 0.357, 95% CI: 0.143–0.894, $P = 0.028$) were associated with a reduced risk of EC, both showing suggestive evidence of a causal relationship. In Asian populations, however, no significant causal effects were found between the 14 micronutrients and EC. The direction of causality was validated across all results.

Conclusion Among European populations, iron and magnesium intake is associated with a reduced risk of EC, a benefit not seen in Asian populations. Personalized strategies and region-specific advice are necessary for EC prevention and control.

Keywords Causality, Esophageal cancer, Mendelian randomization, Micronutrients

Introduction

Esophageal cancer (EC), a frequently occurring cancer in the digestive system, holds the seventh position in global cancer mortality rates. Characterized by its two main subtypes—esophageal adenocarcinoma and squamous cell carcinoma—EC is known for its high incidence and grim prognosis [1, 2]. The International Agency for Research on Cancer (IARC) reported 511,000 new EC cases and 445,000 cancer deaths in their latest 2022 statistics [1]. Early-stage EC often presents with unobtrusive symptoms, delaying diagnosis until the disease has progressed to later stages [3]. Detecting the risk factors for EC is paramount for its prevention, treatment, and prognostic evaluation. Research unveils an intimate link between diet and EC risk, with a particular emphasis on the role of micronutrients [4].

Micronutrients sustain the normal functioning and well-being of the human body, and their importance is not diminished by their small quantities [5, 6]. The debate

*Correspondence:
Wei Zhang
xwk2019zw@163.com
[1]Department of Gastroenterology, Hanzhong Central Hospital, Hanzhong City 723000, China
[2]Department of Thoracic Surgery, Hanzhong Central Hospital, Hanzhong City 723000, China

over the relationship between micronutrients and EC continues. Studies have pointed towards higher zinc, iron, selenium, and calcium concentrations potentially reducing EC risk [7, 8, 9, 10]. A negative association has been noted between the intake of vitamins A, C, and E and the risk of EC [11, 12, 13]. On the other hand, a meta-analysis by Hong et al. [14] reported no significant relationship between higher selenium levels and the risk of esophageal adenocarcinoma. Yin et al. [15] also declared that there is no evident causal association between vitamins A, C, and E and EC. Therefore, the need for more convincing and exhaustive evidence to establish the causality between micronutrients and EC is imperative.

Mendelian randomization (MR), with its use of single nucleotide polymorphisms as instrumental variables (IVs), provides a clear view of causality between exposures and outcomes. This method, unaffected by environmental factors or other confounders, mirrors the randomization of a natural experiment, precluding the possibility of reverse causality [16]. Our research employed a two-sample MR approach to analyze the causal links between 14 micronutrients and EC, with the objective of identifying new targets for the prevention and treatment of EC.

Methods

Research design

This research deployed a two-sample MR approach to investigate the causality between micronutrients and EC among European and Asian populations. As depicted in Figs. 1 and 14 trace elements serve as the exposure variables, and EC as the outcome variable. We utilized publicly available summary statistics from extensive Genome-Wide Association Studies (GWAS). Our MR analysis was grounded in three foundational assumptions: (1) the IVs are directly associated with the 14 micronutrients; (2) the IVs are unrelated to potential confounding factors; (3) the IVs influence EC solely through the 14 micronutrients.

Sources of data on micronutrients and EC

Our research integrated a large-scale dataset from GWAS on micronutrients required by individuals of European ancestry, all publicly accessible through the designated website (https://gwas.mrcieu.ac.uk/) (Table 1). We compiled GWAS data from 64,979 participants for micronutrients including iron, calcium, potassium, magnesium, vitamin B6, B12, C, D, E, and folate; the vitamin A dataset comprised 62,991 participants. Given the scarcity of GWAS data for copper, zinc, and selenium, we incorporated data from the study led by David M. Evans, which included 2,603 samples [17]. Furthermore, we included

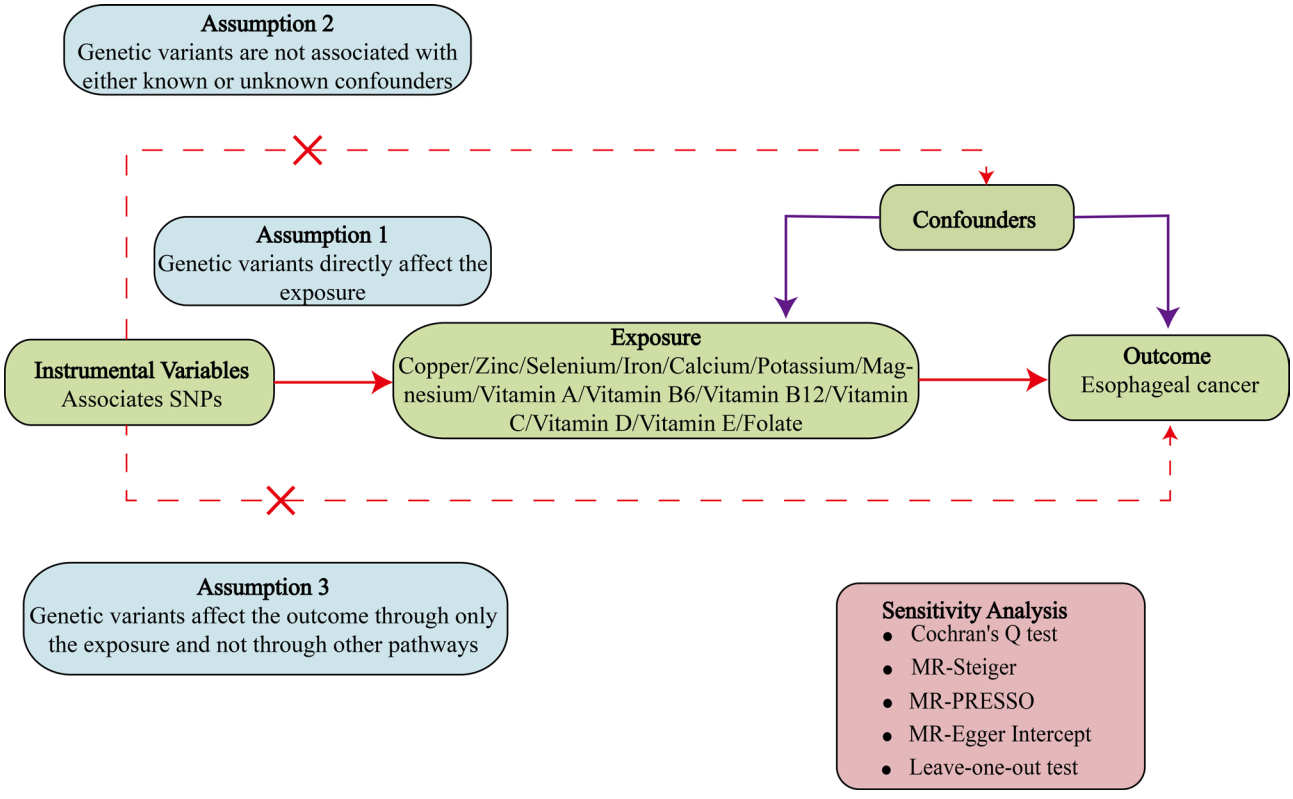

Fig. 1 Flow chart of our study design

Table 1 Dataset of the micronutrient information

Trait	Year	ID	Population	Sample size
Copper (Cu)	2013	ieu-a-1073	European	2,603
Zinc (Zn)	2013	ieu-a-1079	European	2,603
Selenium (Se)	2013	ieu-a-1077	European	2,603
Iron (Fe)	2018	ukb-b-20,447	European	64,979
Calcium (Ca)	2018	ukb-b-8951	European	64,979
Potassium	2018	ukb-b-17,881	European	64,979
Magnesium (Mg)	2018	ukb-b-7372	European	64,979
Vitamin A (Vit A)/Retinol	2018	ukb-b-17,406	European	62,991
Vitamin B6 (Vit B6)	2018	ukb-b-7864	European	64,979
Vitamin B12 (Vit B12)	2018	ukb-b-19,524	European	64,979
Vitamin C (Vit C)	2018	ukb-b-19,390	European	64,979
Vitamin D (Vit D)	2018	ukb-b-18,593	European	64,979
Vitamin E (Vit E)	2018	ukb-b-6888	European	64,979
Folate	2018	ukb-b-11,349	European	64,979
Copper (Cu)	2022	GCST90100524	East Asian (China)	1,798
Zinc (Zn)	2022	GCST90100537	East Asian (China)	1,798
Selenium (Se)	2022	GCST90100532	East Asian (China)	1,799
Iron (Fe)	2020	ukb-e-100011_CSA	South Asian	1,469
Calcium (Ca)	2020	ukb-e-30680_CSA	South Asian	7,697
Potassium	2020	ukb-e-100016_CSA	South Asian	1,469
Magnesium (Mg)	2020	ukb-e-100017_CSA	South Asian	1,469
Vitamin A (Vit A)	2020	ukb-e-100018_CSA	South Asian	1,447
Vitamin B6 (Vit B6)	2020	ukb-e-100012_CSA	South Asian	1,469
Vitamin B12 (Vit B12)	2020	ukb-e-100013_CSA	South Asian	1,469
Vitamin C (Vit C)	2020	ukb-e-100015_CSA	South Asian	1,469
Vitamin D (Vit D)	2020	ukb-e-30890_CSA	South Asian	7,380
Vitamin E (Vit E)	2020	ukb-e-100025_CSA	South Asian	1,469
Folate	2020	ukb-e-100014_CSA	South Asian	1,469

Table 2 Dataset of EC information

Disease	Year	ID	Population	Sample size	Case	Control	PMID
Esophageal cancer	2024	/	European	345,881	763	345,118	36,653,562
Esophageal cancer	2021	ebi-a-GCST90018621	East Asian (Japan)	160,589	1,388	159,201	34,594,039

GWAS data for micronutrients from Asian populations, with 1,469 samples for iron, potassium, magnesium, vitamin B6, B12, C, E, and folate; 7,697 for calcium; 1,447 for vitamin A; and 7,380 for vitamin D (https://gwas.mrcieu.ac.uk/). Lastly, we added GWAS data for 1,798 samples of blood copper and zinc levels and 1,799 samples of selenium levels (https://www.ebi.ac.uk/gwas/studies) [18].

We integrated the GWAS data for the outcome EC, which was derived from the latest version (R11) of the FinnGen database (https://www.finngen.fi/en), which includes 763 cases and 345,118 controls [19]. Data on Asian ancestry were derived from a large GWAS dataset, comprising 1,388 cases and 159,201 controls [20], as detailed in Table 2.

Selection of IVs

The selection of IVs was guided by these principles [21]: (1) SNPs, serving as IVs, were selected with a genome-wide significance threshold of $P < 5e\text{-}8$, but a less stringent threshold ($P < 5e\text{-}6$) was considered due to the paucity of SNPs with substantial effects on trace elements; (2) SNPs underwent clumping to eliminate the impact of linkage disequilibrium ($r^2 = 0.001$, window size = 10,000 kb); (3) The F-statistic was employed to evaluate the strength of the IVs, with an F-statistic exceeding 10 for all SNPs included, signifying robust instruments; (4) SNPs for both exposure and outcome were aligned for consistency, with allele directions synchronized and the removal of SNPs with unclear or discordant directions, as well as the exclusion of outliers.

MR analysis

Our investigation applied a two-sample MR approach, with the Inverse Variance Weighted (IVW) method as the mainstay for evaluating the causal effects of 14 micronutrients on EC. Beyond our core analysis method, we also considered MR-Egger regression, Weighted Median estimation, Weighted Mode, and Simple Mode as supporting

approaches. To reinforce the directionality of associations, Steiger filtering was conducted [22].

Sensitivity analysis

To ensure that IVs impact the outcome exclusively via exposure and to bolster the robustness of our results, we undertook sensitivity analyses with diverse methodologies [23]. First, we applied Cochran's Q heterogeneity test to measure heterogeneity, with a *P*-value over 0.05 denoting no significant heterogeneity. Heterogeneity, if present, was addressed using the multiplicative random-effects IVW method to offset bias from diverse IV associations. The *P*-value of the MR-Egger regression intercept was used to gauge horizontal pleiotropy; a *P*-value surpassing 0.05 indicates no pleiotropy bias. The MR-PRESSO technique detected outlier IVs via a global test and computed the causal effect post-removal of these outliers. Finally, the leave-one-out approach assessed the influence of individual SNPs on the results.

Statistical analysis

R software (version 4.3.1) in conjunction with the "Two Sample MR" (v 0.6.6), "Mendelian Randomization" (v 0.3.0), and "MR-PRESSO" (v 1.0) R packages were used to perform the two-sample MR analysis. The random-effects IVW method was our principal analytical approach for determining causality between exposure and outcome. Heterogeneity across SNPs was evaluated with Cochran's Q test, and both the MR-Egger regression intercept and the MR-PRESSO tool were used to identify and adjust for horizontal pleiotropy. The influence of individual SNPs on the results was examined via the leave-one-out method. In the MR analysis, we used the Bonferroni-corrected *P*-value as the threshold for statistical significance ($P < 0.05/14 = 0.004$). Associations with $P < 0.05$ but exceeding the Bonferroni-corrected threshold ($P = 0.004$) were considered suggestive evidence of a causal relationship.

Results

Causality between trace elements and EC

Among European populations, to eliminate the possibility of weak IV bias, the IVs were selected based on an F-statistics value above 10 for each. The IVs included in this research are outlined in Table S1. As shown in Fig. 2, the IVW results indicated that 2 out of the 14 micronutrients were associated with EC risk. Specifically, iron was associated with a reduced risk of EC (OR = 0.231, 95% CI: 0.073–0.727, $P = 0.012$), while magnesium also demonstrated a causal relationship with EC (OR = 0.357, 95% CI: 0.143–0.894, $P = 0.028$). Both associations showed suggestive evidence of causality. The rest of the micronutrients did not display any significant causality with EC ($P > 0.05$, Table S2). As shown by the scatter plot in Fig. 3, the concordant findings from the other MR methods validated the reliability of the results (details in Table S2). The scatter plot visually demonstrated the inverse causal association between iron and magnesium elements and the risk of EC, with the distribution of all SNP effect sizes supporting a protective trend (Fig. 3). Thus, the intake of iron and magnesium may act as protective factors for EC among Europeans.

For the Asian cohort, the IVs examined are listed in Table S3. The IVW method revealed no evidence of causal associations between the 14 micronutrients and EC (Fig. 4, Table S4).

Sensitivity analysis

To confirm the causality direction between micronutrients and EC, Steiger's filtering was applied, with statistical significance defined by $P < 0.05$, and all elements cleared the causal directionality screening (Table 3). Cochrane's Q test showed that heterogeneity did not influence the

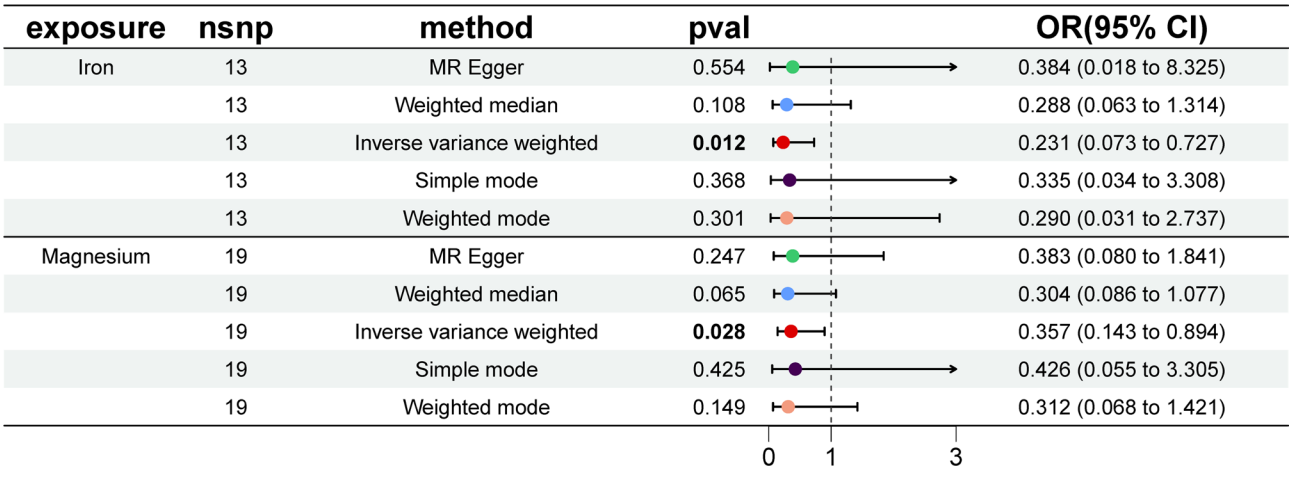

Fig. 2 In the European iron and magnesium Mendelian randomization results with esophageal cancer

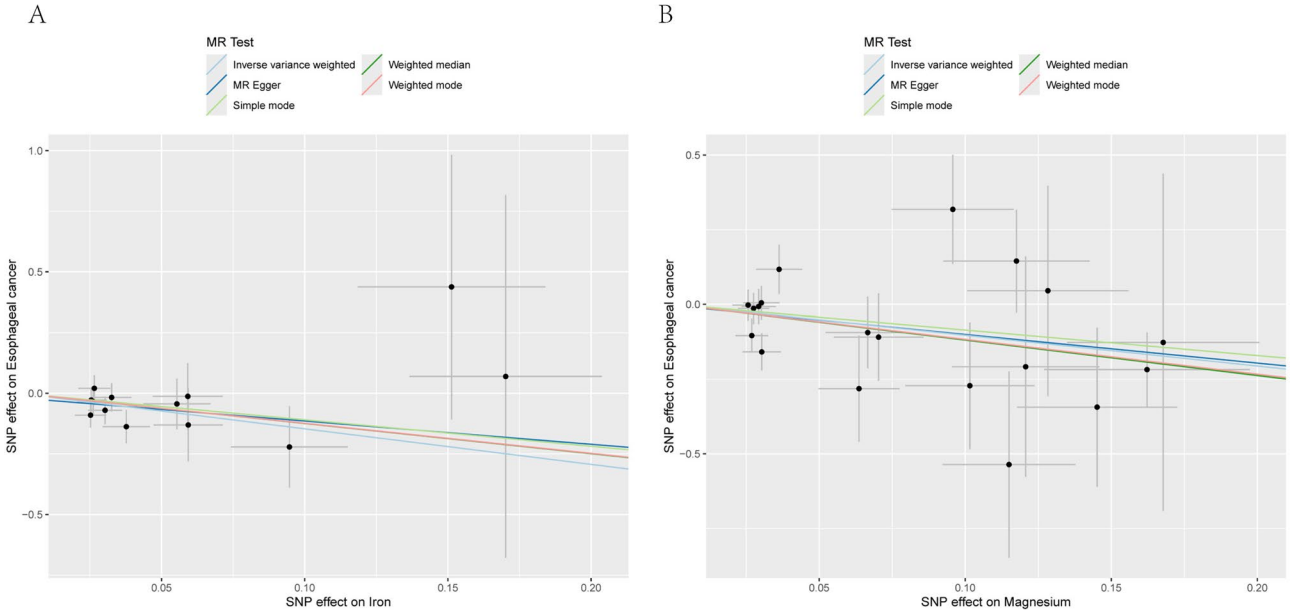

Fig. 3 Scatter plot of iron and magnesium with EC in the European population. (**A**) Scatter plot of SNP effect sizes for iron; (**B**) Scatter plot of SNP effect sizes for magnesium

exposure	outcome	nsnp	method	pval	OR(95% CI)
Calcium	Esophageal cancer	8	IVW	0.633	1.096 (0.751 to 1.600)
Copper		6	IVW	0.552	0.836 (0.463 to 1.508)
Iron		8	IVW	0.806	1.023 (0.852 to 1.229)
Folate		12	IVW	0.135	0.908 (0.801 to 1.030)
Mg		4	IVW	0.199	0.881 (0.726 to 1.069)
Potassium		3	IVW	0.508	1.108 (0.818 to 1.500)
Selenium		4	IVW	0.350	0.891 (0.700 to 1.135)
Vitamin A		4	IVW	0.917	1.010 (0.838 to 1.218)
Vitamin B12		8	IVW	0.528	1.040 (0.920 to 1.176)
Vitamin B6		7	IVW	0.537	0.954 (0.821 to 1.109)
Vitamin C		2	IVW	0.969	1.008 (0.664 to 1.530)
Vitamin D		10	IVW	0.950	1.010 (0.733 to 1.392)
Vitamin E		8	IVW	0.104	0.886 (0.765 to 1.025)
Zinc		5	IVW	0.315	0.896 (0.723 to 1.110)

Fig. 4 Nutrient elements in Asian Mendelian randomization results with esophageal cancer

IVW and MR-Egger regression methods in any analysis ($P_{\text{Cochrane's Q}}$>0.05). A heterogeneity signal was detected in the copper element SNPs in Asian populations (P<0.001), with no other SNPs showing heterogeneity. Post-removal of the outlier SNPs (rs150273297 and rs4766566), heterogeneity was not identified in the adjusted copper intake SNPs (P>0.05). Furthermore, the MR-Egger intercept (P>0.05) suggested minimal horizontal pleiotropy across all analyses. Lastly, the MR-PRESSO global test did not find any outlier SNPs (P>0.05).

The funnel plots demonstrated a symmetrical distribution pattern of SNPs included in the analyses, showing suggestive evidence of causal associations, indicating minimal influence of potential bias on the causal estimates. Results for the European population are presented in Supplementary Fig. 1, while those for the Asian population are shown in Supplementary Fig. 2.Furthermore, the leave-one-out sensitivity analysis confirmed that the removal of any single SNP did not significantly affect the MR analysis, suggesting that the causal associations between iron and magnesium with EC in the European

Table 3 Sensitivity analysis of causal relationship

Exposure	Outcome	Heterogeneity				Pleiotropy				Steiger_pval
		MR Egger		IVW		Egger intercept	SE	*P*-value	MR-PRESSO Global	
		Statistics Q	*P*-Value	Statistics Q	*P*-Value				*P*-value	
Population: European										
Calcium	Esophageal cancer	20.858	0.233	21.461	0.257	-0.046	0.066	0.493	0.278	1.59E-68
Copper	Esophageal cancer	2.132	0.711	2.876	0.719	0.031	0.036	0.437	0.776	5.49E-49
Iron	Esophageal cancer	6.474	0.840	6.596	0.883	-0.019	0.054	0.733	0.896	1.09E-46
Folate	Esophageal cancer	6.319	0.899	8.744	0.792	-0.064	0.041	0.145	0.767	6.83E-52
Magnesium	Esophageal cancer	22.865	0.154	22.882	0.195	-0.004	0.039	0.913	0.236	4.20E-65
Potassium	Esophageal cancer	18.219	0.149	18.240	0.196	-0.008	0.065	0.903	0.218	7.83E-51
Selenium	Esophageal cancer	1.012	0.798	1.020	0.907	-0.005	0.055	0.935	0.931	4.16E-34
Vitamin A	Esophageal cancer	4.300	0.745	4.305	0.829	-0.004	0.065	0.947	0.772	1.68E-35
Vitamin B12	Esophageal cancer	2.763	0.906	6.198	0.625	-0.115	0.062	0.106	0.642	6.52E-33
Vitamin B6	Esophageal cancer	18.306	0.247	18.908	0.273	-0.034	0.049	0.493	0.260	4.00E-61
Vitamin C	Esophageal cancer	6.664	0.672	7.112	0.715	-0.030	0.045	0.520	0.676	6.93E-42
Vitamin D	Esophageal cancer	4.774	0.942	4.836	0.963	0.020	0.080	0.808	0.959	1.53E-48
Vitamin E	Esophageal cancer	9.788	0.459	9.893	0.540	-0.014	0.044	0.752	0.588	9.32E-46
Zinc	Esophageal cancer	3.116	0.682	3.184	0.785	-0.026	0.099	0.804	0.794	9.00E-57
Population: Asian										
Calcium	Esophageal cancer	8.687	0.192	9.266	0.234	0.061	0.096	0.551	0.241	1.36E-49
Copper	Esophageal cancer	53.917	5.48E-11	59.914	1.27E-11	-0.147	0.221	0.541	< 0.001	6.34E-31
Copper_adj	Esophageal cancer	3.449	0.178	3.980	0.264	0.135	0.244	0.635	0.362	3.24E-22
Iron	Esophageal cancer	2.485	0.870	5.329	0.620	-0.357	0.212	0.143	0.571	2.66E-42
Folate	Esophageal cancer	5.332	0.868	7.359	0.769	0.084	0.059	0.185	0.766	5.86E-50
Mg	Esophageal cancer	1.189	0.552	1.254	0.740	0.030	0.117	0.823	0.785	3.58E-20
Potassium	Esophageal cancer	3.891	0.049	3.891	0.143	-0.001	0.316	0.999	NA	3.87E-16
Selenium	Esophageal cancer	2.569	0.277	3.255	0.354	-0.113	0.155	0.541	0.429	9.83E-22
Vitamin A	Esophageal cancer	0.062	0.969	0.268	0.966	0.085	0.188	0.694	0.964	5.62E-22
Vitamin B12	Esophageal cancer	7.362	0.289	7.382	0.390	-0.005	0.042	0.902	0.493	2.12E-40
Vitamin B6	Esophageal cancer	3.144	0.678	5.113	0.529	-0.111	0.079	0.220	0.420	1.22E-35
Vitamin D	Esophageal cancer	5.024	0.755	0.303	0.582	NA	NA	NA	NA	1.32E-12
Vitamin E	Esophageal cancer	3.761	0.709	10.132	0.340	0.091	0.040	0.054	0.347	5.14E-49
Zinc	Esophageal cancer	0.753	0.861	3.892	0.792	0.068	0.188	0.730	0.781	8.15E-42
Calcium	Esophageal cancer	8.687	0.192	3.624	0.459	-0.335	0.198	0.189	0.504	1.19E-26

adj means filtering outlier SNPs

population were robust (Figure S3 for European results and Figure S4 for Asian results).

Discussion

Employing a two-sample MR analysis, this study sought to delineate the causal relationships between 14 micronutrients and EC. The findings indicate that iron and magnesium are protective factors for EC in European populations, while no causal associations were noted between micronutrients and EC in Asian populations.

Iron is a vital element for all living organisms, integral to the synthesis of hemoglobin, myoglobin, cytochromes, and other biologically active materials, and it is also engaged in metabolic functions such as oxygen transport, cellular oxidation, DNA replication, and cell proliferation [24, 25]. The correlation between iron and the risk of esophageal cancer has long been a disputed topic. Findings from a prospective study indicate a significant association between iron supplementation and a reduced risk of adenocarcinoma of the esophagus [26]. A meta-analysis has also shown a notable negative correlation between total iron intake and EC risk, with a 15% risk reduction for every additional 5 mg/day of iron [8]. Research comparing serum micronutrient levels in EC patients versus healthy controls has identified a markedly lower mean iron level in the EC group [27]. Our research corroborates these findings. However, some scholars have obtained divergent results. An embedded case-control study analyzing hair for trace elements in 96 patients with esophageal squamous cell carcinoma found an increased risk with higher iron concentrations [28]. Moreover, a MR analysis of 22 cancers and trace elements

did not establish a causal link between iron and EC [29], possibly due to the limited number of three iron-related IVs included in the study.

Moreover, the elevation of iron levels can lead to the accumulation of reactive oxygen species and the end products of lipid peroxidation, thereby initiating pathways that cause cell death. This type of cell death, identified as ferroptosis, has garnered attention in cancer research [30]. A number of small molecule drugs have been demonstrated to elicit ferroptosis and curb tumor growth, including sorafenib and sulfasalazine. These agents impede the uptake of cysteine and the formation of glutathione peroxidase 4 (GPX4), and they induce lipid peroxidation, hastening ferroptosis in cancer cells [31]. Furthermore, ferroptosis has been acknowledged to have a significant role in cancer immunotherapy [32]. $CD8^+$T cells, through the secretion of interferon-γ, can lower the expression of SLC3A2 and SLC7A11, diminish the cysteine uptake by cancer cells, and foster ferroptosis, thereby enhancing the immune-mediated antitumor activity [33]. In the realm of EC, ferroptosis-related research has been chiefly concerned with its impact on the tumor microenvironment and the ensuing immune response [34]. The modulation of EC by ferroptosis is thought to occur through the enhancement of immune cell infiltration, including an increase in $CD8^+$T cells, macrophages, myeloid dendritic cells, and $CD4^+$T cells, thereby potentially impacting patient prognosis [35, 36]. As such, the targeted triggering of ferroptosis may offer a fresh avenue for cancer therapeutics.

Magnesium, the second most plentiful divalent cation in cells, is a cofactor for over 300 enzymatic reactions, fundamentally involved in all cellular metabolic activities [37]. Despite that, the impact of magnesium on EC has not been broadly investigated, with only a handful of observational studies to date. Some of them suggest that increased magnesium intake from diet and drinking water may correlate with a reduced risk of EC [38, 39]. The beneficial effects of magnesium intake have also been documented in other cancers of the digestive system. Integrated omics studies have revealed that magnesium ions promote the aggregation of F-actin by regulating DBN1S142p, which in turn suppresses MMP2 expression and inhibits the migration of colon cancer cells [40]. Additionally, meta-analyses and case-control have indicated a negative correlation between increased magnesium intake and the development of colorectal cancer (CRC) [41]. Furthermore, dietary magnesium has a favorable impact on the reduction of risks for gastric and pancreatic cancers [42, 43]. Magnesium also has a salient role in cancer therapy by mitigating peripheral neuropathy and acute kidney injury caused by chemotherapy, which is advantageous for patient care [44]. Disruptions in magnesium balance can impair the immune system, reduce the chemosensitivity of cancer cells, and lead to resistance to chemotherapy [45, 46, 47]. Magnesium generally offers protection against digestive system cancers, so its intake will contribute to EC prevention and treatment, but the specific mechanisms need further experimental exploration.

The causality between iron and magnesium and EC is found to be heterogeneous among different ethnic groups, which may be attributed to genetic polymorphisms associated with the disease. Specifically, the polymorphisms MDM2 T309G and PLCE1 rs2274223 are correlated with EC in Asian populations but not in Caucasians [48, 49]. Furthermore, research indicates that esophageal squamous cell carcinoma is more frequently found in Asian populations, in contrast to esophageal adenocarcinoma, which is the main type of EC in Western countries [50]. The onset of esophageal adenocarcinoma is generally linked to obesity, and the consumption of iron and magnesium has been proven to reduce body mass index and waist size, which aids in weight loss for those who are obese [51, 52]. Consequently, the distinct EC types among various ethnic groups could be a factor leading to heterogeneity in causality. Hence, the strategies for EC prevention and treatment should be region-specific. More research needs to be conducted in the future to fully elucidate the racial variations in the impact of iron and magnesium on EC risk.

In addition, this study has the following limitations. First, trace elements may have differential effects on EC patients of different ages or genders. However, the lack of individual-level information in the summary statistics prevented us from stratifying EC cases by age and gender. Second, the current GWAS data on EC does not include information on EC staging, making it difficult to determine whether trace elements have a causal relationship with EC progression. Third, we were unable to evaluate all trace nutrients, such as iodine and vitamin K, due to the absence of suitable GWAS data for MR analysis. Fourth, the sample size of the Asian population in this study was significantly smaller than that of the European population, which may have resulted in insufficient statistical power to detect true associations. Future GWAS data with larger East Asian cohorts are needed to validate our findings. Fifth, although our suggestive associations ($0.004 < P < 0.05$) may reflect an increased type I error rate, their consistency with previous literature [8, 26, 38, 39] and the robustness of the MR analysis (no heterogeneity or pleiotropy) support further investigation. Larger cohort studies are required in the future to confirm these findings. Finally, although this study mitigated the risk of collider bias by using GWAS data without adjusted covariates, MR analysis may still be affected by unmeasured confounding or complex genetic structures. For instance, if IVs are correlated with population

stratification or other environmental factors, they may indirectly distort causal effects. Therefore, the interpretation of the results should be corroborated by future experimental studies or more refined genetic instrument designs.

Conclusion

This study presents genetic validation for the causal connection between micronutrient levels and EC risk. Importantly, in the European demographic, an augmentation of iron and magnesium may mitigate EC risk, assisting clinicians in the nuanced administration of micronutrient intake during EC management.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-025-00940-1.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Author contributions

Conceptualization: Zhuo Diao, Guangyin Peng Data curation: Yige Chen, Jun Wang Formal Analysis: Zhuo Diao, Guangyin Peng Funding acquisition: Wei Zhang Investigation: Jun Wang Methodology: Zhuo Diao, Guangyin Peng Project administration: Jianjun Liu, Zhaopeng Zhang Resources: Zhaopeng Zhang Software: Wei Zhang Supervision: Jianjun Liu Validation: Wei Zhang Visualization: Zhaopeng Zhang Writing– original draft: Zhuo Diao, Guangyin Peng, Jianjun Liu Writing– review & editing: Jianjun Liu, Zhaopeng Zhang, Wei Zhang.

Funding

Not applicable.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 8 October 2024 / Accepted: 12 May 2025
Published online: 22 May 2025

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63.
2. Guo J, Si G, Si F. Association of immune cells and the risk of esophageal cancer: A Mendelian randomization study in a East Asian population. Med (Baltim). 2024;103:e38064.
3. Alsop BR, Sharma P. Esophageal Cancer. Gastroenterol Clin North Am. 2016;45:399–412.
4. Qin X, Jia G, Zhou X, Yang Z. Diet and esophageal Cancer risk: an umbrella review of systematic reviews and Meta-Analyses of observational studies. Adv Nutr. 2022;13:2207–16.
5. Jakubczyk K, Kupnicka P, Melkis K, Mielczarek O, Walczyńska J, Chlubek D et al. Effects of fermentation time and type of tea on the content of micronutrients in Kombucha fermented tea. Nutrients. 2022; 14.
6. Kul AN, Ozturk Kurt B. Comparison of trace elements in peripheral blood and bone marrow of newly diagnosed multiple myeloma patients. Clin Exp Med. 2024;24:78.
7. Fong LY, Huebner K, Jing R, Smalley KJ, Brydges CR, Fiehn O, et al. Zinc treatment reverses and anti-Zn-regulated MiRs suppress esophageal carcinomas in vivo. Proc Natl Acad Sci U S A. 2023;120:e2220334120.
8. Ma J, Li Q, Fang X, Chen L, Qiang Y, Wang J, et al. Increased total iron and zinc intake and lower Heme iron intake reduce the risk of esophageal cancer: A dose-response meta-analysis. Nutr Res. 2018;59:16–28.
9. Cai X, Wang C, Yu W, Fan W, Wang S, Shen N, et al. Selenium exposure and Cancer risk: an updated Meta-analysis and Meta-regression. Sci Rep. 2016;6:19213.
10. Hashemian M, Poustchi H, Abnet CC, Boffetta P, Dawsey SM, Brennan PJ, et al. Dietary intake of minerals and risk of esophageal squamous cell carcinoma: results from the Golestan cohort study. Am J Clin Nutr. 2015;102:102–8.
11. Li K, Zhang B. The association of dietary β-carotene and vitamin A intake on the risk of esophageal cancer: a meta-analysis. Rev Esp Enferm Dig. 2020;112:620–6.
12. Zhong J, Li P, Zheng F, Li Y, Lu W, Chen H, et al. Association between dietary vitamin C intake/blood level and risk of digestive system cancer: a systematic review and meta-analysis of prospective studies. Food Funct. 2024;15:8217–37.
13. Darbani Torshizi M, Younesian O, Aboomardani M, Roshandel G, Hosseinzadeh S, Hosseini Alarzi SS, et al. Serum selenium, vitamin A, and vitamin E levels of healthy individuals in High- and Low-Risk areas of esophageal Cancer. Middle East J Dig Dis. 2022;14:396–403.
14. Hong B, Huang L, Mao N, Xiong T, Li C, Hu L et al. Association between selenium levels and oesophageal adenocarcinoma risk: evidence from a meta-analysis. Biosci Rep. 2016; 36.
15. Yin L, Yan H, Chen K, Ji Z, Zhang X, Ji G et al. Diet-Derived Circulating antioxidants and risk of digestive system tumors: A Mendelian randomization study. Nutrients. 2022; 14.
16. Ference BA, Holmes MV, Smith GD. Using Mendelian randomization to improve the design of randomized trials. Cold Spring Harb Perspect Med. 2021; 11.
17. Evans DM, Zhu G, Dy V, Heath AC, Madden PA, Kemp JP, et al. Genome-wide association study identifies loci affecting blood copper, selenium and zinc. Hum Mol Genet. 2013;22:3998–4006.
18. Yang W, Li L, Feng X, Cheng H, Ge X, Bao Y, et al. Genome-wide association and Mendelian randomization study of blood copper levels and 213 deep phenotypes in humans. Commun Biol. 2022;5:405.
19. Kurki MI, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature. 2023;613:508–18.
20. Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S, et al. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet. 2021;53:1415–24.
21. Li Q, Zhou Z, Xu T, Gao X, Lou Y, Chen Z, et al. Relationship between cathepsins and cardiovascular diseases: a Mendelian randomized study. Front Pharmacol. 2024;15:1370350.
22. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. PLoS Genet. 2017;13:e1007081.
23. Lv X, Shang Y, Ning Y, Yu W, Wang J. Pharmacological targets of SGLT2 inhibitors on IgA nephropathy and membranous nephropathy: a Mendelian randomization study. Front Pharmacol. 2024;15:1399881.
24. Jing Y, Zhang S, Li M, Zhang R, Zhang H, Zheng Y, et al. Structural characterization and biological activities of polysaccharide iron complex synthesized by plant polysaccharides: A review. Front Nutr. 2022;9:1013067.

25. Suciadi LP, Henrina J, Putra ICS, Cahyadi I, Gunawan HFH. Chronic heart failure: clinical implications of Iron homeostasis disturbances revisited. Cureus. 2022;14:e21224.
26. Dawsey SP, Hollenbeck A, Schatzkin A, Abnet CC. A prospective study of vitamin and mineral supplement use and the risk of upper Gastrointestinal cancers. PLoS ONE. 2014;9:e88774.
27. Türkdoğan MK, Karapinar HS, Kilicel F. Serum trace element levels of Gastrointestinal cancer patients in an endemic upper Gastrointestinal cancer region. J Trace Elem Med Biol. 2022;72:126978.
28. Hashemian M, Poustchi H, Sharafkhah M, Pourshams A, Mohammadi-Nasrabadi F, Hekmatdoost A, et al. Iron, copper, and magnesium concentration in hair and risk of esophageal cancer: A nested Case-Control study. Arch Iran Med. 2023;26:665–70.
29. Kim JY, Song M, Kim MS, Natarajan P, Do R, Myung W, et al. An atlas of associations between 14 micronutrients and 22 cancer outcomes: Mendelian randomization analyses. BMC Med. 2023;21:316.
30. Jiang M, Qiao M, Zhao C, Deng J, Li X, Zhou C. Targeting ferroptosis for cancer therapy: exploring novel strategies from its mechanisms and role in cancers. Transl Lung Cancer Res. 2020;9:1569–84.
31. Yin L, Liu P, Jin Y, Ning Z, Yang Y, Gao H. Ferroptosis-related small-molecule compounds in cancer therapy: strategies and applications. Eur J Med Chem. 2022;244:114861.
32. Zhou H, Cheng Y, Huang Q, Xiao J. Regulation of ferroptosis by nanotechnology for enhanced cancer immunotherapy. Expert Opin Drug Deliv. 2024;21:921–43.
33. Wang W, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK, et al. CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy. Nature. 2019;569:270–4.
34. Fan X, Fan YT, Zeng H, Dong XQ, Lu M, Zhang ZY. Role of ferroptosis in esophageal cancer and corresponding immunotherapy. World J Gastrointest Oncol. 2023;15:1105–18.
35. Zhu L, Yang F, Wang L, Dong L, Huang Z, Wang G, et al. Identification the ferroptosis-related gene signature in patients with esophageal adenocarcinoma. Cancer Cell Int. 2021;21:124.
36. Shi ZZ, Tao H, Fan ZW, Song SJ, Bai J. Prognostic and immunological role of key genes of ferroptosis in Pan-Cancer. Front Cell Dev Biol. 2021;9:748925.
37. Liu Y, Gong R, Ma H, Chen S, Sun J, Qi J, et al. Dietary magnesium intake level modifies the association between vitamin D and insulin resistance: A large Cross-Sectional analysis of American adults. Front Nutr. 2022;9:878665.
38. Tang L, Lee AH, Xu F, Zhang T, Lei J, Binns CW. Fruit and vegetable consumption and risk of esophageal cancer: a case-control study in north-west China. Dis Esophagus. 2014;27:777–82.
39. Yang CY, Chiu HF, Tsai SS, Wu TN, Chang CC. Magnesium and calcium in drinking water and the risk of death from esophageal cancer. Magnes Res. 2002;15:215–22.
40. Zhang R, Hu M, Liu Y, Li W, Xu Z, He S et al. Integrative omics uncovers low tumorous magnesium content as A driver factor of colorectal Cancer. Genomics Proteom Bioinf. 2024.
41. Nguyen LTD, Gunathilake M, Lee J, Oh JH, Chang HJ, Sohn DK, et al. The interaction between magnesium intake, the genetic variant INSR rs1799817 and colorectal cancer risk in a Korean population: a case-control study. Int J Food Sci Nutr. 2024;75:396–406.
42. Allehdan S, Hammad SS, Alatrash RM, Al-Jaberi T, Hushki A, Yacoub S, et al. Protective effect of dietary micronutrients on gastric cancer risk among Jordanians. Nutr Hosp. 2024;41:163–74.
43. Hoyt M, Song Y, Gao S, O'Palka J, Zhang J. Intake of calcium, magnesium, and phosphorus and risk of pancreatic Cancer in the prostate, lung, colorectal, and ovarian Cancer screening trial. J Am Nutr Assoc. 2022;41:747–57.
44. Wesselink E, Winkels RM, van Baar H, Geijsen A, van Zutphen M, van Halteren HK et al. Dietary intake of magnesium or calcium and Chemotherapy-Induced peripheral neuropathy in colorectal Cancer patients. Nutrients. 2018; 10.
45. Gupta AA, Shekatkar M, Raj AT, Kheur S. Potential role of magnesium in Cancer initiation and progression. Pathol Oncol Res. 2020;26:2001–2.
46. Sun L, Li X, Xu M, Yang F, Wang W, Niu X. In vitro Immunomodulation of magnesium on monocytic cell toward anti-inflammatory macrophages. Regen Biomater. 2020;7:391–401.
47. Onuma S, Manabe A, Yoshino Y, Matsunaga T, Asai T, Ikari A. Upregulation of chemoresistance by Mg(2+) deficiency through elevation of ATP binding cassette subfamily B member 1 expression in human lung adenocarcinoma A549 cells. Cells. 2021; 10.
48. Chen B, Cao L, Hu KW, Zhang JW, Meng XL, Xiong MM. MDM2 SNP309 is an ethnicity-dependent risk factor for digestive tract cancers. Tumour Biol. 2014;35:3431–8.
49. Guo LY, Yang N, Hu D, Zhao X, Feng B, Zhang Y, et al. PLCE1 rs2274223 polymorphism and susceptibility to esophageal cancer: a meta-analysis. Asian Pac J Cancer Prev. 2014;15:9107–12.
50. Onozato Y, Sasaki Y, Abe Y, Sato H, Yagi M, Mizumoto N, et al. Novel genomic alteration in superficial esophageal squamous cell neoplasms in non-smoker non-drinker females. Sci Rep. 2021;11:20150.
51. Beales ILP, Ogunwobi OO. Leptin activates Akt in oesophageal cancer cells via multiple atorvastatin-sensitive small GTPases. Mol Cell Biochem. 2021;476:2307–16.
52. Jiang S, Ma X, Li M, Yan S, Zhao H, Pan Y, et al. Association between dietary mineral nutrient intake, body mass index, and waist circumference in U.S. Adults using quantile regression analysis NHANES 2007–2014. PeerJ. 2020;8:e9127.

Publisher's note