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Original article

Genetic prediction of micronutrient levels and the risk of colorectal polyps: A mendelian randomization study

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SUMMARY

Objective: Previous epidemiological and experimental studies have yielded conflicting results regarding the influence of human micronutrient levels on the risk of colorectal polyps (CP). In our study, we conducted a two-sample Mendelian randomization (MR) investigation to probe the link between 13 human micronutrients (calcium, selenium, magnesium, phosphorus, folate, vitamins B-6, B-12, C, D, beta-carotene, iron, zinc, and copper) and the genetic susceptibility to CP.

Methods: Summary statistics for CP (n = 463,010) were obtained from pan-European genome-wide association studies, and instrumental variables for 13 micronutrients were screened from published genome-wide association studies (GWAS). After selecting suitable instrumental variables, we performed a two-sample MR study, deploying sensitivity analyses to judge heterogeneity and pleiotropy, using inverse variance weighted methods as our primary estimation tool.

Results: Our study identified that a genetic predisposition to elevated toenail and circulating selenium or serum β-carotene concentrations lowers the risk of CP occurrence. However, no statistically significant association was observed between the other 11 micronutrients and the risk of CP.

Conclusion: The study findings provide evidence that the micronutrient selenium and β-carotene may confer protective effects against the development of CP.

1. Introduction

Colorectal polyps (CP), mainly referring to any lesion protruding into the intestinal lumen originating from the intestinal mucosal epithelium, bear a certain risk of developing colorectal malignancies [1]. A wealth of clinical evidence has highlighted that over 95% of colorectal cancers (CRC) develop from benign adenomatous polyps [2]. The influence of micronutrients on the development of CP has been a subject of debate for years. Although a multitude of reports have shed light on the relationship between several micronutrients and colorectal tumors, the impact of micronutrients on CP and their causal relationship remains contentious. The consistency demonstrated in observational studies often fails to receive ample validation in randomized controlled trial (RCT) studies, with systematic and meta-analytical research showing conflicting results. We screened 13 micronutrients affecting CP from published micronutrient observational studies and meta-analyses, which were calcium, selenium, magnesium, phosphorus, folate, vitamins B-6, B-12, C, D, beta-carotene, iron, zinc, and copper.

In a recent case–control study evaluating the role of oxidative imbalance in the development of CP, vitamin E, D, selenium, and

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zinc levels were found to be negatively correlated with the development of CP; vitamin A and Fe^{2+} concentrations were positively correlated with the risk of colon tumors [3]. Recent meta-analyses suggested that calcium had a protective role in preventing colorectal adenomas (CRA) [4–7]. A meta-analysis, including four RCTs implied that besides being beneficial for the risk of CRA, calcium can also prevent adenoma recurrence, but it did not relate to advanced adenomas [4]. In contrast, other prospective studies suggested that calcium intake can reduce CRA, especially high-risk adenomas [5]. Some prospective studies and meta-analyses demonstrated that higher selenium levels provided some protection against intestinal tumors (including adenomatous polyps [2,8], CRC [9], etc.), while other studies yield inconsistent results [10,11]. Similarly, higher magnesium intake was associated with lower CRC risk [12–14], and the intake and circulating levels of 25-hydroxyvitamin D were negatively correlated with CRA and CRC incidence [15]. A meta-analysis that included 20 studies showed that the intake of vitamin B6 and the blood level of pyridoxal phosphate (PLP) were negatively correlated with CRC risk [16], but previous meta-analysis findings contradicted this [17]. A case–control study from Korea [18] showed that low circulating folic acid levels were associated with new adenoma formation, but some results in another meta-analysis did not support this conclusion. Some experiments involving dietary supplements containing various micronutrients also yield inconsistent results [3,19]. The content and results of the clinical studies for all of the above nutrients are summarized and listed in the Supplementary file (Table S1).

On the other hand, the interaction of multiple micronutrients in studies could lead to various limitations, and data from many observational studies on food and nutrients came from food frequency questionnaires (FFQ) [20], often unable to ensure reliability. Due to potential confounders and reverse causality in previous observational studies, and the general failure of adequately powered trials to support protective associations, evidence from RCTs was limited. The existence and causality of the link between human micronutrient levels and CP remain ambiguous, warranting further research.

Mendelian randomization (MR) is an epidemiological method based on Mendel's second law that uses genetic variants to assess the causal relationship between exposure and outcome. As alleles follow the principle of random distribution and the law of free combination during gamete formation, MR can reduce confounding factors and reverse causality often encountered in traditional epidemiological studies, minimizing research bias [21,22]. Different genotypes determine different intermediate phenotypes (micronutrient levels), and the association effect between the genotype and the final disease (CP) can simulate the effect of exposure factors on the final disease. Therefore, we can use the MR method based on genome-wide association studies (GWAS) to further explore the association between micronutrients and CP.

2. Methods

2.1. Study design

This study employs the MR [23] and the two-sample MR, with the study design based on three key assumptions: (1) the genetic variant is directly and strongly associated with exposure (micronutrient levels); (2) the genetic variant is unrelated to potential confounding factors; (3) the genetic variant affects the outcome (CP) only through exposure and not other pathways. The conceptual MR framework is shown in Fig. 1.

2.2. GWAS data source for micronutrient

We obtained a catalog of micronutrients associated with CP (including colon adenomas and benign colon tumors), from published micronutrient observational studies and meta-analyses by searching Pubmed (https://www.ncbi.nlm.nih.gov/Pubmed, accessed February 15, 2024). These include 20 nutrients: calcium, selenium, magnesium, phosphorus, potassium, sodium, retinol, folate, vitamins B-1, B-2, B- 6, B-12, C, D, E, β-carotene, iron, zinc, copper and K [2–19,24–35]. The micronutrient inventory and the results of the clinical studies have been summarized and presented in the Supplementary file (Table S1).

The exclusion of potassium, sodium, and vitamins B-1, B-2 and K from our study was due to the fact that the above nutrients had not been studied in a GWAS study or that there were no reports of genome-wide significant results [20,36]. Whereas vitamin E and retinol were excluded because GWASs that circulate vitamin E and retinol concentrations adjust for BMI [37,38], and this may lead to collider bias in GWAS and MR estimates [39]. Therefore, 13 micronutrients were finally included in our study: calcium [40], selenium [41], magnesium [42], phosphorus [43], folate [44], vitamins B-6 [45], B-12 [44], C [46], D [47], beta-carotene [48], iron [49], zinc and copper [50]. GWAS study information for the 13 micronutrients is listed in Table 1, with more detailed information in Table S2.

2.3. GWAS data source for CP

GWAS summary statistical data for CP were provided by the MRC Integrative Epidemiology Unit (IEU) at the University of Bristol

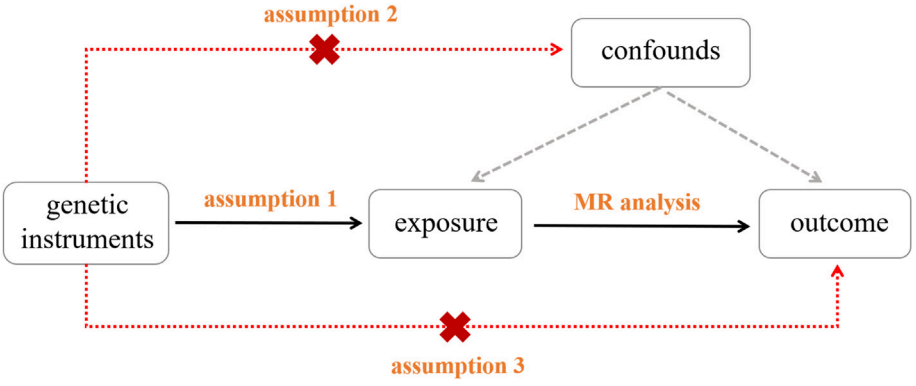

Fig. 1. The conceptual Mendelian randomization framework; MR: Mendelian randomization.

Table 1
Source of exposure genome-wide association study summary data.

Exposure	Sample size	Sample	European ancestry	nSNP	Variance explained	PMID
Ca	39400	serum	100%	5	1.30	24068962
Se	9639	toenail and serum	100%	7	6.90	25343990
Mg	23829	serum	100%	5	1.38	20700443
Folate	28913	serum	100%	2	0.53	23754956
β-carotene	3892	serum	100%	4	8.36	19185284
Fe	23986	serum	100%	3	3.04	25352340
Vit D	122123	serum	100%	6	2.13	29343764
Vit B6	4763	plasma	100%	2	3.07	19744961
Vit B12	25960	serum	100%	4	3.46	23754956
Vit C	52018	plasma	100%	11	1.79	33203707
Zn	2603	erythrocyte	100%	2	4.59	23720494
Cu	2603	erythrocyte	100%	2	4.60	23720494
Phosphorus	21733	serum	100%	4	1.20	20558539

Variance explained: Results are presented in %.
Abbreviations: Ca, Calcium; Se, Selenium; Mg, Magnesium; Fe, iron; Vit D, vitamin D; Vit B6, vitamin B6; Vit B12, vitamin B12; Vit C, vitamin C; Zn, zinc; Cu, Copper.

and were downloaded from Open GWAS (https://gwas.mrcieu.ac.uk/) on January 21, 2024. The precise definition was "Diagnosis-Major ICD10: K63.5 Colon polyps," and the GWAS included 4779 cases and 458,231 controls. All studies were approved by the respective institutional review boards, and all participants provided written informed consent.

2.4. Selection of SNPs

In line with the first assumption, we set $p < 5 \times 10^{-8}$ when selecting effective SNPs, and to avoid linkage disequilibrium, we set $r^2 < 0.001$ (Except for Selenium, for which an $r^2 < 0.3$ was set due to the limited availability of SNPs, consistent with previous studies [51–53]) and distance at 10,000 kb to obtain independent significant SNPs. Next, we only analyzed SNPs that were present in both the exposure and outcome datasets (SNPs rs11951068, rs6859667, rs9469578, rs1525892, rs117456053, rs2336573, rs34528912, and rs41281112 were removed as they were not present in the SNPs database of CRP). Additionally, considering the small number of SNPs in the micronutrients, we used a proxy SNP with high linkage disequilibrium ($r^2 > 0.8$) to replace the missing SNPs (https://snipa.org/snipa3/index.php?task=proxy_search). Information on all proxy SNPs is listed in the Supplemental Table S4. The variance explained by genetic instruments for each nutrient is listed in Table 1.

Palindromic SNPs and with intermediate allele frequencies were also removed from these datasets (calcium: rs1550532, rs780094; selenium: rs10944, rs234709). In addition, we calculated the total F statistic ($F = beta^2/se^2$) [54], requiring the F statistic to be greater than 10 to avoid the influence of weak instrumental bias on the MR analysis results. Subsequently, to fulfill the third core assumption (the genetic variant affects the outcome only through exposure), we extracted the secondary phenotypes of each SNP from PhenoScanner V2 [55] and the GWAS library. SNPs directly related to CP were also removed in each analysis to exclude horizontal pleiotropy. The SNPs for 13 micronutrients in the colorectal polyp database are listed in supplement files Table S3.

2.5. Data analysis

We utilized five different MR methods to evaluate the relationship between micronutrient concentrations and colorectal polyps: Inverse-variance weighted (IVW), Weighted Median (WM), Simple Median, Weighted Simple Median, and MR-Egger methods [56]. Each SNP's impact on CP was assessed using Wald ratios. We used the MR-PRESSO method to detect any outliers and obtain corrected results after their removal (rs13028225 was removed in vitamin C). MR-PRESSO and Steiger direction test for the causal association between circulating micronutrient and outcomes related to colorectal polyps. Additionally, we conducted Leave-one-out tests to evaluate the robustness and validity of the MR results. The heterogeneity test was performed with Cochran's Q test. If heterogeneity was present as identified by the Cochran Q test, we employed the random-effects model of the IVW method; otherwise, we used the fixed-effects model of the IVW method as our primary results [57]. We also used funnel plots to assess potential horizontal pleiotropy. Heterogeneity and pleiotropy analysis of causal relationships between circulating micronutrients and outcomes related to colorectal polyps are shown in Supplementary Table S6, and MR-PRESSO and Steiger Direction Tests are shown in Supplementary Table S7. We conducted power calculations using the online platform (https://shiny.cnsgenomics.com/mRnd/) [58]. Based on the sample sizes used in the meta-analysis, we computed the statistical power for each analysis under a type I error of 5%, and the results are summarized in Supplementary Table S8. Finally, we employed all these techniques to thoroughly investigate the causal relationship.

All statistical analyses were conducted based on R software version 4.3.0, using the "TwoSampleMR" and "MRPRESSO" packages. The threshold for statistical significance was set at $P = 0.05$, and P values less than 0.05 were considered statistically significant.

3. Results

We conducted an MR study to investigate the association between micronutrient levels and the occurrence of CP. Figure 2 shows that genetically predicted toenail and blood selenium concentrations, as well as serum β-carotene concentrations, influenced the incidence of CP ($P < 0.05$). The IVW results for toenail and blood selenium concentration and CP are [Odds Ratio (OR): 0.9986; 95% Confidence Interval (CI): (0.9976, 0.9995); $P = 0.0023$], and the WM method also indicates statistical significance and suggests a consistent direction. The IVW results for serum β-carotene concentration and CP are [Odds Ratio (OR): 0.9975; 95% Confidence Interval (CI): (0.9959,0.999); $P = 0.0012$], the WM method also indicates statistical significance and suggests a consistent direction. Result of other four methods were shown in Supplementary Table S5 (MR-egger, Weight median, Simple mode, Weighted mode). However, genetics predicted that the other 11 micronutrient (calcium, magnesium, phosphorus, folate, vitamins B-6, B-12, C, D, iron, zinc, and copper) concentrations had no effect on the development of CP (Fig. 2).

For the significance and sensitivity analysis, we used Cochran's Q test and the MR-Egger test, which suggests the absence of

Nutrients	OR	95%LCI	95%UCI
Ca	1.0010	0.9939	1.0082
Se	0.9986	0.9976	0.9995
Mg	1.0075	0.9757	1.0403
folate	0.9980	0.9939	1.0020
β-carotene	0.9975	0.9959	0.9990
Fe	1.0009	0.9991	1.0026
Vit D	0.9985	0.9962	1.0007
Vit B6	1.0015	0.9988	1.0042
Vit B12	1.0004	0.9969	1.0039
Vit C	1.0001	0.9960	1.0043
Zn	0.9989	0.9974	1.0003
Cu	0.9998	0.9984	1.0012
Phosphorus	1.0036	0.9950	1.0123

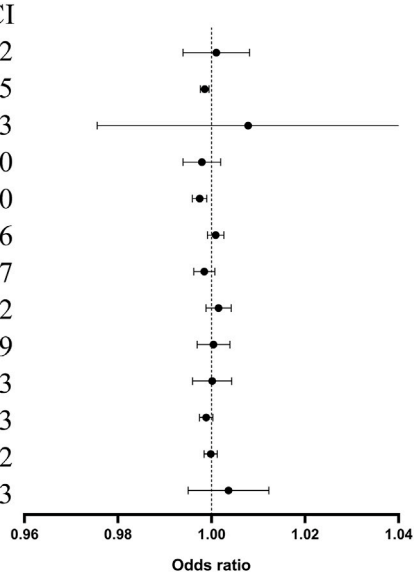

Fig. 2. The IVW results of MR analysis studying the effect of 13 micronutrients concentration on Polyp of colon outcomes; *The IVW results for selenium and β-carotene concentration effect on CP indicates statistical significance. Abbreviations: MR: Mendelian randomization, IVW, Inverse variance weighted; OR, odd ratio; Ca, Calcium; Se, Selenium; Mg, Magnesium; Fe, iron; Vit D, vitamin D; Vit B6, vitamin B6; Vit B12, vitamin B12; Vit C, vitamin C; Zn, zinc; Cu, Copper.

heterogeneity and pleiotropy. Combined with the Leave-one-out Plots and Funnel Plots illustrated in Figs. 3 and 4, we concluded that there is no horizontal pleiotropy. Finally, we conclude that there is an association between toenail and blood concentrations of selenium, as well as serum concentrations of β-carotene, and the development of CP.

4. Discussion

To our knowledge, this is the first study employing the MR method to investigate the causal relationship between the 13 micronutrients (calcium, selenium, magnesium, vitamin C, vitamin D, vitamin B6, vitamin B12, folic acid, β-carotene, zinc, copper, phosphorus and iron) levels and CP risk. We investigated whether the concentration of micronutrients is associated with the risk of CP by improving causal inference in observational epidemiology using MR. Our study found that higher toenail and blood selenium and serum β-carotene concentrations have a protective effect against CP. But no effect of the levels of the other 11 micronutrients on the risk of CP was found, which is consistent with some previous observational studies and the results of RCTs.

4.1. Selenium and colorectal tumors

Numerous clinical observational studies and animal experiments have found that the micronutrient selenium has a protective effect against the incidence and mortality of colorectal tumors [10,11,20,59]. One Iran study suggested that high selenium levels may reduce the risk of colon cancer in men [60]. A secondary analysis of an early RCT study suggested that selenium supplementation reduced the incidence of CRC by 61% [61]. However, some studies showed not. One large selenium and vitamin E cancer prevention trial did not observe any benefit of selenium on the incidence of colorectal tumors [62]. In a randomized controlled trial of selenium and celecoxib alone or in combination for the prevention of CRA, selenium did not show a preventive effect, only showing a slight benefit in patients with late-stage adenomas [63]. In addition, other MR studies have tested related selenium protein gene SNPs in CRA and CRC patients and found that some of them are significantly related to the risk of CRC, but it is controversial that these findings of this study did not retain significance after multiple test corrections [64]. Therefore, elevated selenium levels seem to exhibit a protective effect against the occurrence and malignant transformation of CP, yet no explicit clinical evidence suggests that higher selenium levels can inhibit the incidence and progression of these polyps. The role of selenium levels in the development of CP, whether protective or promotive, remains to be clarified due to the confusion and resulting reverse causality often introduced by traditional observational studies. In contrast, our study found that genetically predicted a protective effect against CRP associated with higher concentrations of selenium in both toenail and blood, supporting the findings of some previous observational studies and RCTs. Recent epidemiological and experimental investigations have linked the risk of cancer to deficiencies in the intake of trace elements [59], and selenium has been studied as a potential chemopreventive agent for colorectal tumors [65]. Hence, our results suggest that the supplementation of selenium, especially in populations with low baseline selenium levels, should be carefully considered for the prevention of CP and, subsequently, CRC.

The mechanism of the association between selenium and CP is also in line with our findings. As selenium is biologically inactive, its effects on the human body are mediated through selenoproteins. Past research has suggested that genetic variations and reduced expression of selenium proteins may promote the development of colorectal tumors [64,66,67]. Moreover, the abnormal expression of selenium proteins is closely related to the prognosis of CRC patient [68], and the sensitivity of chemotherapy and immunotherapy [69]. This might be related to selenoproteins' antioxidant [66,70,71], immune response-enhancing [70], and DNA-repairing effects [70,72]. Recent research suggested that oxidative imbalance increases the risk of CP and CRC. And selenoprotein, as an antioxidant, may have a positive effect on CP and CRC with sufficient intake [3,73]. Some research also demonstrated that selenoprotein protected against inflammation and tumor development by mitigating pro-inflammatory immune cell polarization [66,74]. Besides, selenoprotein prevented DNA mutations [70], controlled transcription factor activity, and cell proliferation, which led to decreased tumor cell growth [72].

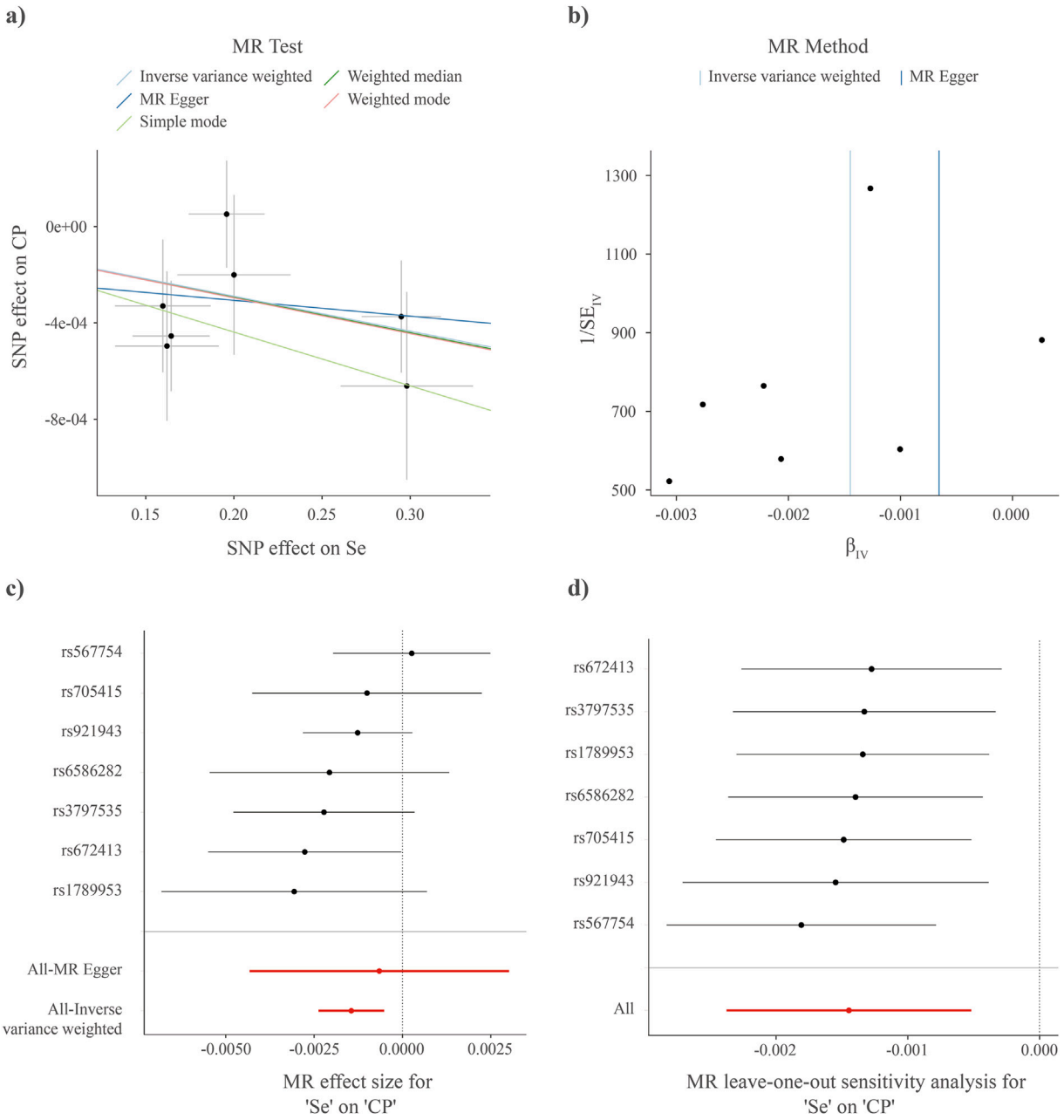

Fig. 3. Four plots of all selenium levels-related SNPs on the risk of CP conclude that there is no horizontal pleiotropy. a) scatter plot; b) funnel plots; c) forest plot; d) leave-one-out plot of the overall IVW estimate.

4.2. β-carotene and colorectal tumors

β-carotene, as one of phytochemicals, is natural compounds found in fruits, vegetables, and plants, which has received special attention for their potential to intervene in the formation and development of tumors. β-carotene has been shown to have a preventive effect on tumors, such as colorectal tumors, breast cancer, and prostate cancer, in several previous clinical studies [32,33,75–77]. For example, in a follow-up study of 29,363 men, β-carotene intake was found to be negatively associated with the risk of colorectal adenomas [76]. Another study of 845 colorectal cancer cases and 845 age- and sex-matched controls found a strong negative correlation between beta-carotene intake and colorectal cancer risk [77]. However, some clinical studies have also had mixed results, suggesting that β-carotene is ineffective in preventing colorectal tumors [78–80]. In addition in vitro experiments suggest that β-carotene can inhibit the growth of colon cancer cells by inducing apoptosis [81] and affect cell cycle arrest and apoptosis in human colon adenocarcinoma cell lines [82]. Side by side, this supports our findings.

The molecular mechanisms underlying the preventive effects of β-carotene on colorectal tumors are still unclear, and previous studies have suggested that it has antioxidant properties, inhibits malignant tumor growth and induces apoptosis [83]. For example, β-carotene has an inhibitory effect on COX-2, the causative factor of colorectal adenomatous polyps [84]; and the effect on The tumor microenvironment of adenoma formation may be due to the inhibitory effect on M2 macrophage polarization and fibroblast activation [85]. Recent studies suggest that the combination of β-carotene and Oxaliplatin upregulates the apoptosis- and stem cell-

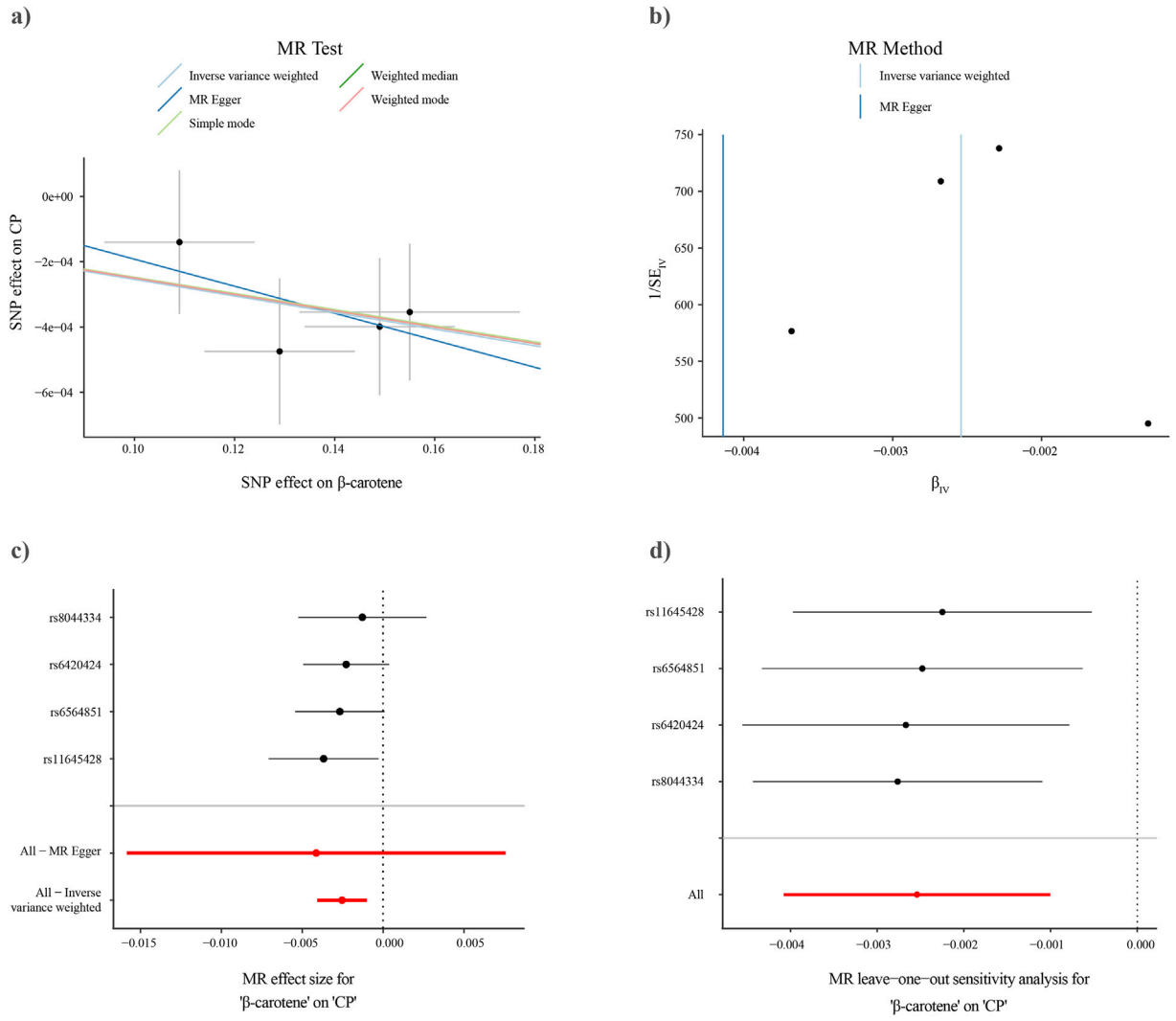

Fig. 4. Four plots of all β-carotene levels-related SNPs on the risk of CP conclude that there is no horizontal pleiotropy. a) scatter plot; b) funnel plots; c) forest plot; d) leave-one-out plot of the overall IVW estimate.

related JAK/STAT signaling pathway, inhibiting cancer stem cell marker expression and self-replicative capacity [86]. β-carotene is also able to upregulate the expression of 39-monooxygenase 1 (BCMO1), which inhibits the increase in invasiveness associated with colon cancer cells MMP7 and MMP28 associated with increased invasiveness of colon cancer cells [87]. Another 2023 study further demonstrated the ability of B-carotene supplementation to inhibit metabolic disturbances induced by cancer cachexia while restoring the status of the gut microbiota in the cancer cachexia state [88].

4.3. Strengths and weaknesses

The paramount advantage of the MR method is the use of genetic variations as instrumental variables. As genetic variations associated with different micronutrient levels form naturally during conception, individuals are exposed to these variations, circumventing reverse causality. Simultaneously, we minimized bias by excluding genetic variations associated with confounding factors and pleiotropy [21,22,51]. The reliability of MR results hinges can be compromised by population stratification and pleiotropy [89]. We limited our study to individuals of European descent to minimize population stratification [51]. For pleiotropy, we performed sensitivity analyses to assess and adjust it. In these sensitivity analyses, the associations of genetically predicted selenium and β-carotene concentrations with CP were robust. Notably, blood selenium concentration reflects about 17 weeks, while toenails reflect approximately 26–52 weeks of selenium exposure [41]. Therefore, to fully capture selenium levels, we opted for a GWAS study that includes both toenail and blood selenium concentrations. Lastly, our study incorporated large-scale cohort studies on selenium and β-carotene levels and CP among Europeans, making the inference credible.

But several limitations of this study should be noted. Firstly, our genetic analysis was based on individuals of European descent, so it is uncertain whether the results can be generalized to other racial groups. In particular, micronutrient levels in different ethnic groups may vary considerably depending on factors such as geographic distribution and dietary habits. Secondly, due to the limitation of the number of cases of CP in the GWAS data and the fact that some of the micronutrient instrumental variables showed varying degrees of low statistical power, there is still some possibility of bias, although the F-values of all instrumental variables were greater than 10, indicating a low probability of weak instrumental bias. At the same time, the SNPs for selenium that we used in our investigation were from only two loci (chr5 and chr21), with r^2 set to <0.3,

and there may be a potential effect from linkage disequilibrium. In order to improve statistical power and reduce the offset, future GWAS studies on larger scale micronutrient, CP-related traits are necessary. Third, some micronutrients, as well as subtypes of different CPs, could not be adequately studied because GWAS studies were not performed or significant genome-wide results were not reported. Larger clinical studies are needed in the future to further confirm these findings and explore the underlying mechanisms.

5. Conclusion

Our MR study explored the relationship between 13 trace nutrients in the human body (calcium, selenium, magnesium, phosphorus, folate, vitamins B-6, B-12, C, D, β-carotene, iron, zinc, and copper) and the genetic susceptibility to CP, proposing a causal link between selenium and β-carotene levels and the incidence of CP. We observed a correlation between higher genetically-predicted concentrations of selenium in toenails and blood or β-carotene in serum and a lower incidence rate of CP, suggesting that the supplementation of selenium and β-carotene can take precautions against CP and CRC. Nonetheless, further research and clinical trials are needed to investigate the underlying mechanisms linking selenium and β-carotene with CP, as well as the other 11 trace nutrients.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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Data availability statement

Original contributions from this study are included in the article/supplementary material; for further inquiries, please contact the corresponding author.

Conflicts 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.

Acknowledgements

SL raised the idea for the study, and contributed to the study design and the data analysis. SL and YD wrote the manuscript. JH and YH contributed to conceptualization and investigation. WY contributed to the funding, writing, reviewing, and editing. XS and RX handled supervision in our study. All authors contributed to the article and approved the submitted version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.04.019.

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