Dried fruit intake can lower the risk of ulcerative colitis: evidence from a Mendelian randomization study

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ABSTRACT

Background and Objectives: This study aims to examine the causal relationship between dietary factors and ulcerative colitis (UC). **Methods and Study Design:** The analysis utilized data from genome-wide association studies (GWAS). Dried fruit, vegetables, processed meat, fresh fruit, and cereal intake were examined as exposure factors. UC was considered the outcome. Two-sample Mendelian randomization (TSMR) analysis was performed using methods. Heterogeneity and horizontal pleiotropy assessments were conducted to ensure the robustness of our findings. Additionally, we applied False Discovery Rate (FDR) corrections for multiple tests. **Results:** The analysis revealed a significant inverse causal relationship between dried fruit intake and UC risk (odds ratio [OR]: 0.488, 95% confidence interval [CI]: 0.261 to 0.915, $p = 0.025$). No significant association was observed between vegetable intake (OR: 1.742, 95% CI: 0.561 to 5.415, $p = 0.337$), processed meat intake (OR: 1.136, 95% CI: 0.552 to 2.339, $p = 0.729$), fresh fruit intake (OR: 0.977, 95% CI: 0.465 to 2.054, $p = 0.952$), cereal intake (OR: 1.195, 95% CI: 0.669 to 2.134, $p = 0.547$). The low heterogeneity observed across analyses and the confirmation of stability through leave-one-out analysis reinforce the reliability of these results. Moreover, after adjusting for multiple tests, none of the dietary factors reached a p-value below the conventional significance threshold of 0.05. **Conclusions:** This study provides evidence of a potential association between dried fruit intake and a reduced risk of UC. Further MR studies incorporating larger GWAS datasets are needed to confirm these findings.

Key Words: Ulcerative colitis, dietary factors, genome-wide association studies, Mendelian randomization, Inverse-Variance Weighted

INTRODUCTION

Ulcerative colitis (UC) is an idiopathic and chronic inflammatory disease of the colonic mucosa characterized by persistent inflammation, continuous rectal lesions, and varying degrees of colon involvement.[1] Over the past two decades, UC has emerged as a global health challenge with evolving epidemiological trends.[2, 3] The global prevalence of UC was estimated to reach 5 million cases in 2023.[4] UC is characterized by recurrent episodes of onset and remission, which profoundly impact patients' quality of life and health while also contributing to escalating healthcare costs associated with disease management.[5, 6] Epidemiological surveys estimate that Europe spends approximately 12.5 billion to 29.1

billion euros annually on UC-related expenses. At the same time, the United States allocates around 8.1 billion to 14.9 billion dollars per year for this purpose.[5]

Numerous retrospective studies have consistently demonstrated the association between UC, genetic predisposition and environmental factors.[7] Potential environmental factors that influence the development or progression of UC include early life events, such as breastfeeding, and daily behavioural habits like smoking, exercise, and dietary patterns.[7] Moreover, extensive research has revealed the significant role of diet in shaping the human intestinal microbiota.[8, 9] For instance, studies have shown that nuts benefit the gut microbiota of healthy adults.[10] Recent investigations have highlighted Westernized dietary changes in developing countries' impact on the risk of UC.[5] However, existing retrospective studies primarily focus on alterations in intestinal bacterial composition and specific food intake, lacking comprehensive clinical investigations into how the overall dietary structure influences the occurrence of UC.[9]

Mendelian randomization (MR) is a robust and flexible research method in genetic epidemiology that utilizes Mendel's law and single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to infer potential causal associations between exposure factors and outcomes.[11] It is increasingly favoured over conventional observational studies due to its ability to mitigate biases from confounding factors and measurement errors, enabling the investigation of potential causal relationships between exposures and outcomes.[12] By leveraging the random allocation of genes at conception, genetic variants precede disease development and remain unaffected by external environmental factors or social behaviour. MR studies establish a reliable temporal sequence for inferring causal associations, thereby minimizing confounding bias and reverse causality.[13-15] The two-sample MR approach, which utilizes separate exposure and outcome variables, enhances statistical power and analysis reliability.[16] For example, Li et al. conducted a bidirectional two-sample Mendelian randomization study to explore the causal relationship between inflammatory bowel disease and psoriasis.[17] Another study conducted by Freuer employed a Mendelian randomization approach to investigate the link between inflammatory bowel disease and Parkinson's disease.[18]

This research will provide a deeper understanding of the impact of dietary factors on the risk of UC and examine the causal relationship between dietary factors and UC, enabling clinicians to develop personalized prevention and treatment strategies. Consequently, it will contribute to reducing the occurrence and burden of UC while enhancing individuals' physical well-being and overall quality of life.

MATERIALS AND METHODS

Study design

The schematic representations of our study are depicted in Figure 1, illustrating the basic schema of MR analysis and the study design employed in our MR analysis. As our study utilized publicly available data that had already been published, no additional ethical approval was required.

Reporting standards

This study was reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[19]

Participants and data source

This study utilized the genome-wide association study (GWAS) summary data from the IEU GWAS database (https://gwas.mrcieu.ac.uk/) and selected relevant SNPs in the European population as IVs. IEU GWAS database is an open source, open database with strict quality control.[20] This study examined the associations between dried fruit intake (GWAS ID: ukb-b-16576, Sample size: 421,764), vegetable intake (GWAS ID: ukb-b-8089, Sample size: 448,651), processed meat intake (GWAS ID: ukb-b-6324, Sample size: 461,981), fresh fruit intake (GWAS ID: ukb-b-3881, Sample size: 446,462), cereal intake (GWAS ID: ukb-b-15926, Sample size: 441,640) and the risk of UC (GWAS ID: finn-b-K11_ULCER, Sample size: case: 4,320, control: 210,300). The dietary factors data in our study were derived from the UK Biobank, a large-scale biomedical database and research resource containing in-depth genetic and health information from half a million UK participants. Each of these dietary factors was assessed using self-reported frequency and portion size data from food frequency questionnaires provided by UK Biobank participants.[21] The data of UC were sourced from a FinnGen database. The FinnGen database aims to explore the relationship between genomic information and health traits in populations. The goal of the project is to provide a deeper understanding of disease research, drug development and personalised medicine by collecting genetic, clinical and health data.[22] Table 1 presents the relevant information on the five dietary factors and the outcome.

Instrumental variable selection

This study ensured that all selected SNPs met three key assumptions for IVs: (1) a high correlation with the exposure of interest, (2) independence from confounding factors that may

influence the outcome, and (3) a causal effect on the outcome only through their association with the exposure. We chose IVs that met these criteria using a genetic distance threshold of 10,000 kb, a linkage disequilibrium threshold of 0.001 (r^2), and a *p*-value threshold 5×10-8. We excluded SNPs influenced by weak IVs with an F-statistic less than 10 using an F-test.23, 24 To harmonize the exposure and outcome data and ensure the reliability of the MR analysis results, we used the harmonize_data() function in the TwoSampleMR package and the run_mr_presso() position in the MR-PRESSO method to identify and remove outliers.[25, 26]

Statistical analysis

We evaluated heterogeneity using the mr_heterogeneity() function and performed heterogeneity tests using Cochran's Q for the inverse-variance weighted (IVW) method. A *p*-value greater than 0.05 indicated no significant heterogeneity among the IVs. We primarily used the IVW method for our MR analysis, which does not consider the intercept term during regression and uses the inverse of the outcome variance as weights for fitting. Under the assumption that all selected genetic variants are valid IVs and have causal solid effects, the IVW method is a valid and effective analysis approach.[27] We also used the MR-Egger regression, the weighted median, simple mode, and weighted mode method to supplement the conclusions.[28] A *p*-value less than 0.05 was used as the threshold for statistical significance, and the odds ratio (OR) was used to evaluate the potential causal relationship between dietary factors and UC. To assess the presence of horizontal pleiotropy, we also conducted a pleiotropy test using the mr_pleiotropy_test() method. The intercept value in MR-Egger was used to evaluate pleiotropy. If the intercept term was close to 0, then the MR-Egger regression model was very close to IVW. The lower the possibility of horizontal pleiotropy, the less significant pleiotropy was, indicating that SNP was only associated with exposure, not with other confounding variables.[28] In addition, we performed sensitivity analyses by sequentially leave-one-out SNPs to evaluate their impact on the MR estimates.[29] To mitigate the risk of false positives arising from multiple tests, we applied a False Discovery Rate (FDR) correction. We determined statistical significance based on a threshold of *p*-FDR < 0.05. If the p-value was less than 0.05 and the *p*-FDR was greater than 0.05, it was considered to have potential significance between exposure and outcome.[30, 31] Statistical analyses were performed using R version 4.3.0 and the TwoSample MR and MR-PRESSO packages.

RESULTS

SNPs information for IVs

For the causal association analysis between various dietary factors and UC, we excluded SNPs with a linkage disequilibrium parameter (r2) greater than 0.01 and SNPs not present in the outcome GWAS. We chose 41 SNPs for dried fruit intake, 17 for vegetable intake, 23 for processed meat intake, 53 for fresh fruit intake, and 43 for cereal intake as the final IVs for two-sample MR analysis. All F-statistics exceeded 10.

MR analysis

According to the findings presented in Table 2, the analysis revealed a significant inverse causal relationship between dried fruit intake and UC risk [OR: 0.488, 95% confidence interval (CI): 0.261 to 0.915, $p = 0.025$)], However, no significant associations were observed between vegetable intake (OR: 1.742, 95% CI: 0.561 to 5.415, $p = 0.337$), processed meat intake (OR: 1.136, 95% CI: 0.552 to 2.339, $p = 0.729$), fresh fruit intake (OR: 0.977, 95% CI: 0.465 to 2.054, $p = 0.952$), cereal intake (OR: 1.195, 95% CI: 0.669 to 2.134, $p = 0.547$), and the risk of UC.

In summary, the analysis emphasizes a significant inverse causal relationship between dried fruit intake and UC risk, suggesting that consuming dried fruit may be associated with a decreased risk of UC. However, no significant associations were observed between the other dietary variables (vegetable intake, processed meat intake, fresh fruit intake, and cereal intake) and UC risk.

In MR studies, multivariable analysis seeks to incorporate exposures that have positive associations into a multivariate model to isolate their independent effects on the outcome.[32] Nonetheless, the exclusive positive association detected between dried fruit consumption and UC risk precluded further multivariable analysis, as no other exposures with positive associations were present for inclusion.

Sensitivity analysis

Table 3 displays the sensitivity analysis results, encompassing both heterogeneity and horizontal pleiotropy assessments. All p-values were above 0.05, signifying low heterogeneity across the SNPs. Similarly, horizontal pleiotropy analysis showed *p*-values exceeding 0.05, indicating a consistent association between exposures and outcomes. The funnel plot demonstrates symmetry among all assessed SNPs, suggesting a uniform distribution of causal association points and minimal variability among IVs. This uniformity implies a reduced

likelihood of potential bias influencing the causal inference (Figure 2). The leave-one-out sensitivity analysis, which iteratively excludes individual SNPs, did not reveal any SNPs with significant effects on the causal estimate (Figure 3).

Multiple tests

After adjusting for multiple tests using the FDR method, it is evident from Table 4 that none of the exposure-outcome pairs exhibit *p*-values below the 0.05 threshold, indicating a lack of statistically significant associations between the variables studied. Notwithstanding, instances where the *p*-value is less than 0.05, but the corresponding *p*-FDR exceeds 0.05, may imply a potential association between dried fruit intake and an increased risk of UC, warranting further investigation.

DISCUSSION

This study represents the first use of MR to analyze the association between various dietary patterns and the risk of UC. MR is an advanced methodology that tackles issues related to unobserved confounding effects and reverse causation.[33] The process of MR analysis comprises three key stages. Firstly, it is imperative to establish a robust association between the genetic instrument and the exposure variable.[34] To accomplish this, we carefully selected SNPs that exhibited a significant association ($p < 5 \times 10^{-8}$) with the respective exposures. Secondly, it is necessary to demonstrate the genuine impact of the genetic instrument on the exposure variable. To achieve this, we conducted an MR-Egger intercept test, which allowed us to assess and confirm our study's absence of horizontal pleiotropy. This step is crucial to ensure that the influence of the genetic instrument on the exposure remains independent of other factors. Lastly, it is crucial to ascertain that the genetic instrument is not affected by confounding factors that may influence the outcome variable. We thoroughly evaluated and minimized the influence of confounding factors on the genetic instrument to ensure the validity of our findings.

We examined the associations between five common dietary patterns (dried fruit intake, vegetable intake, processed meat intake, fresh fruit intake, and cereal intake) and the risk of UC. The results showed that individuals who consumed dried fruit had a significantly lower risk of UC than non-consumers. This association was observed using the Inverse-variance weighted method. The analysis of our study revealed low heterogeneity.

Dietary pattern analysis has emerged as an alternative approach to studying the relationship between nutrition and disease.[10] Dried fruits are commonly rich in dietary fiber, potassium,35

protein, plant sterols, antioxidants, and various minerals and vitamins. They also have a favorable fatty acid composition.[36] In a study by Masako Nakanishi et al., it was found that walnuts are abundant in alpha-linolenic acid. This fatty acid that can be converted into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Both EPA and DHA are known for their anti-inflammatory properties.[37] Extensive research on animals and various cell culture systems has revealed various of health benefits of walnuts. These benefits are likely mediated, at least partially, through their effects on immune-related and inflammatory cells. Koh et al. conducted a study investigating the effects of a walnut phenolic extract on acute and chronic colitis models in mice.38 The extract demonstrated inhibition of NF-κB signaling, directly decreasing in the expression of pro-inflammatory mediators.[39]

According to a study by Yunxia Wang, Grape Seed Polyphenols found in raisins have been proven to alleviate various symptoms associated with UC.[40] These symptoms include weight loss, diarrhea, bloody stool, mucosal damage, and inflammatory infiltration. Additionally, Grape Seed Polyphenols were found to downregulate the mRNA expression of inflammatory cytokines such as IL-6, IL-1β, and TNF-α. Furthermore, they inhibited the phosphorylation of STAT3, thereby improving intestinal epithelial cell apoptosis. These findings suggest that Grape Seed Polyphenols protect against UC induced by dextran sulfate sodium. This protective effect is likely achieved through the suppression of inflammation and apoptosis.

Recent research has identified proanthocyanidins derived from Sicilian pistachios as the crucial bioactive compound that modulates the inflammatory response in human intestinal epithelial cells. This mechanism involves inhibiting the activation of nuclear factor kappa B (NF-κB).[41] Additionally, pistachios exhibited noteworthy anti-inflammatory effects in a rat model of UC inflammation.[42] Furthermore, another study conducted in the same year demonstrated that regular consumption of pistachios improved inflammation in obese mice, possibly attributed to positive alterations in the gut microbiota composition.[43]

Our study has confirmed the potential association of dried fruit intake in reducing the risk of UC, and the results of sensitivity analysis support the stability of our research findings. However, it is crucial to acknowledge certain limitations. While the results suggest a potential association between dried fruit intake and a reduced risk of UC, the specific types of dried fruits responsible for this benefit are not specified. Due to limited data resources, our results predominantly rely on European populations and may not generalize to other ethnic groups. Furthermore, our conclusions may require additional validation using larger sample sizes. Moreover, the results of multiple tests suggest a potential link between dried fruit intake and

an increased risk of UC; however, the results lack statistical strength, thus further research is required to determine their validity.

To address these limitations, future studies should conduct individual investigations on specific types of dried fruits, include diverse ethnic populations, increase sample sizes, and explore underlying biological mechanisms through complementary studies, such as large-scale cohort investigations. By incorporating these approaches into future research, we can enhance our understanding of the impact of different dietary structures on UC.

Conclusion

This study provides evidence supporting a potential association between the dried fruit intake and a reduced risk of UC. Regular consumption of dried fruits may serve as a preventive measure against UC. However, further MR studies utilizing more extensive genome-wide association studies datasets are required to validate these findings and investigate the protective effects of specific types of dried fruits.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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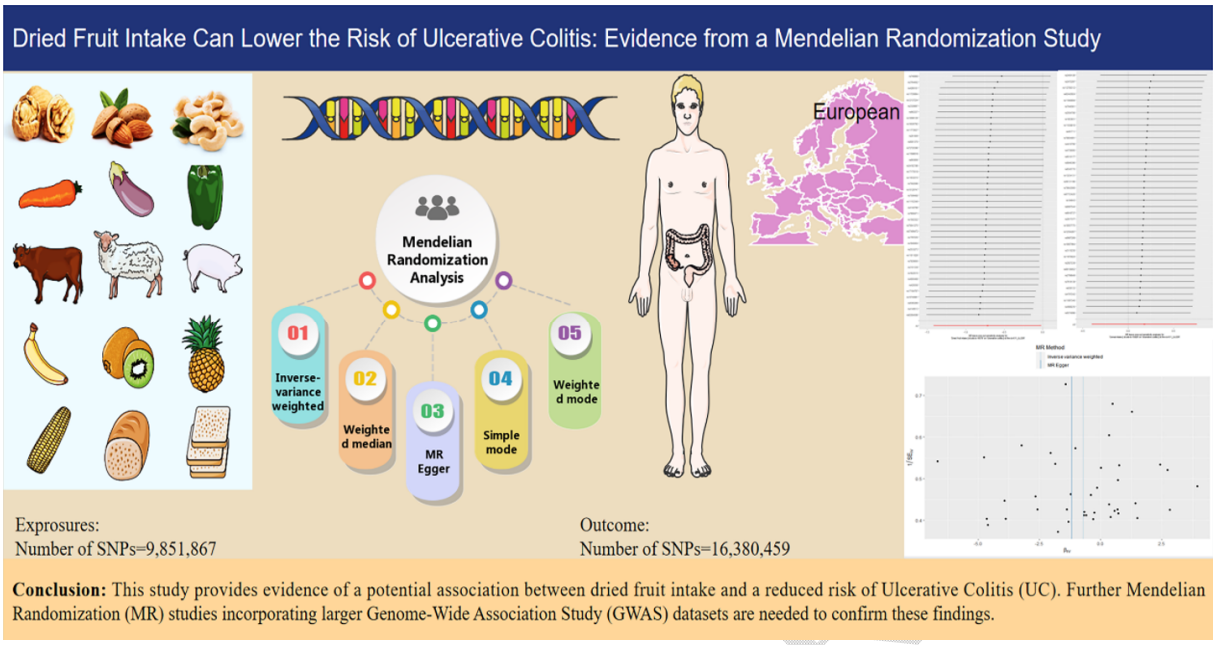

Graphical abstract

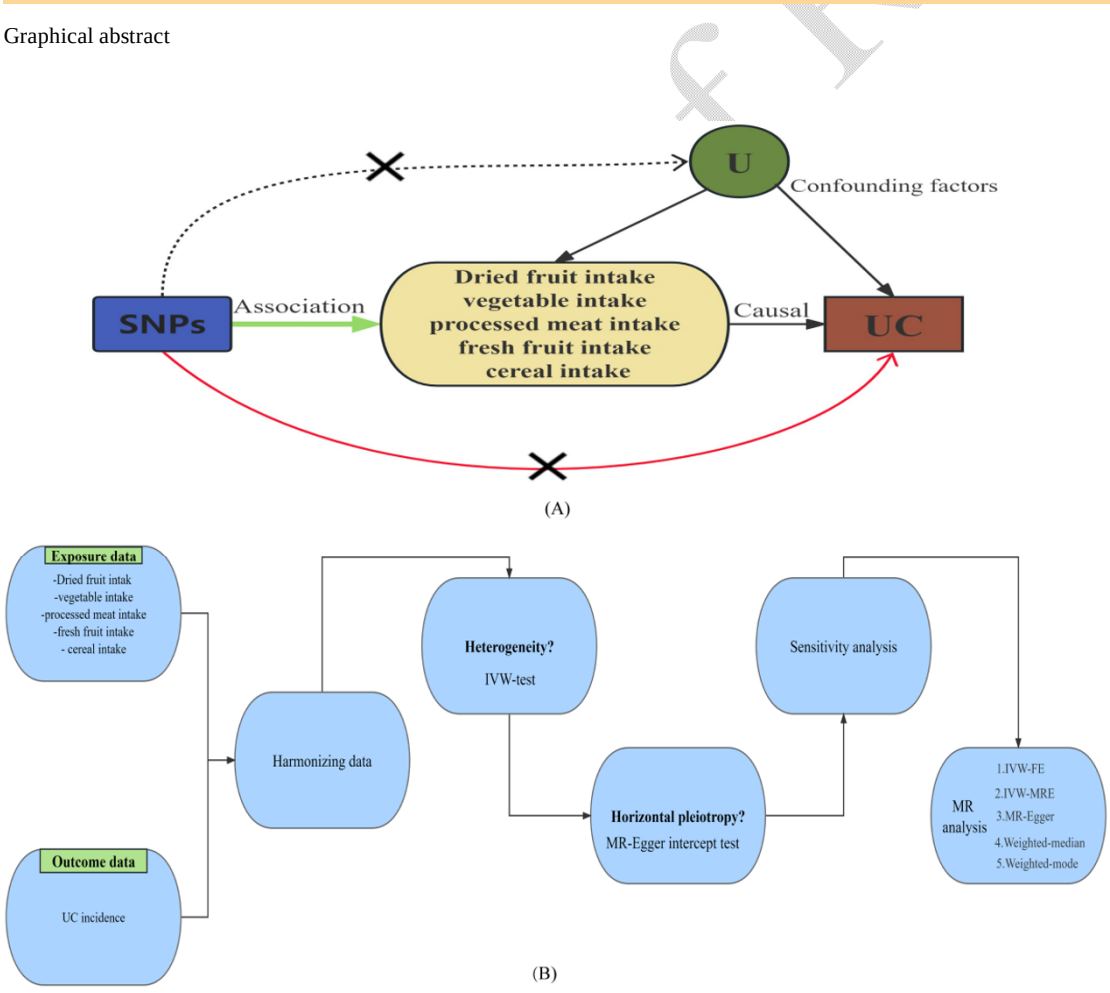

Figure 1. Schematic representations of the study. (A) Basic schema of Mendelian randomization (MR) analysis. (B) Study design of MR analysis. IVW-FE: Fixed-effect inverse variance weighted model. IVW-MRE: Multiplicative random-effect inverse variance weighted model.

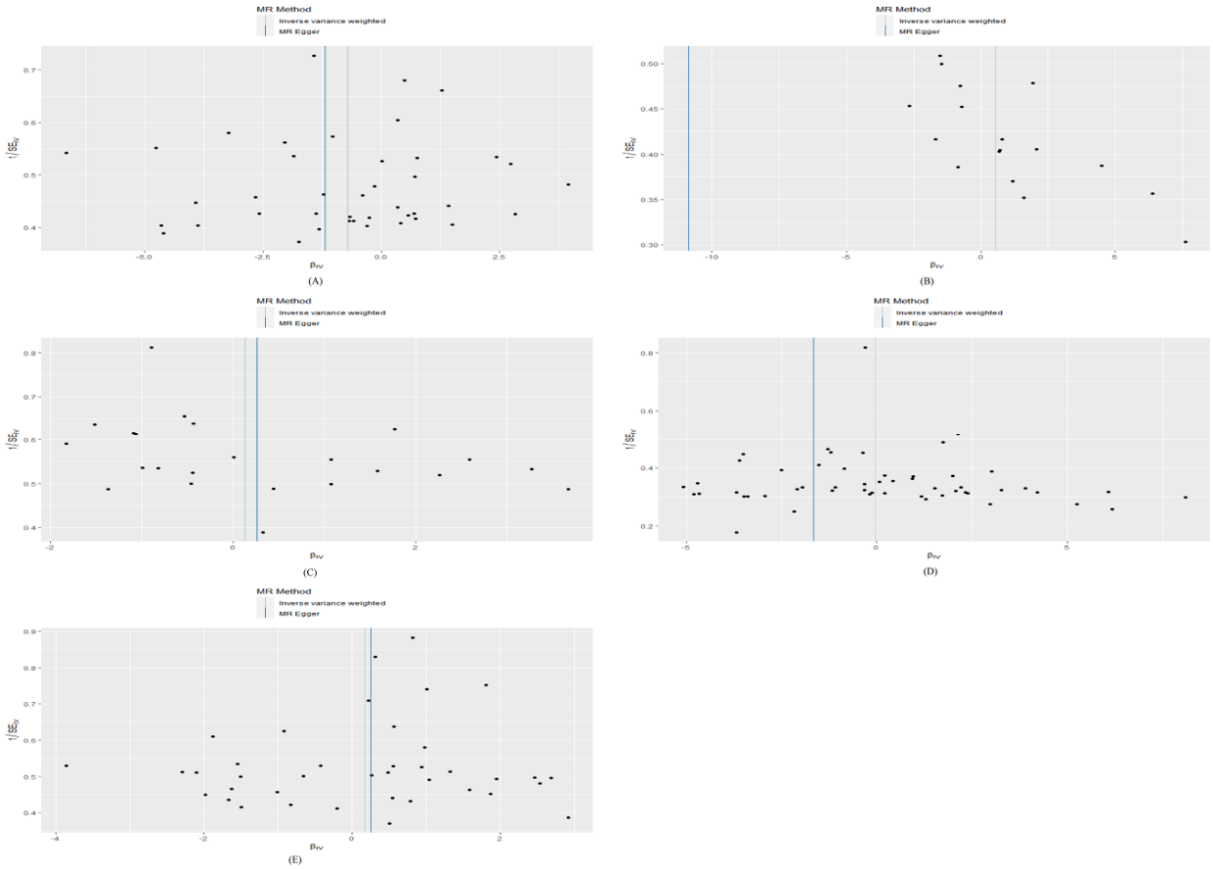

Figure 2. Funnel plots of two-sample Mendelian randomization results. (A) Funnel plot of dried fruit intake and ulcerative colitis. (B) Funnel plot of vegetable intake and ulcerative colitis. (C) Funnel plot of processed meat intake and ulcerative colitis. (D) Funnel plot of fresh fruit intake and ulcerative colitis. (E) Funnel plot of cereal intake and ulcerative colitis

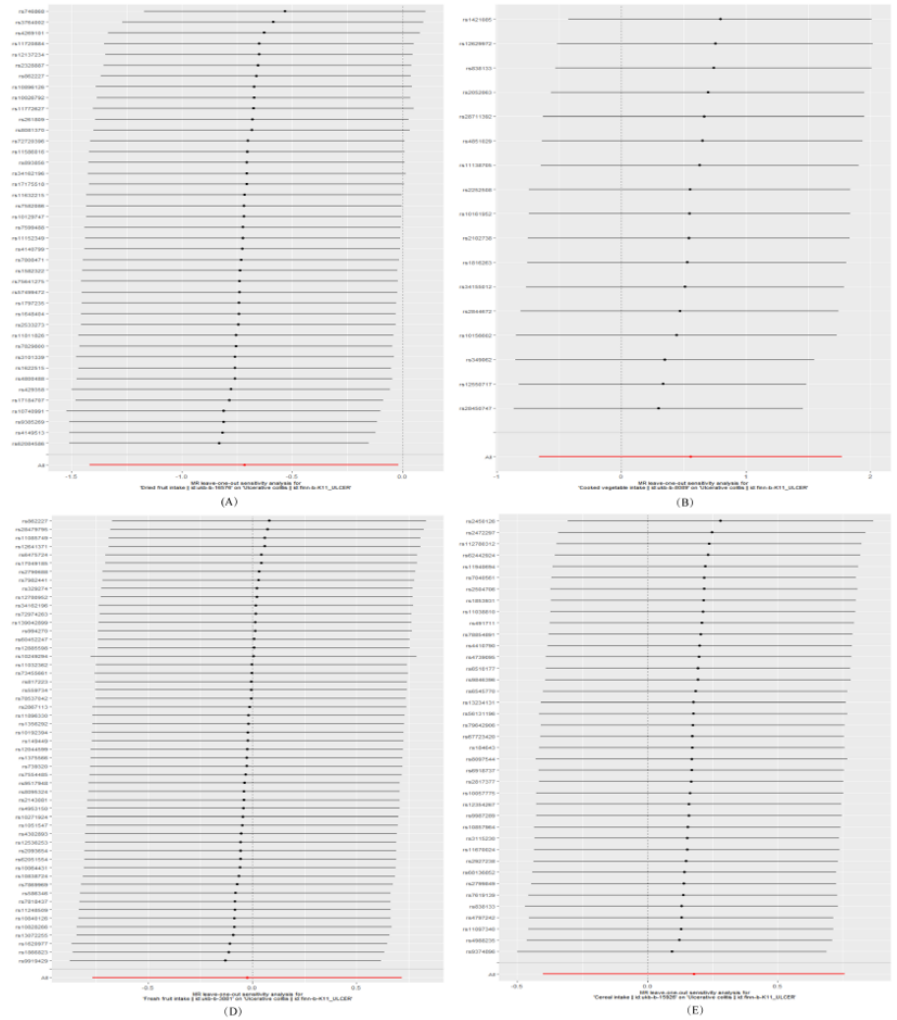

Figure 3. Forest plots depicting the effect of dietary factors on ulcerative colitis. (A) Forest plot of dried fruit intake and ulcerative colitis. (B) Forest plot of vegetable intake and ulcerative colitis. (C) Forest plot of processed meat intake and ulcerative colitis. (D) Forest plot of fresh fruit intake and ulcerative colitis. (E) Forest plot of cereal intake and ulcerative colitis

Table 1. Basic information on exposures and outcomes from the GWAS database[†]

Name	Number of SNPs	Sample size	Population
Dried fruit intake	9,851,867	421,764	European
Vegetable intake	9,851,867	448,651	European
Processed meat intake	9,851,867	461,981	European
Fresh fruit intake	9,851,867	446,462	European
Cereal intake	9,851,867	441,640	European
Ulcerative colitis	16,380,459	214,620	European

[†]Data from GWAS database, access can be achieved by linking to https://gwas.mrcieu.ac.uk/.

Table 2. Results of two-sample mendelian randomization analysis[†]

Exposure and Methods	b	SE	*p*	OR	95%CI
Dried fruit intake					
Inverse-variance weighted	-0.717	0.320	0.025	0.488	0.261, 0.915
Weighted median	-0.311	0.467	0.505	0.733	0.294, 1.829
MR Egger	-1.182	1.621	0.470	0.307	0.013, 7.353
Simple mode	0.114	1.000	0.910	1.121	0.158, 7.954
Weighted mode	0.260	0.943	0.785	1.296	0.204, 8.232
Vegetable intake					
Inverse-variance weighted	0.555	0.579	0.337	1.742	0.561, 5.415
Weighted median	0.122	0.809	0.881	1.129	0.231, 5.512
MR Egger	-10.867	6.361	0.108	<0.001	0.000, 4.953
Simple mode	0.371	1.330	0.784	1.449	0.107, 19.651
Weighted mode	-0.890	1.223	0.477	0.411	0.037, 4.515
Processed meat intake					
Inverse-variance weighted	0.128	0.368	0.729	1.136	0.552, 2.339
Weighted median	-0.454	0.503	0.366	0.635	0.237, 1.701
MR Egger	0.264	1.848	0.888	1.303	0.035, 48.727
Simple mode	-0.770	0.927	0.425	0.463	0.072, 2.964
Weighted mode	-0.825	0.868	0.349	0.438	0.081, 2.375
Fresh fruit intake					
Inverse-variance weighted	-0.023	0.379	0.952	0.977	0.465, 2.054
Weighted median	-0.268	0.571	0.639	0.765	0.250, 2.345
MR Egger	-1.661	1.295	0.206	0.190	0.015, 2.406
Simple mode	0.204	1.259	0.872	1.227	0.104, 14.464
Weighted mode	-0.198	0.981	0.841	0.820	0.120, 5.612
Cereal intake					
Inverse-variance weighted	0.178	0.296	0.547	1.195	0.669, 2.134
Weighted median	0.503	0.415	0.226	1.654	0.733, 3.732
MR Egger	0.254	1.274	0.843	1.289	0.106, 15.637
Simple mode	0.697	0.864	0.425	2.007	0.369, 10.906
Weighted mode	0.697	0.699	0.325	2.007	0.510, 7.905

[†]Results were obtained through the R studio TwoSampleMR package

Table 3. Results of sensitivity analyses

Exposure	Heterogeneity		horizontal pleiotropy	
	Q†	*p*†	Egger intercept	*p*
Dried fruit intake	49.700	0.140	0.006	0.770
Vegetable intake	18.312	0.306	0.118	0.091
Processed meat intake	16.950	0.766	-0.002	0.941
Fresh fruit intake	49.505	0.573	0.016	0.192
Cereal intake	25.028	0.948	-0.001	0.952

†Results were obtained through the Inverse variance weighted method

Table 4. Multiple test results

Exposure	*p*†	p-FDR†
Dried fruit intake	0.025	0.126
Vegetable intake	0.337	0.843
Processed meat intake	0.729	0.911
Fresh fruit intake	0.952	0.952
Cereal intake	0.547	0.684

†Results were obtained through the Inverse variance weighted method