Original Article

Association between fruit intake and non-small cell lung cancer: a Mendelian randomization study

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Background: Several studies have explored the potential relationship between fruit consumption and non-small cell lung cancer (NSCLC). However, the impact of dried fruit on NSCLC risk remains unclear. Additionally, the presence of confounding variables in these observational investigations could not be avoided. Therefore, the aim of this article was to explore the potential relationship between fruits intake and NSCLC.

Methods: We extracted fruit intake data from the UK Biobank and utilized a genome-wide association study (GWAS) encompassing 218,792 individuals for NSCLC data. We employed a two-sample Mendelian randomization (MR) analysis to investigate the potential causal associations between fruit intake and the risk of NSCLC. The major method of analysis was the inverse variance weighted (IVW). Furthermore, we conducted sensitivity analyses to corroborate the robustness of our findings.

Results: The result of our study showed convincing evidence suggesting that dried fruit intake is effective in reducing the risk of NSCLC. Specifically, the odds ratios (ORs) for NSCLC exhibited a noteworthy reduction at 0.32 [95% confidence interval (CI): 0.15, 0.67; P=0.003] with respect to dried fruit intake.

Conclusions: Our study underscores a significant correlation between dried fruit consumption and reduced NSCLC risk. In contrast, the association with fresh fruit intake did not reach statistical significance. To substantiate and validate these findings, further prospective randomized controlled trials (RCTs) are warranted in the future.

Keywords: Non-small cell lung cancer (NSCLC); Mendelian randomization (MR); fruit intake

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Introduction

Lung cancer is known as one of the important reasons of cancer death. According to the latest cancer statistics in the United State, the incidence of lung cancer among adults under the age of 50 years old is increasing by 2% per year (1). That means that lung cancer is occurring at an increasingly younger age. This concerning trend accentuates the urgency of early preventative measures, including lifestyle modifications and dietary interventions, particularly targeting the younger population to mitigate the susceptibility to lung cancer.

Some studies have shed light on the potential anticancer properties of certain constituents found in fruits, which have spurred interest in their role in cancer risk reduction (2,3). Notably, a diet rich in fruits has been associated with lung cancer prevention owing to the abundance of antioxidants present in these natural sources. These antioxidants, encompassing compounds like retinol, ellagic acid, and carotenoids, exhibit protective attributes against the development of lung cancer (4). Furthermore, the bioactive compounds present in fruits have demonstrated significant regulatory capabilities over intracellular enzyme reactions, thus influencing the survival pathways of cancer cells (5). Empirical evidence from foundational studies and case-control trials has also underscored the potential of heightened fruit consumption in diminishing the risk of lung cancer (5,6).

Although several studies have reported a correlation between fruit consumption and the incidence of lung cancer, it is essential to acknowledge the inherent methodological limitations. These limitations include confounding factors that may distort the association between fruit intake and disease development, as well as the potential for reverse causation (7). On the other side, these investigations did not provide any evidence suggesting a divergence in the effects of consuming dried fruit versus fresh fruit. These limitations highlight the need for alternative approaches, such as the utilization of genetic methodologies, which furnish a more robust avenue for causal analysis. In this regard, the utilization of Mendelian randomization (MR) emerges as a promising solution.

Therefore, we opted to employ the MR approach, which harnesses genetic variants as instrumental variables (IVs) for the exposure variable—in this case, dried fruit consumption—to establish causal inferences (8). Given the absence of randomized controlled trials (RCTs) or prospective studies, the MR framework assumes a pivotal role in facilitating causal inference. This innovative strategy capitalizes on the random assortment of genetic variants during meiosis, thereby mimicking the core principles of an RCT (9). Through this exploitation of inherent genetic randomness, the MR design provides valuable insights into causal relationships.

In our study, we performed MR analyses to analyze the causal association between fruit intake and the risk of non-small cell lung cancer (NSCLC). In addition, we categorized fruits and analyzed the effect of fresh and dried fruit intake on NSCLC risk separately. By employing this approach, we were able to evaluate the genetic evidence supporting a decrease in NSCLC risk with higher daily fruit intake. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-276/rc).

Highlight box

Key findings

- Our Mendelian randomization (MR) study shows a significant protective effect of dried fruit intake against non-small cell lung cancer, with an odds ratio of 0.32 (P=0.003). In contrast, fresh fruit intake did not demonstrate a statistically significant association.

What is known and what is new?

- Previous studies have established a connection between fruit consumption and various health outcomes, indicating potential benefits in reducing cancer risks.
- This manuscript employs a MR approach, providing genetic-level evidence that highlights a significant association between dried fruit consumption and reduced lung cancer risk, while fresh fruit intake showed no significant impact. Clinically, these findings suggest that promoting dried fruit consumption may be an effective strategy for lung cancer prevention, warranting further exploration in dietary guidelines.

What is the implication, and what should change now?

- The findings suggest that incorporating dried fruits into dietary recommendations may have significant implications for lung cancer prevention. Future research should further investigate the mechanisms through which dried fruits confer these benefits and consider expanding studies to diverse populations.

Methods

Study overview

MR studies rely on the following three fundamental assumptions: (I) the genetic variants utilized as IVs should exhibit a robust association with fruit intake; (II) the genetic variants employed as IVs should not demonstrate any

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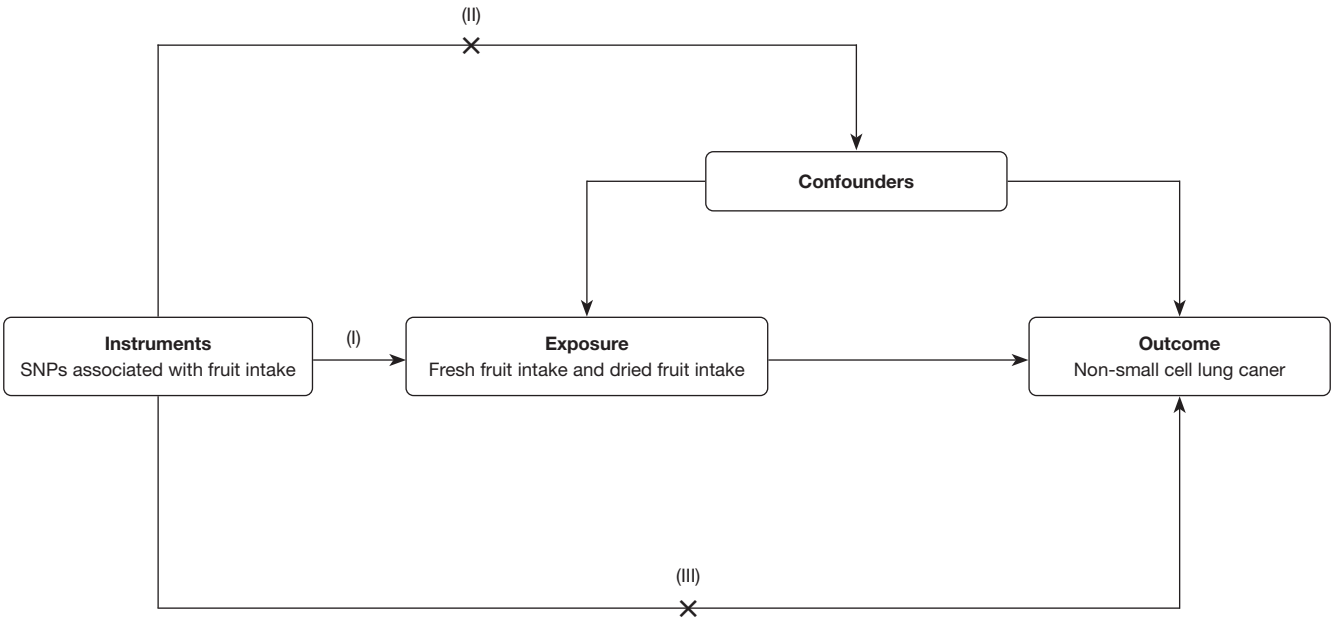

Figure 1 Model for a Mendelian randomization study. (I) The genetic variants utilized as instrumental variables should exhibit a robust association with fruit intake, (II) the genetic variants employed as instrumental variables should not demonstrate any correlation with confounding factors that are associated with the link between fruit intake and NSCLC, and (III) the genetic variants should solely influence the risk of NSCLC through their impact on fruit intake. "X" indicates that this inference cannot be established under the principles of Mendelian randomization. SNP, single-nucleotide polymorphism; NSCLC, non-small cell lung cancer.

correlation with confounding factors that are associated with the link between fruit intake and NSCLC; and (III) the genetic variants should solely influence the risk of NSCLC through their impact on fruit intake (*Figure 1*) (10). This study was conceived using the summary-level data sourced from publicly accessible genome-wide association studies (GWAS). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data source

We obtained data on fruit intake from analyzed version of Medical Research Council Integrative Epidemiology Unit (MRC-IEU) based on UK Biobank. The dataset of fresh fruit intake was ukb-b-3881 (sample size for fresh fruit intake =446,462) while the dried fruit intake was ukb-b-16576 (sample size for dried fruit intake =421,764). The actual intake of fresh fruit was assessed by asking, "About how many pieces of FRESH fruit do you eat per DAY? (Count one apple, one banana, 10 grapes, etc., as one piece; put '0' if you do not eat any)". The intake of dried fruit was measured with the question, "About how many pieces of DRIED fruit do you eat per DAY? (Count one prune, one dried apricot, 10 raisins, etc., as one piece; put '0' if you do not eat any)". Quality control identified responses reporting consumption of more than 50 pieces of fresh fruit or more than 100 pieces of dried fruit as invalid.

GWAS summary statistics for NSCLC were obtained from the FinnGen consortium R8 release (11). The dataset named "non-small cell lung cancer" was used in this study. This GWAS included 263,448 (3,865 cases versus 259,583 controls) European adult male and female subjects.

Instrument selection criteria

In a GWAS with 446,462 participants of European origin, we set genome-wide significance thresholds ($P<5\times10^{-8}$), while excluding single nucleotide polymorphisms (SNPs) with the threshold for linkage disequilibrium (LD) set $r^2>0.001$ and clump distance <10,000 kb (12,13). As a result, we identified 49 SNPs as IVs for fresh fruit intake. Additionally, we selected 36 SNPs from a GWAS involving 421,764 participants of European descent as IVs for dried fruit intake. The use of genome-wide significance thresholds served as a rigorous criterion to establish the association of SNPs with their respective exposures, ensuring a high

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degree of statistical confidence. The information of the filtered SNPs can be found in tables available at https://cdn.amegroups.cn/static/public/tlcr-24-276-1.zip.

Statistical analysis

In this study, various MR methods were employed, included inverse variance weighted (IVW), MR-Egger regression, weighted median, to investigate the potential genetic causal relationship between fruit intake and NSCLC. The IVW method used a meta-analysis approach, combining Wald estimates for each SNP, to derive an overall estimation of the impact of fruit intake on NSCLC. If horizontal pleiotropy did not exist, the result of IVW would be unbiased. Analyzing Wald estimates for each SNP and combining them, to derive an overall estimation of the effect of fruit intake on NSCLC (14). The MR-Egger method, basing on the assumption of InSIDE (Instrument Strength Independent of Direct Effect), represents an approach for estimating consistent causal effects. It can also have directed multidirectional effects. However, MR-Egger method may cause the bias of results and increase Type 1 error rate. That is because this method was easily effected by violations of the InSIDE assumption (15). While the MR-Egger approach is acknowledged for its relative resilience against pleiotropy, it is important to acknowledge that it may be influenced by reduced statistical power, thereby warranting careful interpretation.

We evaluated the deviation of the MR-Egger intercept from zero to assess the existence of horizontal pleiotropy, allowing us to compare the IVW results with MR-Egger regression results. The MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) analysis, a sophisticated technique utilized in this study, adeptly identifies and endeavors to mitigate the impact of horizontal pleiotropy through the identification and removal of noteworthy outliers. This meticulous approach enhances the robustness and reliability of the findings by effectively addressing potential confounding factors (16).

To evaluate potential heterogeneity within our study, we performed a Cochran's Q test using the inverse-variance weighted model and MR-Egger model. Additionally, to verify causality and ensure the correct directionality, we employed the MR Steiger directionality test.

The robustness of IVs was evaluated through the calculation of the F-statistic, employing the formula $F = R^2 \times (N-2)/(1-R^2)$, wherein R^2 signifies the proportion of variance in the exposure variable explained by the genetic variants and N denotes the sample size. A F-statistic greater than 10 (F-statistic >10) was deemed indicative of the absence of significant weak instrumental bias, thereby bolstering the validity of the IV analysis (17).

In addition to conducting the aforementioned analyses, we employed various visualization techniques to present our findings. Forest plots, scatter plots, leave-one-out plots, and funnel plots were utilized to visualize the results of our analyses. The forest plot allows for the visualization of the effects of each SNP on the outcomes. Additionally, we used MR-Steiger method to infer the causal direction between two phenotypes.

All intricate statistical analyses were conducted utilizing the R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria), a powerful platform renowned for its robust capabilities. For the MR analyses, the tools of two-sample MR (version 0.5.6) and MR-PRESSO (version 1.0) were employed.

Results

The outcomes of our MR study, as presented in *Figure 2*, delineate notable insights. Specifically, the odds ratios (ORs) were 0.74 [95% confidence interval (CI): 0.31, 1.79; P=0.50] for fresh fruit intake, 0.32 (95% CI: 0.15, 0.67; P=0.003) for dried fruit intake. This discernible disparity underscored a distinctive pattern—while dried fruit consumption appeared to confer a protective effect against NSCLC, fresh fruit intake failed to manifest a statistically significant influence.

Importantly, we did not found evidence of heterogeneity in the dried fruit intake. Although a visual examination of scatter plots (*Figure 3*) did identify certain IVs associated with dried fruit consumption as potential outliers, it is noteworthy that the preponderance of data points closely adheres to the fitted linear regression line.

Additionally, the comprehensive MR-PRESSO analysis revealed no compelling evidence of significant outliers (global test P>0.05) within the association between dried fruit intake and NSCLC. Consequently, these findings collectively suggest a paucity of substantial support for the existence of horizontal pleiotropy in this specific association.

We did not found evidence of heterogeneity in the dried fruit intakes ($P_{Cochran's\ Q}$>0.05), indicating that the estimation of fixed-effects IVW is convincing (Tables S1-S6). Furthermore, the outcomes of the *F*-statistic showed the statistical robustness inherent in the entirety of the selected SNPs, as shown in table available at https://cdn.amegroups.cn/static/public/tlcr-24-276-2.pdf.

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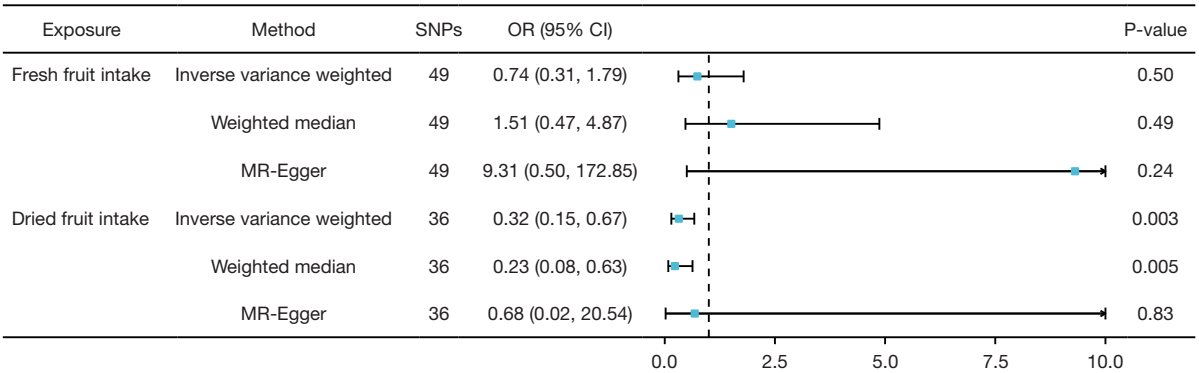

Figure 2 Forest plot shows results from MR study. We used forest plot to show results from MR study to assess associations between fruit intake and risk of non-small cell lung cancer. SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

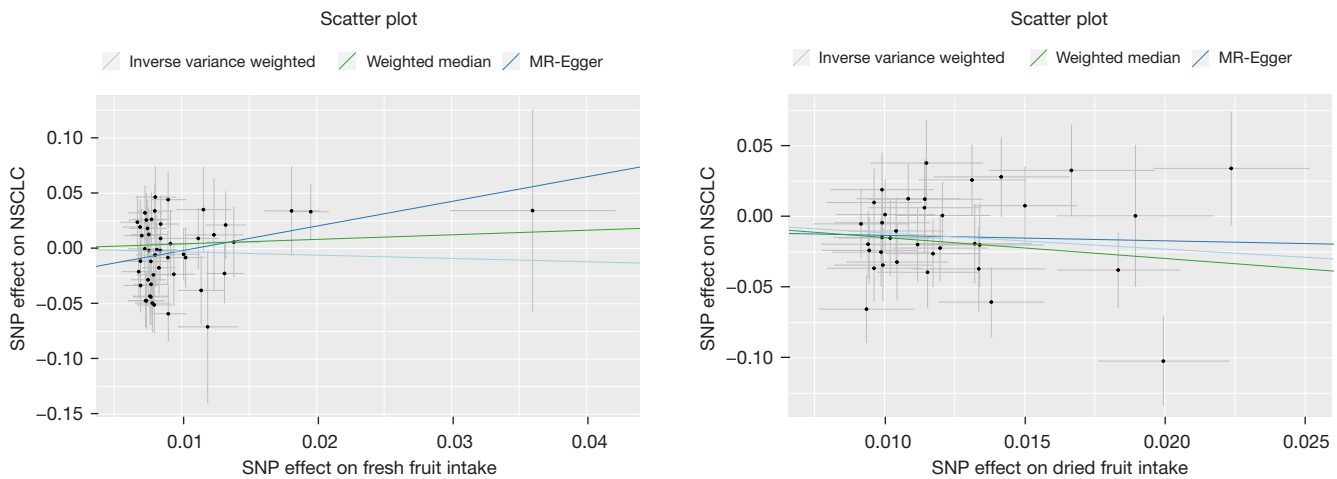

Figure 3 Scatter plots were generated to depict the effects of SNPs on fruit intake and NSCLC. Regression lines were employed to illustrate the causal effect of the exposure on the outcome, utilizing IVW, MR-Egger, and weighted median methods for estimating the causal effects. MR, Mendelian randomization; SNP, single-nucleotide polymorphism; NSCLC, non-small cell lung cancer; IVW, inverse-variance weighted.

In the MR Steiger directionality test, we discovered strong directional causality in both fruit analyses. The result of MR Steiger showed there might be a low risk of reverse causation, thus reinforcing the integrity of our findings in a causal framework.

The results of leave-one-out plots and funnel plots were shown in Figure S1 and Figure S2.

Discussion

In summary, our investigation employed a two-sample MR approach, leveraging data from the UK Biobank and a comprehensive GWAS encompassing over 218,000 individuals, to explore the potential relationship between fruit consumption and lung cancer risk. Our findings reveal compelling evidence suggesting a significant and noteworthy reduction in lung cancer risk associated with dried fruit intake. Intriguingly, this effect was not observed with fresh fruit intake, where the association did not reach statistical significance. These results emphasize the potential health benefits of dried fruit consumption in reducing lung cancer risk, shedding light on a specific aspect of fruit consumption that warrants further attention.

Dried fruits, abundant in diverse bioactive compounds

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endowed with potent antioxidant attributes, emerge as potential sources of substantial health benefits (4). Certain types of dried fruits have the potential to modulate the composition of the human gut microbiota in a beneficial manner (18). This presents a potentially significant pathway through which dried fruits may impact the development of NSCLC.

However, it is noteworthy that there are only a paucity of clinical investigations exclusively focusing on dried fruit consumption and its association with lung cancer. An observational study involving 34,192 participants from the California Seventh-day Adventist population revealed a significant inverse association between increased dried fruit consumption and the risk of developing lung cancer (7). Two studies conducted by Jin *et al.* and Yan *et al.* using MR further support the protective effect of dried fruits against lung cancer development (19,20). It is important to note that these prior studies analyzed data encompassing multiple subtypes of lung cancer, which introduces a potential bias in the classification of these subtypes. In our analysis, we included a larger cohort of 218,792 subjects, thereby surpassing the sample sizes of the aforementioned studies.

In a prospective trial involving 92,327 participants, the Experimenter Gateway conducted an analysis to investigate the potential relationship between 92 dietary factors and the risk of developing lung cancer. The results of that study suggest that there may be a negative association between the consumption of fruit and vitamin C and the incidence of squamous cell lung cancer (21). This study may also shed light on potential distinctions in the impact of fresh fruit consumption compared to dried fruit consumption on NSCLC.

Our study has several methodological strengths. Firstly, the MR approach minimizes the presence of reverse causality and residual confounding, which are inherent issues in observational studies. Moreover, by solely considering individuals of European population structure and adjusting for it in the GWASs, population stratification bias was effectively reduced in our study. The selection of SNPs and the utilization of summary data from NSCLC were specifically based on this population group. Additionally, the consistent results obtained from various sensitivity analyses, along with the absence of evidence indicating the presence of horizontal pleiotropy, further support the robustness of our study's findings. These findings specifically pertain to the association between fruit consumption and NSCLC, suggesting that the observed results are unlikely to be influenced by horizontal pleiotropy.

However, certain limitations warrant consideration. Firstly, despite we used some manners to control, there is still a possibility of unmeasured confounding due to IVs. Secondly, the validity of many IVs relies on the assumption of monotonicity. In our case, the IV is a genetic variant identified from the UK Biobank. While we have information regarding the size of this cohort, specific stratifications and characteristics of this subgroup remain unknown. The study population was restricted to the European, thus caution should be exercised when generalizing the results to other regions.

Conclusions

In summary, our study offers compelling and causally suggestive evidence that genetically predicted dried fruit consumption is associated with a lowered risk of lung cancer. However, our results do not support the relationship between fresh fruit intake and lung cancer. The findings highlight the potential significance of increasing dried fruit intake as an important dietary modification in the prevention of lung cancer in the future.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-276/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-276/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-276/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

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conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Cochran's Q test to evaluation the heterogeneity of dried fruit intake on non-small cell lung cancer

Outcome	Exposure	Method	Q	Q_df	Q_pval
finngen_R8_C3_LUNG_NONSMALL_EXALLC	Dried fruit intake	MR Egger	45.34939013	34	0.092356269
		Inverse variance weighted	46.96630326	35	0.085133316

df, degree of freedom; pval, P value; MR Egger, Mendelian Randomization Egger.

Table S2 Cochran's Q test to evaluation the heterogeneity of fresh fruit intake on non-small cell lung cancer

Outcome	Exposure	Method	Q	Q_df	Q_pval
finngen_R8_C3_LUNG_NONSMALL_EXALLC	Fresh fruit intake	MR Egger	54.8482492	45	0.149188004
		Inverse variance weighted	56.82191231	46	0.131666331

df, degree of freedom; pval, P value; MR Egger, Mendelian Randomization Egger.

Table S3 MR-PRESSO test to evaluation the horizontal pleiotropy of dried fruit intake on non-small cell lung cancer

Outcome	Exposure	Method	Global test P value
finngen_R8_C3_LUNG_NONSMALL_EXALLC	Dried fruit intake	MR-PRESSO	0.07866667

MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

Table S4 MR-PRESSO test to evaluation the horizontal pleiotropy of fresh fruit intake on non-small cell lung cancer

Outcome	Exposure	Method	Global test P value
finngen_R8_C3_LUNG_NONSMALL_EXALLC	Fresh fruit intake	MR-PRESSO	0.1316667

MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

Table S5 MR-Egger intercept test to evaluation the horizontal pleiotropy of dried fruit intake on non-small cell lung cancer

Outcome	Exposure	MR-Egger intercept	se	pval
finngen_R8_C3_LUNG_NONSMALL_EXALLC	Dried fruit intake	0.024450107	0.022206683	0.278619866

se, standard error; pval, P value; MR-Egger, Mendelian Randomization-Egger.

Table S6 MR-Egger intercept test to evaluation the horizontal pleiotropy of fresh fruit intake on non-small cell lung cancer

Outcome	Exposure	MR-Egger intercept	se	pval
finngen_R8_C3_LUNG_NONSMALL_EXALLC	Fresh fruit intake	0.017831008	0.014012464	0.209727713

se, standard error; pval, P value; MR-Egger, Mendelian Randomization-Egger.

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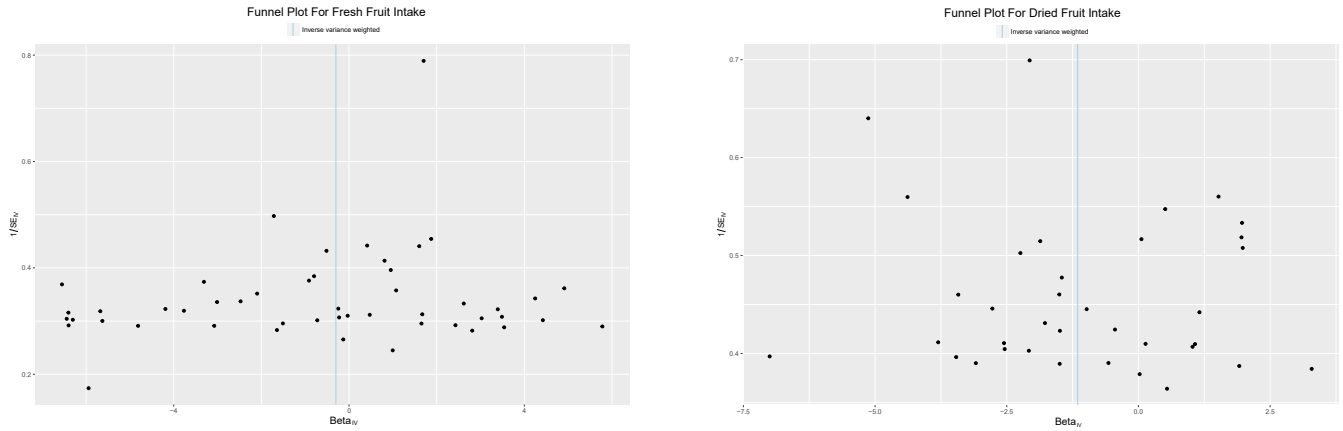

Figure S1 Funnel Plot. We used Funnel Plot to check for the presence of heterogeneity in individual genetic variants, and when there is no heterogeneity, the funnel plots take on a symmetrical shape. SE, standard error; IV, instrumental variable.

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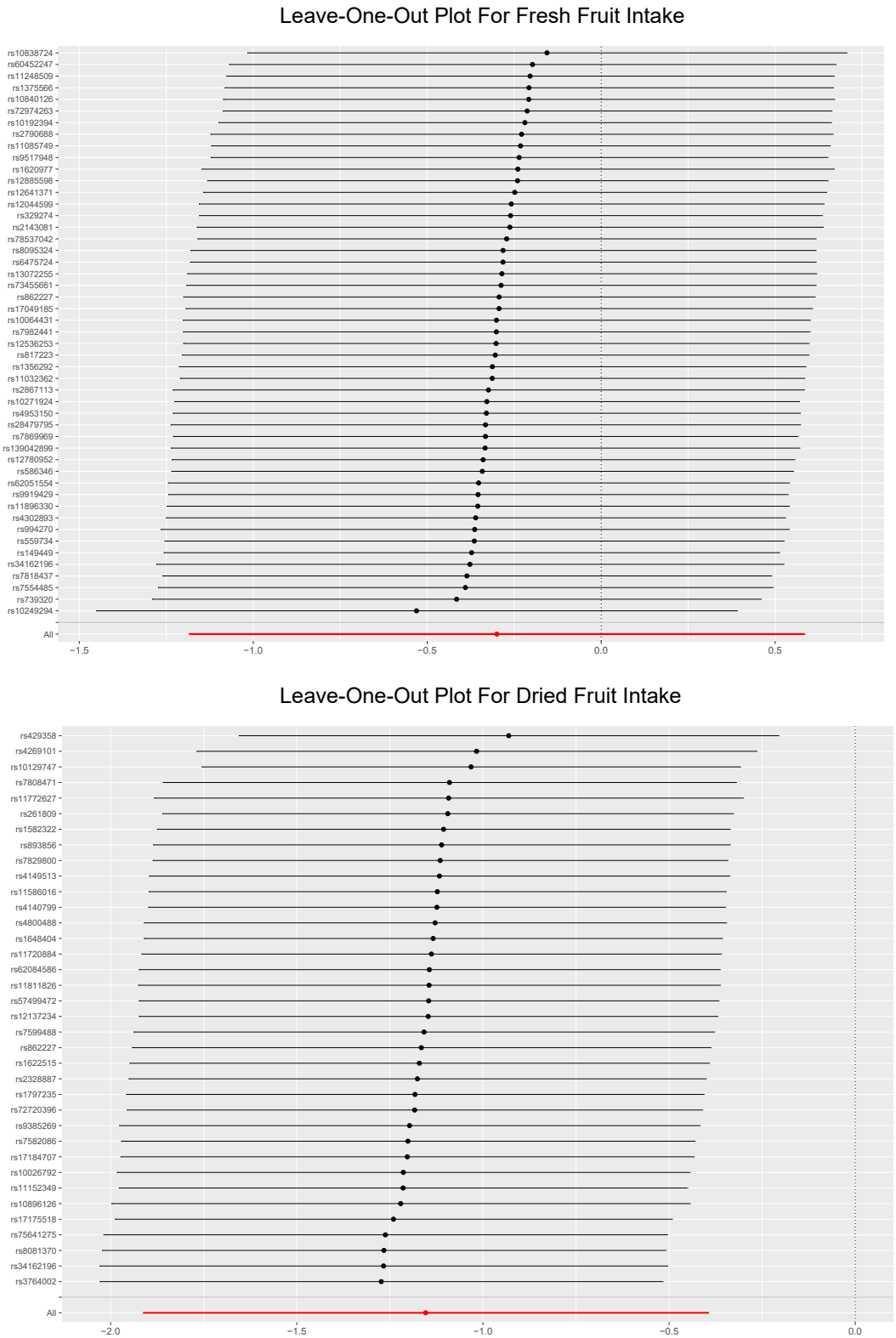

Figure S2 Leave One Out Plot. We used Leave One Out Plot to show the MR estimation results after removing each individual SNP. SNP, single-nucleotide polymorphism.

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