• Mendelian Randomization •

Causal relationship between multiple types of food intake and myopia: a Mendelian randomization study

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Abstract

● **AIM:** To investigate the causal relationship between dietary intake and myopia using Mendelian randomization (MR) analysis.

● **METHODS:** Genome-wide association study (GWAS) data from the IEU Open GWAS database were utilized to examine associations between myopia and various dietary factors. MR analysis, incorporating both univariable and multivariable approaches, assessed the impact of food intake on myopia risk through five analytical methods, with inverse variance weighted (IVW) serving as the primary reference. Sensitivity analyses, including heterogeneity assessment, horizontal pleiotropy evaluation, and leave-one-out analysis, were conducted to validate the MR findings.

● **RESULTS:** Univariable MR analysis identified a causal link between food intake and myopia. Consumption of breaded fish, canned soup, sweet biscuits, and certain fruits correlated with a lower risk of myopia, whereas intake of low-calorie hot chocolate and cereal was associated with an increased risk. Multivariable MR analysis further confirmed that breaded fish consumption exerted a direct protective effect against myopia, particularly when consumed alongside other dietary components. These findings highlight the intricate interplay between specific dietary factors and myopia development, offering valuable insights for further research.

● **CONCLUSION:** MR analysis provides evidence supporting a potential causal relationship between breaded fish intake and myopia, underscoring its relevance in targeted myopia prevention strategies.

● **KEYWORDS:** myopia; genome-wide association study; food intakes; univariable Mendelian randomization analysis; multivariable Mendelian randomization analysis

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INTRODUCTION

Myopia, commonly referred to as near-sightedness, is a global public health concern[1] primarily resulting from excessive axial elongation of the eyeball, which shifts the focal point of incoming light anterior to the retina, leading to blurred vision[2]. High myopia is a leading cause of visual impairment in children and adolescents[3], often progressing to complications such as myopic maculopathy and optic neuropathy[4]. The etiology of myopia involves a combination of genetic predisposition and environmental factors, including prolonged near-work activities[5], insufficient outdoor exposure[6-8], and dietary patterns[9-10].

Several clinical interventions are available to mitigate myopia progression, including low-dose atropine eye drops[11], orthokeratology lenses, soft contact lenses designed for myopia control, and spectacles incorporating aspheric lenses[4,12]. However, orthokeratology lenses remain costly, pharmacological treatments may induce adverse effects, and the intense academic demands on students often restrict outdoor activity. These limitations highlight the need for alternative strategies in myopia prevention and management. Given the emerging evidence on the role of nutrition in ocular health, this study aims to explore the relationship between dietary factors and myopia onset and progression, with the goal of identifying novel, effective preventive approaches.

Existing research underscores the substantial influence of dietary intake on visual health[13-14]. Notably, serum 25-hydroxy vitamin D [25(OH)D] levels have been found to be negatively correlated with myopia prevalence in young adults, with lower 25(OH)D concentrations being associated with a higher risk of myopia[15]. The biosynthesis of 25(OH)D primarily occurs through ultraviolet B-mediated conversion of 7-dehydrocholesterol in the skin, with additional contributions from dietary intake[16-18]. This has led to the hypothesis that vitamin D metabolism may partially mediate the protective effects of outdoor exposure against myopia development[19-20]. Moreover, essential micronutrients—including vitamins C, E, and A, as well as cis-β-carotene—have been implicated in maintaining ocular health[21-24]. Vitamin A and β-carotene are critical for retinal function, while trace elements such as zinc and selenium play pivotal roles in enhancing the ocular immune response[25].

Diets rich in vitamins E and C, primarily from fruits and vegetables, are associated with a reduced risk of myopia[25-26]. Additionally, the intake of ω-3 polyunsaturated fatty acids (ω-3 PUFAs), predominantly found in fish, has been linked to alleviation of eye fatigue and dry eye symptoms[27]. Notably, ω-3 PUFAs have been shown to mitigate near-work-induced reductions in choroidal blood perfusion in young adults, potentially lowering myopia incidence[28]. These dietary components, integral to ocular health, are readily obtainable from common food sources such as grains, meats, and fruits.

Despite these findings, empirical evidence on the role of dietary factors in myopia remains limited, with few studies investigating the potential protective effects of specific food groups against myopia development. This gap underscores the need for further research to elucidate the precise relationship between nutrition and myopia prevention.

The International Myopia Institute (IMI) has highlighted the complexities of statistical analysis in this field, emphasizing the influence of variable covariation and the necessity of robust methodologies such as Mendelian randomization (MR) or randomized clinical trials to establish causality[29]. MR analysis, which utilizes genetic variants as instrumental variables (IVs), effectively minimizes confounding and reverse causation—challenges that often undermine traditional observational studies—thereby enabling more reliable causal inferences[30-31]. While observational studies have suggested a strong association between diet and myopia, inconsistencies in findings likely stem from dietary heterogeneity and confounding factors, complicating clinical investigations. To address these limitations, this study employs MR analysis to assess the genetic causal relationship between myopia and specific dietary components, including low-calorie hot chocolate, plain cereal, sweet biscuits, canned soup, breaded fish, and other fruit consumption. By mitigating external confounders, this approach provides a more precise understanding of the dietary influences on myopia risk.

MATERIALS AND METHODS

Data Collection and Preprocessing In this study, myopia was designated as the outcome variable, while the intake of different food types served as the exposure factor. The myopia dataset was obtained from the Genome-Wide Association Studies (GWAS) database (https://gwas.mrcieu.ac.uk/), comprising 1640 myopic cases and 210 931 controls, with a total of 16 380 455 single nucleotide polymorphisms (SNPs) associated with myopia (GWAS ID: finn-b-H7_MYOPIA, population: European). Similarly, based on GWAS database records, the respective sample sizes were 1206 for low-calorie hot chocolate intake (ukb-e-100540_AFR, population: African American or Afro-Caribbean), 1469 for plain cereal intake (ukb-e-100830_CSA, population: South Asian), 1207 for sweet biscuit intake (ukb-e-102360_AFR, population: African American or Afro-Caribbean), 1469 for canned soup intake (ukb-e-102540_CSA, population: South Asian), 1207 for breaded fish intake (ukb-e-103170_AFR, population: African American or Afro-Caribbean), and 1207 for other fruit intake (ukb-e-104590_AFR, population: African American or Afro-Caribbean). The number of SNPs corresponding to these dietary factors was 15 533 605, 9 797 409, 15 533 605, 9 797 409, 15 533 528, and 15 533 528, respectively. Further details on the GWAS data are provided in Table 1. An overview of the study design is illustrated in Figure 1. As all data were retrieved from publicly available databases, additional ethical approval from an institutional review board was not required.

Selection of Eligible Instrumental Variables The MR study adhered to three fundamental assumptions: 1) IVs exhibit a strong and robust association with the exposure; 2) the IVs are independent of confounding factors; 3) the IVs influence the outcome exclusively through the exposure, without involvement in alternative pathways. To ensure compliance with these assumptions, IVs were selected using the extract_instruments function in the TwoSampleMR (v. 0.5.6) R package, with selection criteria set at $P<5\times10^{-8}$[32] and $R^2=0.8$[33]. Following IV selection, independent SNPs were subjected to clumping with linkage disequilibrium (LD) thresholds set at $R^2=0.001$ and a physical distance of 10 000 kb within a 10-megabase window to prevent redundant counting and mitigate bias in causal effect estimation. The harmonization process was subsequently performed to align SNPs across exposure and outcome GWAS datasets, ensuring strand consistency. In this step, palindromic SNPs with intermediate allele frequencies were excluded to prevent ambiguity, and SNPs directly associated with the outcome were removed to uphold instrument validity. To ensure the robustness of IV selection, only exposure-related SNPs exceeding a minimum threshold of two were retained, and the F-statistic was required to exceed 10 to mitigate weak instrument bias. The F-statistic was calculated using the formula: (sample size.exposure-2)$\times$[$R^2/(1-R^2)$], while R^2 represents the proportion of variance explained by each SNP, and was derived using the formula: $R^2=\beta^2\times(1-EAF)\times2\times EAF$. The beta ($\beta$) coefficient associated

Table 1 The information on GWAS in this study

Id	Trait	Case, *n*	Year	Author	Sex	Population	Build	Control, *n*	SNP, *n*
ukb-e-102360_AFR	Sweet biscuits intake	1207	2020	Pan-UKB team	Males and Females	African American or Afro-Caribbean	HG19/GRCh37	0	15533528
ukb-e-100540_AFR	Low calorie hot chocolate intake	1206	2020	Pan-UKB team	Males and Females	African American or Afro-Caribbean	HG19/GRCh37	0	15533605
finn-b-H7_MYOPIA	Myopia	1640	2021	NA	Males and Females	European	HG19/GRCh37	210931	16380455
ukb-e-100830_CSA	Plain cereal intake	1469	2020	Pan-UKB team	Males and Females	South Asian	HG19/GRCh37	0	9797409
ukb-e-104590_AFR	Other fruit intake	1207	2020	Pan-UKB team	Males and Females	African American or Afro-Caribbean	HG19/GRCh37	0	15533528
ukb-e-103170_AFR	Breaded fish intake	1207	2020	Pan-UKB team	Males and Females	African American or Afro-Caribbean	HG19/GRCh37	0	15533528
ukb-e-102540_CSA	Canned soup intake	1469	2020	Pan-UKB team	Males and Females	South Asian	HG19/GRCh37	0	9797409

GWAS: Genome-wide association study; SNP: Single nucleotide polymorphism.

with the exposure factor, and EAF was the allele frequency of the variant gene.

Mendelian Randomization Analysis Based on the selected SNPs, univariable MR analysis was conducted to evaluate the causal effects of different food intake variables on myopia risk, with food intake as the exposure and myopia as the outcome. This approach facilitated the estimation of the total causal effects of various dietary components on myopia development. Five MR methods were employed: MR Egger[34], weighted median[35], inverse variance weighted (IVW)[36], simple mode[33], and weighted mode[37], with IVW serving as the primary reference [P<0.05, odds ratio (OR)≠1]. In the IVW framework, a P-value below 0.05 and an OR differing from 1 indicated a statistically significant causal association between the exposure and outcome. The β coefficient represented the estimated causal effect size, while the OR quantified the association strength. An OR greater than 1 suggested that increased exposure elevated myopia risk, whereas an OR less than 1 indicated a protective effect. The results were visualized using scatter plots, forest plots, and funnel plots, each serving distinct analytical purposes. Scatter plots illustrated the causal relationship between dietary exposure and myopia, forest plots demonstrated the diagnostic efficiency of SNP loci in predicting myopia risk, and funnel plots assessed whether the MR analysis adhered to MR's second assumption, ensuring instrumental variable validity.

To assess the robustness of MR findings, a series of sensitivity analyses were conducted, including heterogeneity testing (Cochran's Q test, P>0.05), horizontal pleiotropy evaluation (P>0.05), and leave-one-out (LOO) analysis. If Cochran's Q test yielded P>0.05, indicating no significant heterogeneity, the fixed-effects IVW model was applied. Conversely, for P<0.05, the random-effects IVW model was adopted to account for heterogeneity.

To further refine the analysis, multivariable MR (MVMR) analysis was performed to investigate the joint causal effects of multiple dietary components on myopia risk. MVMR extends univariable MR by simultaneously assessing multiple exposures, thereby controlling for confounding effects among correlated dietary factors. SNP selection for MVMR followed the same criteria as univariable MR, and identical analytical methods were applied. IVW remained the primary reference method (P<0.05, OR≠1) to ensure consistency and statistical rigor.

RESULTS

All 6 Types of Diets Exhibited a Causal Relationship with Myopia In the primary analysis, a total of 38 SNPs reaching genome-wide significance were selected as IVs for assessing the association between low-calorie hot chocolate intake and myopia. Similarly, 8 SNPs were identified for plain cereal

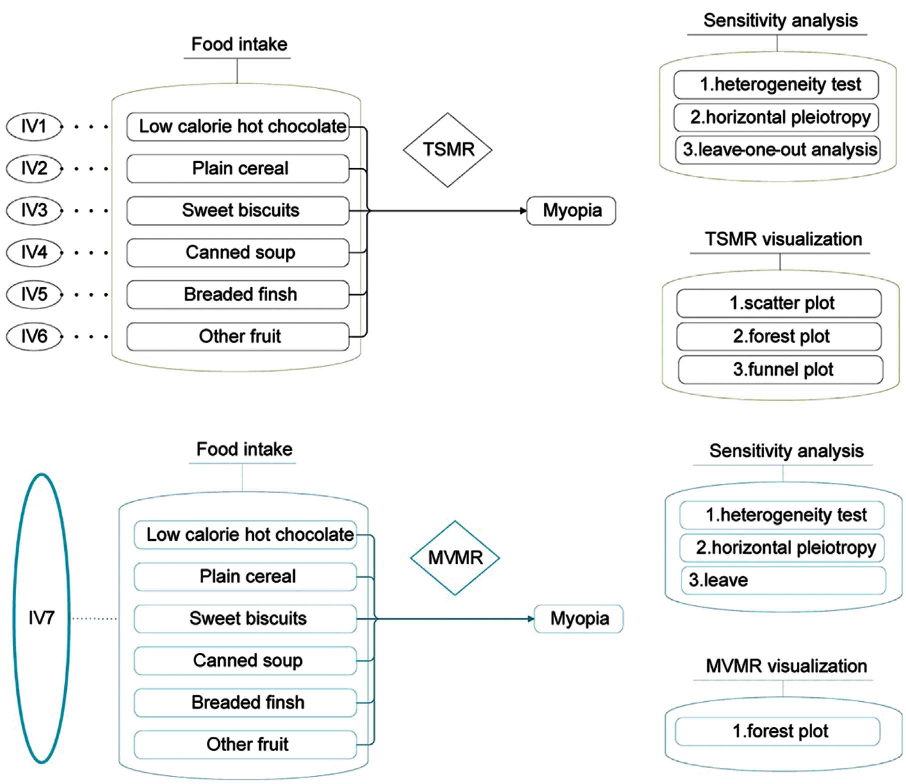

Figure 1 Workflow diagram for this study TSMR: Two-sample Mendelian randomization; MVMR: Multivariable Mendelian randomization.

Table 2 Results for the univariable MR analysis using the IVW method

Id.exposure	Id.outcome	Outcome	Exposure	Method	nSNP	β	SE	*P*	OR
ukb-e-100540_AFR	finn-b-H7_MYOPIA	Myopia	Low calorie hot chocolate intake	Inverse variance weighted (fixed effects)	38	0.061	0.028	0.029	1.063
ukb-e-100830_CSA	finn-b-H7_MYOPIA	Myopia	Plain cereal intake	Inverse variance weighted (fixed effects)	8	0.149	0.076	0.049	1.161
ukb-e-102360_AFR	finn-b-H7_MYOPIA	Myopia	Sweet biscuits intake	Inverse variance weighted (fixed effects)	3	-0.082	0.038	0.031	0.921
ukb-e-102540_CSA	finn-b-H7_MYOPIA	Myopia	Canned soup intake	Inverse variance weighted (fixed effects)	37	-0.119	0.047	0.012	0.888
ukb-e-103170_AFR	finn-b-H7_MYOPIA	Myopia	Breaded fish intake	Inverse variance weighted (fixed effects)	101	-0.069	0.020	0.001	0.934
ukb-e-104590_AFR	finn-b-H7_MYOPIA	Myopia	Other fruit intake	Inverse variance weighted (fixed effects)	14	-0.081	0.041	0.048	0.922

MR: Mendelian randomization; IVW: Inverse variance weighted; nSNP: Number of SNP; β: The estimated causal effect between the exposure factor and the outcome. The plus or minus sign denotes the direction of the causal relationship between the exposure factor and the outcome. SE: Standard error of the β value; OR: Odds ratio.

intake, 37 for canned soup intake, 3 for sweet biscuits intake, 101 for breaded fish intake, and 14 for other fruit intake in relation to myopia risk. Univariable MR analysis indicated a statistically significant causal relationship between these six dietary components and myopia (P<0.05). Notably, breaded fish intake (OR=0.934), canned soup intake (OR=0.888), sweet biscuit intake (OR=0.921), and other fruit intake (OR=0.922) exhibited inverse causal associations with myopia, suggesting a protective effect (OR<1). These results imply that increased consumption of these foods may contribute to a lower risk of myopia. Conversely, low-calorie hot chocolate intake (OR=1.063) and plain cereal intake (OR=1.161) demonstrated positive causal associations with myopia (OR>1), identifying them as potential risk factors that may elevate myopia incidence (Table 2).

Scatter plots demonstrated that among the five MR algorithms, low-calorie hot chocolate intake and plain cereal intake exhibited a positive causal relationship with myopia, as indicated by the positive slope in the IVW method. Conversely, the negative slopes observed for breaded fish intake, canned soup intake, sweet biscuit intake, and other fruit intake suggested an inverse causal relationship with myopia occurrence (Figure 2). Additionally, the intercepts of the IVW method for all six exposure factors were close to zero, implying minimal confounding effects in this MR analysis (Figure 2). Forest plots further corroborated these findings, with SNP points corresponding to low-calorie hot chocolate intake and plain cereal intake aligning to the right, supporting their classification as myopia risk factors (Figure 3). In contrast, SNP points for breaded fish intake, canned soup intake, sweet biscuit intake, and other fruit intake were positioned to the left of zero, reinforcing their protective effects against myopia (Figure 3). Furthermore, the overall diagnostic efficacy of All-IVW for low-calorie hot chocolate and plain cereal intake was

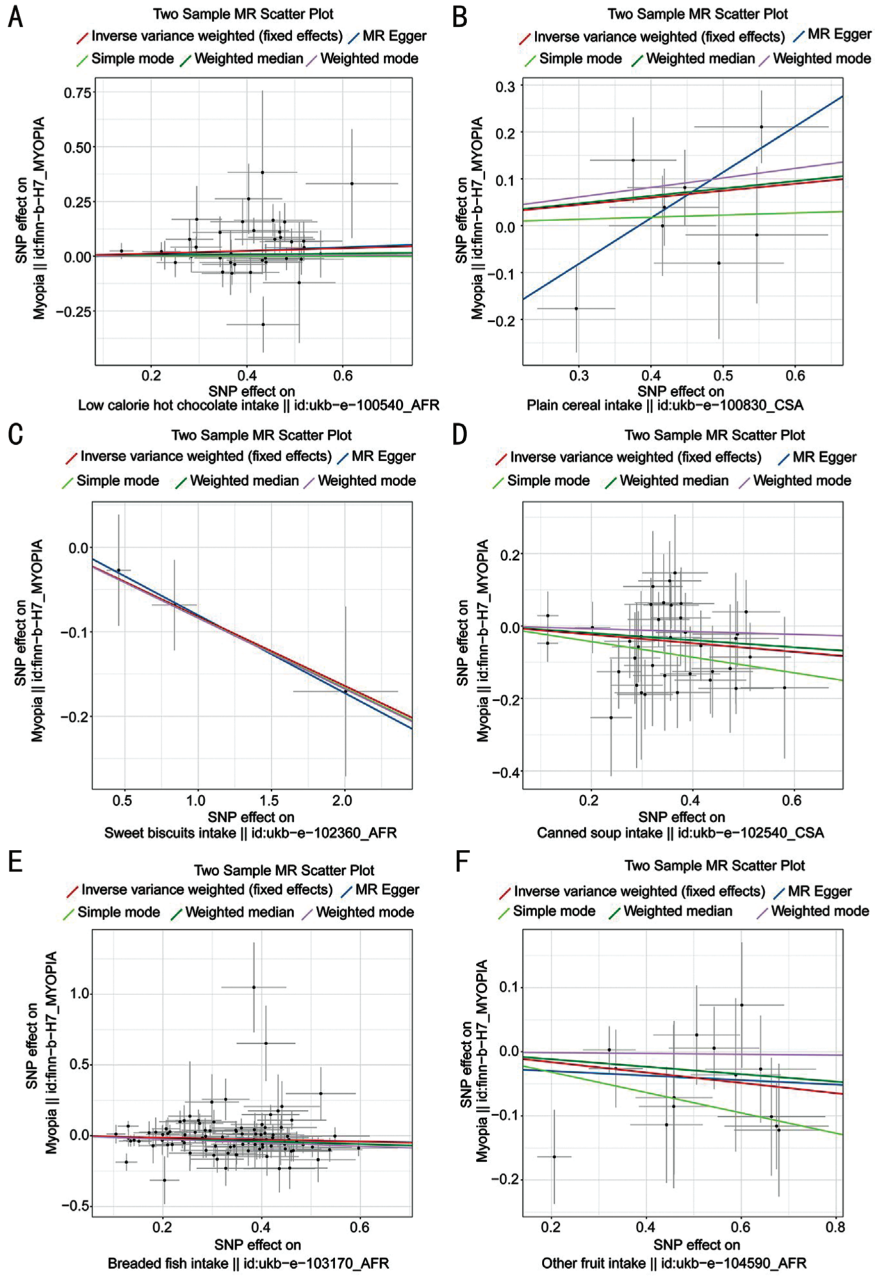

Figure 2 Scatter plot illustrating the MR associations between exposure factors and myopia The x-axis represents the effect of SNPs on exposure factors, while the y-axis denotes the effect of SNPs on the outcome. Colored lines indicate the fitted regression results of different MR algorithms. A: Low-calorie hot chocolate intake; B: Plain cereal intake; C: Sweet biscuit intake; D: Canned soup intake; E: Breaded fish intake; F: Other fruit intake. SNP: Single nucleotide polymorphism; MR: Mendelian randomization; AFR: African; CSA: Central & South Asian.

positioned on the right side of zero, confirming their role as risk factors, while the efficacy of breaded fish intake, canned soup intake, sweet biscuit intake, and other fruit intake was on the left side of zero, indicating their protective effects (Figure 3). Funnel plot analysis revealed that SNPs for all exposure factors were approximately symmetrically distributed on both sides, suggesting consistency with Mendelian randomization's second assumption and confirming the validity of the IVs (Figure 4).

Sensitivity analysis results indicated no evidence of heterogeneity across all six exposure factors, as reflected by $P>0.05$ in Cochran's Q test (Table 3). Similarly, horizontal pleiotropy was absent, with $P>0.05$ (Table 4). The LOO forest plot showed that all error bars remained to the right of zero, indicating the absence of outlier SNPs influencing the results. Sequentially excluding individual SNPs did not alter the estimated causal effects, demonstrating the robustness of the MR analysis (Figure 5).

Multivariable Mendelian Randomization Analyses Multivariable MR analysis results demonstrated that, after adjusting for the effects of low-calorie hot chocolate intake, plain cereal intake, sweet biscuit intake, canned soup intake, and other fruit intake, breaded fish intake retained a statistically significant direct effect on myopia occurrence ($P<0.05$). When

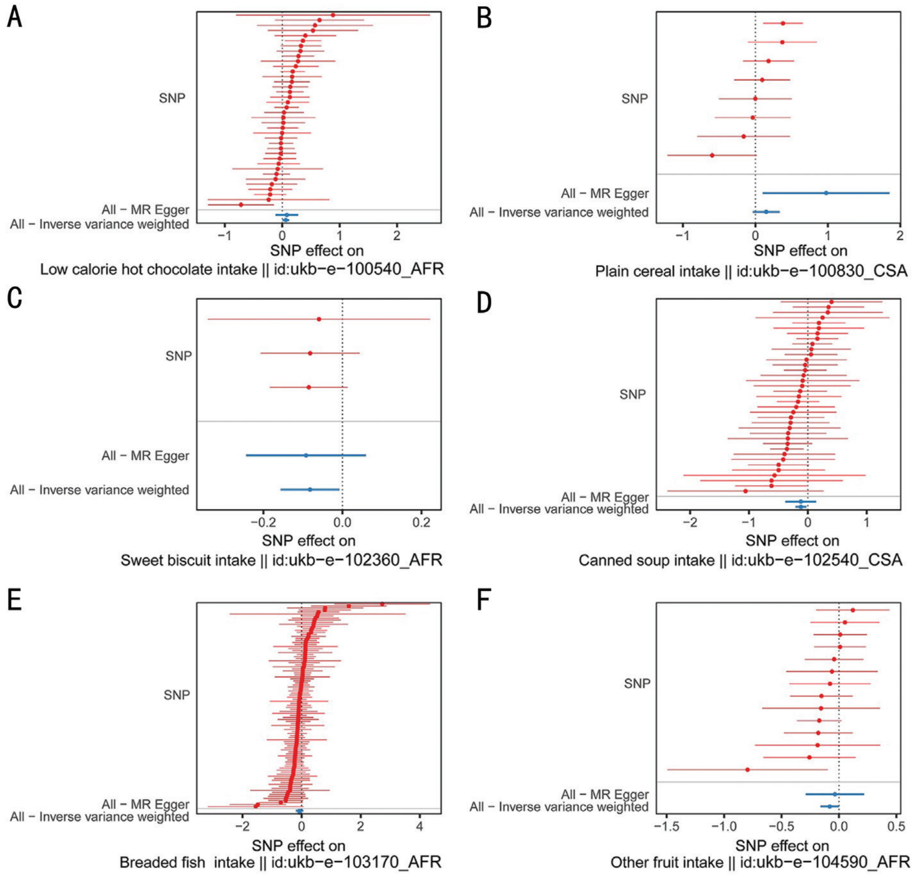

Figure 3 Forest plot depicting the associations between SNP variants and myopia risk Red dots positioned to the right of zero indicate a positive association between the SNP locus and myopia, whereas red dots on the left denote a negative association. A: Low-calorie hot chocolate intake; B: Plain cereal intake; C: Sweet biscuit intake; D: Canned soup intake; E: Breaded fish intake; F: Other fruit intake. SNP: Single nucleotide polymorphism; AFR: African; CSA: Central & South Asian; MR: Mendelian randomization.

considering the simultaneous consumption of multiple dietary components, breaded fish intake emerged as an independent protective factor against myopia, with higher intake associated with a lower myopia risk (OR<1; Table 5, Figure 6).

In conclusion, a causal relationship was identified between the intake of six dietary components and myopia development. Breaded fish intake, canned soup intake, sweet biscuit intake, and other fruit intake emerged as protective factors, whereas low-calorie hot chocolate and plain cereal intake were associated with an increased risk of myopia. Multivariable MR analysis further demonstrated that, after adjusting for the effects of other dietary factors, breaded fish intake remained significantly associated with a reduced risk of myopia. This finding suggests that breaded fish intake exerts a direct protective effect against myopia, even when consumed in conjunction with various other foods.

DISCUSSION

While empirical evidence remains limited, dietary changes—particularly increased carbohydrate intake—among populations undergoing economic transition have been implicated in the rapid rise of myopia[38]. Certain nutrients and dietary patterns have been associated not only with myopia but also with various other ocular diseases[15]. However, findings on this topic remain inconsistent, as illustrated by a study in Singapore that reported no significant association between diet and myopia in 9-year-old children[39]. To date, the role of dietary factors in myopia development remains unclear. This study elucidates the relationship between food intake and myopia risk, providing the first clear evidence of a causal association through MR analysis. Our findings reveal that breaded fish intake, canned soup intake, sweet biscuit intake, and other fruit intake function as protective factors against myopia. Notably, MVMR analyses highlighted the significant inhibitory effect of breaded fish intake, aligning with prior research on the benefits of ω-3 PUFAs.

Fish is a well-established source of ω-3 PUFAs, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)[40]. Studies have demonstrated that ω-3 PUFA supplementation alleviates near-work-induced declines in choroidal blood perfusion (ChBP) and counteracts hypoxia-induced transdifferentiation of human scleral fibroblasts. Additionally, animal studies have shown that ω-3 PUFAs significantly mitigate form-deprivation myopia in guinea pigs and mice, as well as lens-induced myopia in guinea pigs[28].

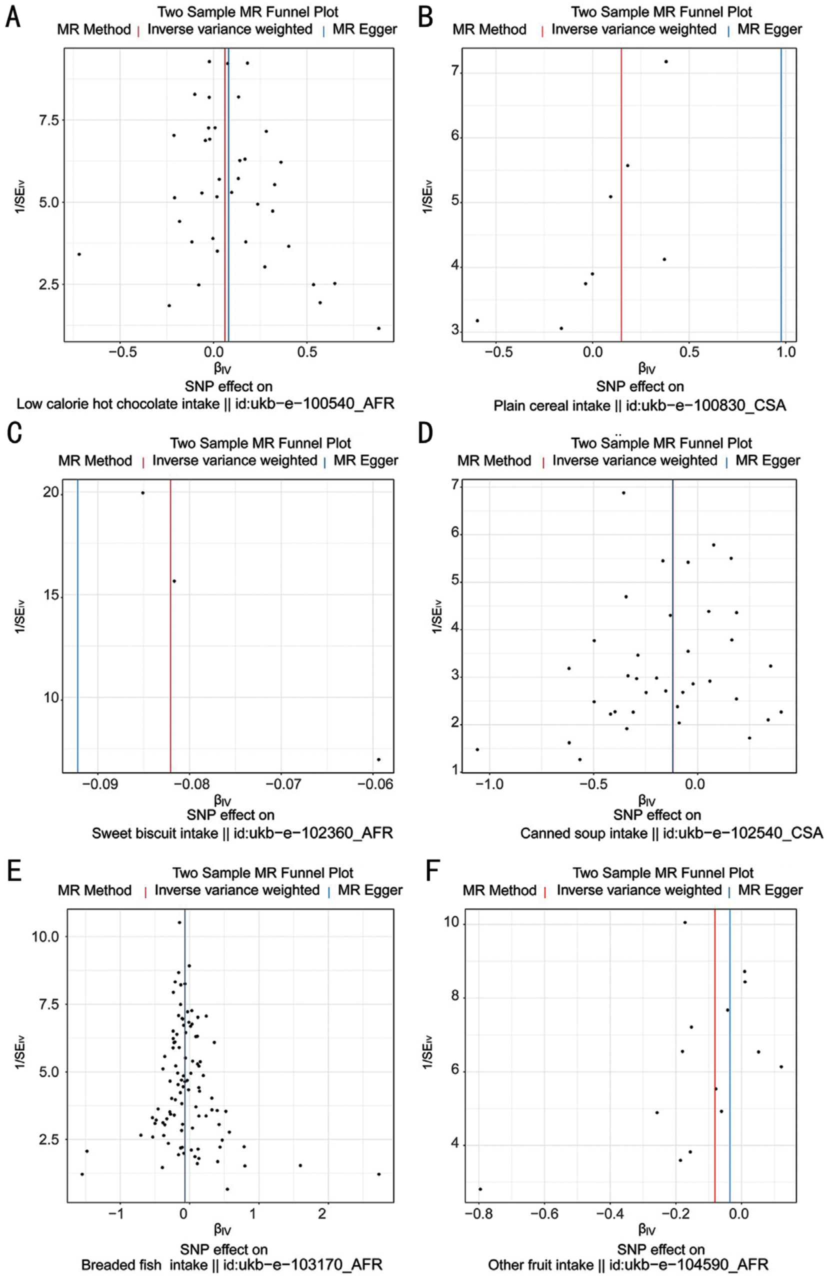

Figure 4 Funnel plot of the MR analysis The x-axis represents the β values of the instrumental variables (IVs), while the y-axis shows the inverse standard error of the IVs. A: Low-calorie hot chocolate intake; B: Plain cereal intake; C: Sweet biscuit intake; D: Canned soup intake; E: Breaded fish intake; F: Other fruit intake. SE: Standard Error; SNP: Single nucleotide polymorphism; AFR: African; CSA: Central & South Asian; MR: Mendelian randomization.

Furthermore, evidence suggests that n-3 PUFAs exert their myopia-alleviating effects through anti-inflammatory and choroidal vasodilation mechanisms[41]. Collectively, these findings support the notion that incorporating ω-3 PUFA-rich fish into the diet represents a feasible and accessible strategy for myopia prevention[28]. Although frying may degrade a portion of ω-3 PUFAs, the remaining bioactive compounds could still exert protective effects against myopia. Our investigation demonstrated a significant causal relationship between breaded fish intake and myopia risk reduction in both univariable and multivariable MR analyses, reinforcing its role as a protective factor. These findings suggest that, even when consumed alongside other foods, the inclusion of breaded fish in the diet may contribute to lowering myopia incidence.

Our findings also reveal a positive correlation between low-calorie hot chocolate intake and myopia occurrence, identifying it as a risk factor. This aligns with previous studies indicating that the consumption of pastries, preserves, sugar, and foods such as fruit, chocolate, and ice cream is more prevalent among children with myopia and is positively associated with its incidence[42]. However, the precise impact of added sugars or refined carbohydrates in sweets on myopia development, as well as the underlying physiological mechanisms, warrants further investigation. One possible explanation involves the

Table 3 Results of heterogeneity test

Id.exposure	Id.outcome	Outcome	Exposure	Method	Q	Q_df	Q_pval
ukb-e-100540_AFR	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Low calorie hot chocolate intake || id:ukb-e-100540_AFR	Inverse variance weighted	40.0727071	37	0.33547782
ukb-e-100830_CSA	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Plain cereal intake || id:ukb-e-100830_CSA	Inverse variance weighted	11.0647137	7	0.135821045
ukb-e-102360_AFR	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Sweet biscuits intake || id:ukb-e-102360_AFR	Inverse variance weighted	0.028703728	2	0.985750633
ukb-e-102540_CSA	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Canned soup intake || id:ukb-e-102540_CSA	Inverse variance weighted	28.02271951	36	0.826389878
ukb-e-103170_AFR	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Breaded fish intake || id:ukb-e-103170_AFR	Inverse variance weighted	119.5227826	100	0.089136022
ukb-e-104590_AFR	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Other fruit intake || id:ukb-e-104590_AFR	Inverse variance weighted	10.1374783	13	0.682655488

AFR: African; CSA: Central & South Asian.

Table 4 Results of horizontal pleiotropy test

Id.exposure	Id.outcome	Outcome	Exposure	Egger_intercept	SE	*P*
ukb-e-100540_AFR	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Low calorie hot chocolate intake || id:ukb-e-100540_AFR	-0.007727426	0.038523084	0.842146503
ukb-e-100830_CSA	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Plain cereal intake || id:ukb-e-100830_CSA	-0.374375052	0.198783941	0.108652778
ukb-e-102360_AFR	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Sweet biscuits intake || id:ukb-e-102360_AFR	0.011724462	0.078004988	0.905024444
ukb-e-102540_CSA	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Canned soup intake || id:ukb-e-102540_CSA	0.000649142	0.046327552	0.988899967
ukb-e-103170_AFR	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Breaded fish intake || id:ukb-e-103170_AFR	-0.001088328	0.021470649	0.959675406
ukb-e-104590_AFR	finn-b-H7_MYOPIA	Myopia || id:finn-b-H7_MYOPIA	Other fruit intake || id:ukb-e-104590_AFR	-0.022968745	0.061930207	0.717190646

AFR: African; CSA: Central & South Asian.

Table 5 Results for the TSMR and MVMR analysis of exposure factors

OR	OR_low 95%CI	OR_up 95%CI	*P*	Indicator
1.000	1.000	1.000	NA	TSMR
0.934	0.897	0.971	0.001	Breaded fish intake
0.888	0.810	0.974	0.012	Canned soup intake
1.063	1.006	1.123	0.029	Low calorie hot chocolate intake
0.922	0.851	0.999	0.048	Other fruit intake
1.161	1.000	1.346	0.049	Plain cereal intake
0.921	0.855	0.992	0.031	Sweet biscuits intake
1.000	1.000	1.000	NA	MVMR
0.938	0.892	0.986	0.012	Breaded fish intake
0.849	0.631	1.144	0.282	Canned soup intake
1.042	0.974	1.115	0.230	Low calorie hot chocolate intake
0.930	0.824	1.050	0.241	Other fruit intake
1.079	0.811	1.437	0.601	Plain cereal intake
1.021	0.969	1.076	0.440	Sweet biscuits intake

OR: Odds ratio; CI: Confidence interval; TSMR: Two-Sample Mendelian randomization; MVMR: Multivariable Mendelian randomization.

metabolic effects of low-calorie hot chocolate and its additives, which may disrupt systemic metabolic balance and influence insulin secretion. Dysregulation of insulin signaling pathways, including those mediated by insulin-like growth factors (IGFs), has been implicated in ocular growth modulation and myopia progression[43-45]. Nonetheless, these potential mechanisms remain speculative and require further exploration.

Conversely, some studies have suggested that diets rich in refined carbohydrates—such as refined grains, desserts, sweet snacks, and sugar-sweetened beverages—as well as high-protein diets, are not associated with myopia incidence[26]. Moreover, research has identified whole grain intake (>50%) as an independent protective factor against myopia[13]. However, our study found that plain cereal intake was positively correlated with myopia risk, designating it as a contributing factor. The discrepancy in findings may be attributed to variations in the type, quantity, and processing of grains, highlighting the need for further research on the specific effects of different grain forms on myopia development. Additionally, studies have reported that students consuming fresh fruit at least twice daily had a 31% lower risk of developing myopia compared to those who did not consume fruit[10]. This finding is consistent with our results, which demonstrated a protective effect of fruit intake against myopia.

Unlike conventional myopia interventions, behavioral strategies such as increasing outdoor exposure effectively slow myopia progression, albeit with inherent limitations[46-47]. However, highly competitive education systems and increasingly screen-centric lifestyles significantly constrain outdoor activity. Pharmacological interventions, including

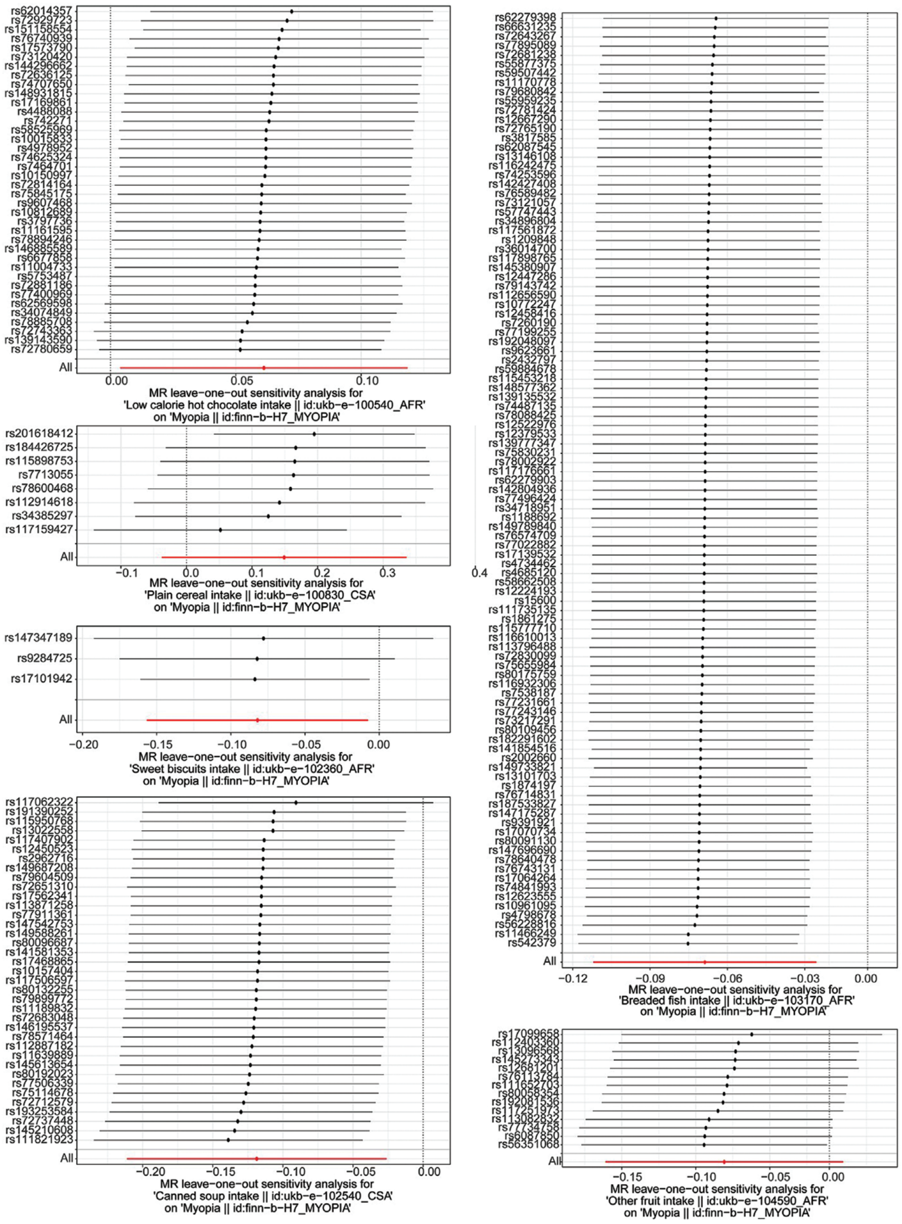

Figure 5 Leave-one-out sensitivity analysis results Each horizontal solid line represents the estimated effect of a single SNP. Solid lines entirely on the left side of zero indicate that the SNP contributes to a reduced risk of myopia, while those entirely on the right suggest an increased risk. Lines crossing zero indicate non-significant associations. The "All" category represents the overall effect. SNP: Single nucleotide polymorphism; AFR: African; CSA: Central & South Asian.

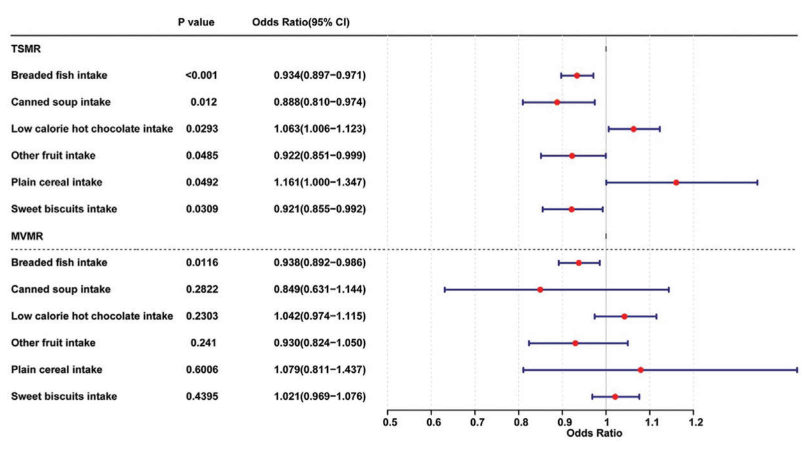

Figure 6 Forest plot of the TSMR and MVMR analyses The first column lists the MR analysis methods and exposure factors, the second column displays the *P*-values, and the third column presents the OR along with their 95%CI. TSMR: Two-sample Mendelian randomization; MVMR: Multivariable Mendelian randomization; MR: Mendelian randomization; OR: Odds ratio; CI: Confidence interval.

atropine eye drops, demonstrate efficacy in myopia control but face challenges such as off-label use in many regions and adverse effects, including chronic pupil dilation, impaired light adaptation, and diminishing long-term effectiveness, limiting widespread adoption[48-49]. Optical interventions, such as orthokeratology and peripheral defocus lenses, carry risks of infectious keratitis, necessitate professional supervision, and impose a substantial financial burden[50-51]. Given the absence of universally effective treatments, the development of a safe, accessible dietary approach for myopia control is of paramount importance, particularly considering the heightened safety concerns surrounding pharmacological interventions in children. Dietary modifications offer a non-invasive and sustainable alternative, with the potential for long-term adherence through adjustments to daily nutrition, despite a relatively gradual onset of effects.

While numerous studies have explored associations between dietary intake and myopia, none have identified specific foods. This study categorizes distinct food types to enhance the granularity of understanding. However, the application of bioinformatics in nutritional epidemiology necessitates larger sample sizes and further validation. Notably, this study represents the first to employ MR analysis to establish a causal link between the consumption of six different food types and myopia, effectively mitigating confounding biases inherent in traditional observational studies. Nonetheless, the study population is limited to individuals of European ancestry, necessitating further research to assess broader applicability. Given the high prevalence of myopia in Asia, particularly among children and adolescents, subsequent investigations will focus on an expanded cohort study in Chinese youth to elucidate the interplay between genetic, dietary, and environmental factors in myopia development.

In conclusion, MR analysis confirmed a potential causal relationship between breaded fish consumption and myopia, providing valuable insights for targeted prevention strategies. This study underscores the potential of dietary interventions in myopia control, emphasizing the need to optimize dietary composition by increasing the intake of protective foods while reducing the consumption of risk-associated foods. However, extensive future research is required to validate and expand upon these findings, ultimately refining dietary guidelines for myopia prevention and management.

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