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Exploring the causal effects of physical activity, diet, and nutrition on hypertension and hyperlipidemia: a multivariable Mendelian randomization analysis

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Abstract

Background and aim Hypertension and hyperlipidaemia are major risk factors for cardiovascular diseases, contributing to significant morbidity and mortality worldwide. Lifestyle interventions, including modifications in diet, nutrition, and physical activity, are commonly recommended, but their causal effects on these conditions remain uncertain. This study aims to explore the causal effects of these factors on hypertension and hyperlipidaemia using multivariate Mendelian randomisation analysis, providing insights for effective cardiovascular prevention strategies.

Methods and results Genetic data related to physical activity, diet, and nutrition were obtained from public databases and analyzed using multivariate Mendelian randomisation. The analysis employed MR Egger, weighted median, and inverse variance weighting (IVW) methods, with tests for heterogeneity and multiplicity ensuring the reliability of the results. In the hypertension analysis, low-calorie diets showed a positive association in weighted median and IVW analyses, with weighted median analysis showing an association of 1.122 (95% CI: 1.014–1.243, $P=0.026$) and IVW analysis showing an association of 1.095 (95% CI: 1.013–1.184, $P=0.023$). However, MR Egger's analysis showed no significant association (association of 0.688, 95% CI: 0.411–1.155, $P=0.230$). Calcium supplements and dietary fibre did not demonstrate significant associations across all methods. Physical activity also did not show significant causal links with hypertension. Regarding hyperlipidaemia, calcium supplements exhibited significant effects across all methods, though with notable variation, while dietary fibre and physical activity showed no significant impacts.

Conclusions The study suggests a positive association between low-calorie diets and hypertension, as indicated by significant results from weighted median and IVW analyses. Other dietary factors, physical activity, and calcium supplementation exhibited varied or non-significant effects on hypertension and hyperlipidaemia. These findings highlight the need for further research to understand the underlying mechanisms and support the development of effective public health interventions.

Keywords Multivariate Mendelian randomisation analysis, Hypertension, Hyperlipidaemia, Physical activity, Diet, Nutrition

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Introduction

Hypertension and hyperlipidaemia are chronic diseases that are prevalent worldwide and pose a serious threat to human health. According to the World Health Organisation (WHO) [1, 2], about 1.1 billion people worldwide suffer from hypertension, and more than 9 million deaths are caused by hypertension-related complications each year. Meanwhile, hyperlipidaemia, especially hypercholesterolaemia, has become a major public health problem [3]. The Global Cardiovascular Disease Risk Factor Survey shows that about 39 per cent of adults have high cholesterol, and this percentage is more significant in some high-income countries and regions [4, 5]. The prevalence of hypertension and hyperlipidaemia is on the rise with changing lifestyles and an ageing population.

Epidemiological studies have shown that the onset of hypertension and hyperlipidaemia is closely related to unhealthy lifestyles, including diets high in salt and fat, lack of physical activity, smoking and alcohol abuse [6]. In addition, genetic factors also play an important role in the development of these diseases. Despite significant advances in modern medicine in the management and treatment of these diseases, a large number of patients are still suffering from conditions that are not effectively managed, especially in low- and middle-income countries and regions [7, 8]. These countries often lack well-developed healthcare infrastructure and public health policies, leading to challenges in the management of hypertension and hyperlipidaemia [9].

Hypertension and hyperlipidaemia are not only independent risk factors, but can also lead to a variety of serious complications. Uncontrolled hypertension damages the walls of the arteries and increases the risk of heart disease, stroke and kidney failure [10–12]. Specifically, people with high blood pressure are significantly more likely to develop coronary heart disease and heart failure, while the incidence of stroke is significantly higher than in normotensive people. In addition, hypertension is strongly associated with the development of retinopathy, aortic aneurysm and peripheral arterial disease [13]. Hyperlipidaemia, especially hypercholesterolaemia, is a major risk factor for atherosclerosis. Atherosclerosis leads to hardening of the arteries and narrowing of the blood vessels, which increases the risk of myocardial infarction and stroke. Studies have shown that elevated levels of low-density lipoprotein cholesterol (LDL-C) are positively correlated with the incidence of coronary heart disease [14, 15], whereas reduced levels of high-density lipoprotein cholesterol (HDL-C) are associated with an increased risk of cardiovascular events. Hyperlipidaemia can also lead to other health problems such as fatty liver, pancreatitis and kidney disease. These complications not only have a serious impact on patients' quality of life [16], but also place a significant burden on the healthcare system. As the disease progresses, patients require frequent medical interventions and long-term treatment, which not only increases the financial burden on individuals and families, but also places greater demands on the public health system [17]. Therefore, prevention and control of hypertension and hyperlipidaemia are important to reduce the burden of cardiovascular disease and improve public health.

Exploring the causal effects of physical activity, diet and nutrition on hypertension and hyperlipidaemia can provide a scientific basis for the prevention and control of these diseases. Studies have shown that regular physical activity can effectively lower blood pressure levels and improve lipid profiles, thereby reducing the risk of cardiovascular disease [18, 19]. Exercise not only enhances cardiopulmonary function and improves blood circulation, but also reduces stress by regulating the neuroendocrine system, thus achieving the effect of lowering blood pressure [20]. In terms of diet, a low-salt, low-fat and high-fibre dietary pattern has been proven to have a positive effect on controlling blood pressure and blood lipids. For example, the Mediterranean diet, which is rich in fruits, vegetables, whole grains, fish and olive oil, is considered an ideal dietary pattern for the prevention of cardiovascular diseases [22–24]. In addition, increased dietary fibre intake can help to reduce cholesterol levels and improve gut health, thereby reducing the incidence of hyperlipidaemia. Through multivariate Mendelian randomisation (MR) analysis, we were able to explore in depth the causal effects of physical activity, diet and nutrition on hypertension and hyperlipidaemia using genetic variants as instrumental variables [25]. This approach is effective in avoiding confounding factors and reverse causation issues found in traditional observational studies, leading to more reliable conclusions. Studying the causal relationship of these factors not only helps to formulate more scientific public health policies, but also provides a basis for individualised treatment and intervention [26–28].

The aim of this study was to explore the causal effects of physical activity, diet and nutrition on hypertension and hyperlipidaemia through multivariate Mendelian randomisation analysis. These studies not only help to deepen our understanding of the etiology of hypertension and hyperlipidaemia, but also provide new perspectives and approaches for the prevention and treatment of related diseases.

Methods

Study design

This study employed a multivariate Mendelian randomisation (MR) analysis to investigate the causal effects of physical activity, diet, and nutrition on hypertension and hyperlipidaemia. We considered multiple exposure factors, including physical activity, low-calorie diet, calcium supplements, and dietary fibre, with hypertension and hyperlipidaemia as outcome variables. To conduct a robust MR study, three key assumptions must be satisfied: first, the selected single nucleotide polymorphisms (SNPs) should be significantly associated with the exposure factors; second, the SNPs should be independent of potential confounders; and third, the SNPs should only be associated with the outcome variables through the exposure factors. We ensured these assumptions were met by carefully selecting and justifying our SNPs. Pooled data from published studies, with informed consent and ethical approval obtained from participants, were utilised in this analysis (Clinical trial number: not applicable).

Data resources

The Genome Wide Association Study (GWAS) pooled data on physical activity and diet were sourced from large-scale biobanks, including the UK Biobank (UKB) and the FinnGen study. The UK Biobank is a large prospective cohort study that successfully recruited over 500,000 men and women aged 40 to 69, focusing on their long-term health status. The FinnGen study included 218,792 participants of European origin. These data were used to assess the effects of physical activity, low-calorie diet, calcium supplements, and dietary fibre on hypertension and hyperlipidaemia, ensuring that the exposure and outcome variables were clearly defined and measured.

Selection of genetic instrumental variables

We selected genetic variants associated with physical activity, diet, and nutrition that reached a genome-wide level of significance ($P < 5 \times 10$^−8) as instrumental variables (IV). To avoid bias due to linkage disequilibrium, we selected independent SNPs (defined as r^2 < 0.001 with a clustering window ≥ 10,000 kb). Subsequently, we removed SNPs associated with potential confounders, such as cancer, neoplasms, long-term diseases, and fractures. We also implemented SNP coordination to correct the orientation of the alleles and used the F statistic to screen for SNPs highly associated with exposure factors, ensuring that our selection process was transparent and reliable.

Statistical analyses

In this study's MR analyses, the inverse variance weighting (IVW) method served as the primary analysis method. We assessed heterogeneity between the estimates of individual genetic variants using Cochran's Q-test and selected between random and fixed effects models based on the *p*-value. Supplementary analyses included weighted median methods, maximum likelihood estimation, MR-Egger regression methods, and penalised weighted median methods. To address potential bias due to horizontal multinomials, we employed the robust adjusted profile scoring (RAPS) method. Finally, we validated the IVW model results using MR Polyvalence Residuals and Outliers (MR-PRESSO) to test and calibrate for horizontal polyvalence outliers, ensuring a comprehensive and transparent statistical approach.

Sensitivity analyses

To identify possible pleiotropy, we conducted MR-Egger tests, which indicated the absence of horizontal pleiotropy if the *p*-value of the MR-Egger intercept was greater than 0.05. We performed exclusion-by-exclusion sensitivity analyses to assess the stability of the results by excluding one SNP at a time. Funnel plots and forest plots were generated to directly explore the presence of pleiotropy, providing a thorough examination of the robustness of our findings.

Results

In this study, we employed multivariate Mendelian randomization analysis to explore the causal effects of physical activity, diet, and nutrition on hypertension. Table 1 and Fig. 1 summarize the effects of different diet types, mineral supplements, dietary fiber, and physical activity on hypertension. For low-calorie diets, MR Egger's analysis showed an association with hypertension of 0.688 (95% CI: 0.411–1.155, $P = 0.230$), indicating no significant association. However, Weighted Median and Inverse Variance Weighted analyses showed associations of 1.122 (95% CI: 1.014–1.243, $P = 0.026$) and 1.095 (95% CI: 1.013–1.184, $P = 0.023$), respectively, suggesting a positive association between low-calorie diets and hypertension. These discrepancies may reflect methodological or instrumental variable limitations, particularly the sensitivity of MR-Egger to pleiotropy. For calcium supplements, MR Egger analysis showed an association with hypertension of 0.950 (95% CI: 0.400–2.258, $P = 0.918$), which was not significant, while Weighted Median and Inverse Variance Weighted analyses showed associations of 1.172 (95% CI: 0.862–1.593, $P = 0.312$) and 1.183 (95% CI: 0.916–1.528, $P = 0.198$), respectively, again showing no significant association. For dietary fiber, MR Egger analysis showed a non-significant association of 0.975 (95% CI: 0.739–1.287, $P = 0.870$), while Weighted Median and Inverse Variance Weighted analyses showed associations of 0.996 (95% CI: 0.952–1.043, $P = 0.070$) and 0.997 (95% CI: 0.951–1.046, $P = 0.910$), respectively, neither of which showed a significant association. Analysis of physical activity showed an association of 1.539 (95% CI: 0.328–7.221, $P = 0.592$) for MR Egger analysis, suggesting a non-significant association. Weighted Median and Inverse Variance Weighted analyses showed associations of 1.006 (95% CI: 0.895–1.129, $P = 0.924$) and 0.972 (95% CI: 0.833–1.135, $P = 0.724$), respectively, neither of which showed a significant association. In conclusion,

Table 1 Mendelian randomisation of exercise, diet and nutrition in hypertension

		Hypertension				
		or	**or_lci95**	**or_uci95**	***P*-Value**	**Beta**
Type of special diet followed: Low calorie	MR Egger	0.688663962	0.410577879	1.155098892	0.230373573	−0.373001845
	Weighted median	1.12230656	1.013652312	1.242607547	0.026350347	0.115385996
	Inverse variance weighted	1.094993144	1.012511378	1.184194087	0.023135847	0.090748102
Mineral and other dietary supplements: Calcium	MR Egger	0.950151963	0.39987277	2.257689998	0.918390738	−0.051133346
	Weighted median	1.17188441	0.861885566	1.593382142	0.311617712	0.15861306
	Inverse variance weighted	1.183081309	0.915837937	1.528306839	0.198096177	0.168122314
Englyst dietary fibre	MR Egger	0.975206672	0.738986609	1.286935435	0.870490334	−0.025105859
	Weighted median	0.996368163	0.951712604	1.043119019	0.876408199	−0.003638448
	Inverse variance weighted	0.997279786	0.951253112	1.045533475	0.910038923	−0.002723921
physical activity	MR Egger	1.53919032	0.328090372	7.220897167	0.592034356	0.431256512
	Weighted median	1.005675648	0.895444203	1.129476863	0.923878345	0.005659602
	Inverse variance weighted	0.97245662	0.832988936	1.135275436	0.723622482	−0.027929811

this study revealed a positive association between low-calorie diets and hypertension by multivariate Mendelian randomization analysis, while no significant causal associations were observed for other diets and physical activity in hypertension. Future studies should further validate these findings and explore the underlying mechanisms.

Table 2 demonstrates the results of sensitivity analyses in the Mendelian randomization analyses regarding exercise, diet, and nutrition on hypertension. In the low-calorie diet group, in the heterogeneity test, the Q-value of the MR-Egger method was 0.080214777 with 4 degrees of freedom and a *p*-value of 0.999216884; the Q-value of the inverse-variance-weighted method was 3.24145308 with 5 degrees of freedom and a *p*-value of 0.662816412; and in the test of multivalence, the intercept value was 0.004666732 with a standardized error of 0.002624728, and a *p*-value of 0.150035849. In the calcium supplementation group, the MR-Egger method had a Q-value of 1.713490647, with a degree of freedom of 2, and a *p*-value of 0.424541582; the inverse variance weighted method had a Q-value of 1.983687402, with a degree of freedom of 3, and a *p*-value of 0.57579934; and in the test of multivalence had an intercept value of 0.000913997, a standard error of 0.001758348, and a *p*-value of 0.655008563. The Englyst dietary fiber group showed significant heterogeneity, with a Q-value of 12.63149388, a degree of freedom of 3, and a *p*-value of 0.00550524 by the MR-Egger method; and an inverse-variance weighted method with a Q-value of 12.74101842, with a degree of freedom of 4 and a p-value of 0.012613061; the intercept value for the test of multiple validity was 0.000816232, with a standard error of 0.005060861 and a *p*-value of 0.882119955. The physical activity group, in the test of heterogeneity, had a Q-value of 79.19475391 for the MR-Egger method, with a degree of freedom of 16, and a *p*-value of 2.32E-10; the Q-value of the inverse variance weighting method was 80.8904904, with a degree of freedom of 17, and a *p*-value of 2.66E-10; and the intercept value of the test of multiple validity was −0.002759349, with a standard error of 0.004714282, and a *p*-value of 0.566499148. These results indicate the presence of heterogeneity among different groups and pleiotropic differences, suggesting that the causal effects of these factors need to be interpreted with caution in the analyses.

Table 3 and Fig. 2 demonstrate the results of assessing the effects of exercise, diet, and nutrition on hyperlipidaemia by Mendelian randomisation. For mineral and other dietary supplements (calcium), all three methods of analysis (MR Egger, weighted median, and inverse variance weighted) showed significant effects on hyperlipidaemia. Notably, the MR Egger method showed an OR of 612.2273971 for calcium supplements with a 95% confidence interval of 0.001792083 to 209154580.8, a *p*-value of 0.427634572, and a β-value of 6.417103777. The weighted median method showed an OR of 47.08069091 with a 95% confidence interval of 0.051412693 to 43,113.70046, with a *p*-value of 0.268280818 and a β-value of 3.851862958; the inverse variance weighted method shows an OR of 84.91560056, with a 95% confidence interval of 0.235845254 to 30573.68799, with a *p*-value of 0.139144651 and a β-value of 4.441657829.

For the effect of Englyst dietary fibre, the MR Egger method showed an OR of 2.47797558 with a 95% confidence interval of 0.027497506 to 223.306178,

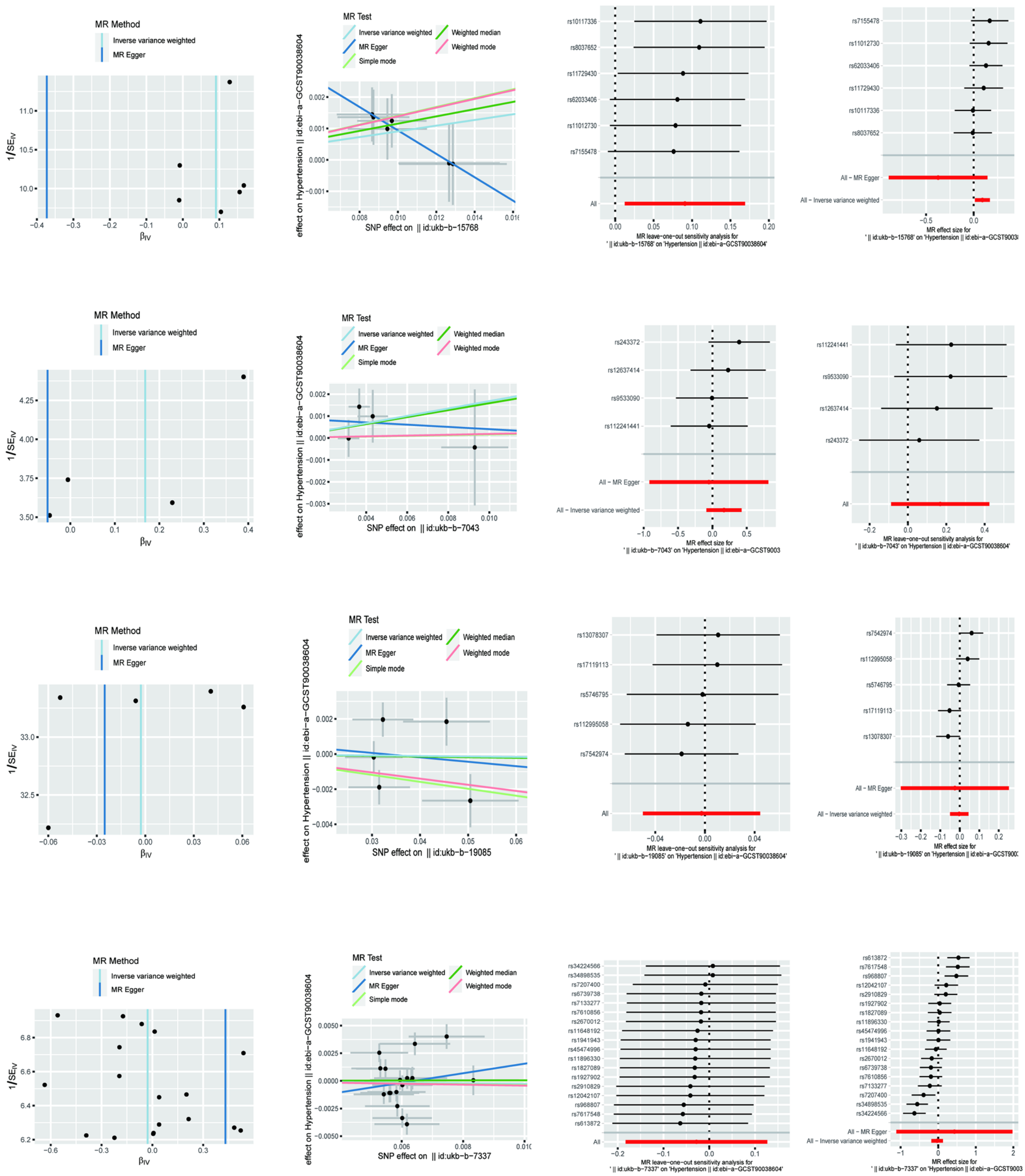

Fig. 1 Mendelian randomisation of exercise, diet and nutrition in hypertension

p-value of 0.730897542, and β-value of 0.907441928; and the weighted median method showed an OR of 1.362289348 with a 95% confidence interval of 0.387450194 to 4.789860211, *p*-value of 0.629844753, and β-value of 0.309166628; the inverse variance-weighted method shows an OR of 1.361220365, 95% confidence interval of 0.483720638 to 3.830559913, and a *p*-value of 0.559087378 and a β-value of 0.308381625.

Table 2 Sensitivity analysis of Mendelian randomisation of exercise, diet and nutrition in hypertension

	Heterogeneity test						Pleiotropy test		
	MR-Egger			Inverse variance weighted			MR-Egger		
	Q	Q_df	Q_pval	Q	Q_df	Q_pval	Intercept	se	p
Type of special diet followed: Low calorie	0.080214777	4	0.999216884	3.24145308	5	0.662816412	0.004666732	0.002624728	0.150035849
Mineral and other dietary supplements: Calcium	1.713490647	2	0.424541582	1.983687402	3	0.57579934	0.000913997	0.001758348	0.655008563
Englyst dietary fibre	12.63149388	3	0.00550524	12.74101842	4	0.012613061	0.000816232	0.005060861	0.882119955
Physical activity	79.19475391	16	2.32E-10	80.8904904	17	2.66E-10	−0.002759349	0.004714282	0.566499148

Table 3 Mendelian randomised effects of exercise, diet and nutrition on hyperlipidemia

		Hyperlipidemia:				
		or	or_lci95	or_uci95	*P*-Value	Beta
Mineral and other dietary supplements: Calcium	MR Egger	612.2273971	0.001792083	209154580.8	0.427634572	6.417103777
	Weighted median	47.08069091	0.051412693	43113.70046	0.268280818	3.851862958
	Inverse variance weighted	84.91560056	0.235845254	30573.68799	0.139144651	4.441657829
Englyst dietary fibre	MR Egger	2.47797558	0.027497506	223.306178	0.730897542	0.907441928
	Weighted median	1.362289348	0.387450194	4.789860211	0.629844753	0.309166628
	Inverse variance weighted	1.361220365	0.483720638	3.830559913	0.559087378	0.308381625
Physical activity	MR Egger	1.71E-09	8.33E-42	3.51E+23	0.613977001	−20.18677329
	Weighted median	4.942426499	0.00889867	2745.082203	0.620204532	1.597856405
	Inverse variance weighted	2.885096828	0.019332454	430.560127	0.678223768	1.059558462

For the effect of physical activity, the MR Egger method showed an OR of 1.71E-09 with a 95% confidence interval of 8.33E-42 to 3.51E+23, a *p*-value of 0.613977001, and a β-value of −20.18677329; and the weighted median method showed an OR of 4.942426499 with a 95% confidence interval of 0.00889867 to 2745.082203, with a *p*-value of 0.620204532 and a β-value of 1.597856405; the inverse variance weighted method shows an OR of 2.885096828, with a 95% confidence interval of 0.019332454 to 430.560127, with a *p*-value of 0.678223768 and a β-value of 1.059558462.

Taking these results together, although some analyses showed statistical significance, overall, the effect of calcium supplementation on hyperlipidaemia varied considerably between methods, suggesting that there may be other confounders or limitations of the study methodology. The effects of dietary fibre and physical activity on hyperlipidaemia were more consistent between methods of analysis, but their significance was insufficient and further research is needed to validate these results.

In the present study, to assess the causal effects of exercise, diet, and nutrition on hyperlipidaemia, multivariate Mendelian Randomization (MR) analyses were performed and the results were subjected to sensitivity analysis. Table 4 demonstrates the results of the MR heterogeneity and multiplicity tests of different variables on hyperlipidaemia. For calcium in minerals and other dietary supplements, we found that the MR-Egger method had a Q value of 2.122502156 with a degree of freedom of 2 and a *p*-value of 0.346022638, whereas the Inverse Variance Weighted (IVW) method had a Q value of 2.24919623 with a degree of freedom of 3 and a *p*-value of 0.522323361, indicating that neither showed significant heterogeneity. The MR-Egger method had an intercept term of −0.016172349, a standard error of 0.046806269, and a *p*-value of 0.762663531, indicating no significant pleiotropy. For Englyst dietary fibres, the MR-Egger method had a Q-value of 1.722323409 with 2 degrees of freedom and a *p*-value of 0.422670779, and the IVW method had a Q-value of 1.794167402 with 3 degrees of freedom and a *p*-value of 0.616204996, indicating no significant heterogeneity. Its intercept term was −0.024147719, standard error was 0.09009089, and *p*-value was 0.813784123, showing no significant

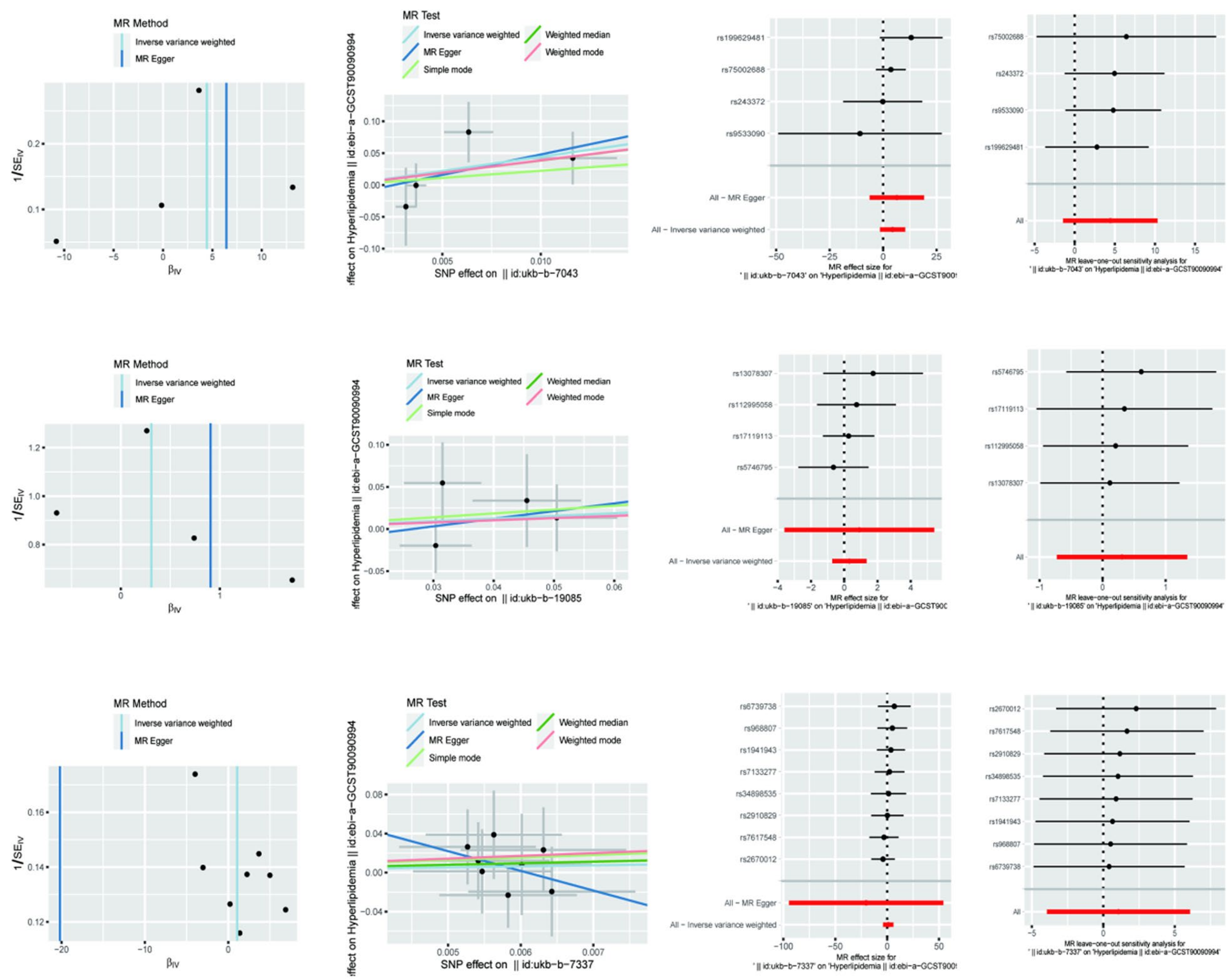

Fig. 2 Mendelian randomisation of exercise, diet and nutrition in hyperlipidemia

Table 4 Sensitivity analysis of Mendelian randomised effects of exercise, diet and nutrition on hyperlipidemia

	Heterogeneity test						Pleiotropy test		
	MR-Egger			Inverse variance weighted			MR-Egger		
	Q	Q_df	Q_pval	Q	Q_df	Q_pval	Intercept	se	p
Mineral and other dietary supplements: Calcium	2.122502156	2	0.346022638	2.24919623	3	0.522323361	−0.016172349	0.046806269	0.762663531
Englyst dietary fibre	1.722323409	2	0.422670779	1.794167402	3	0.616204996	−0.024147719	0.09009089	0.813784123
Physical activity	1.779407227	6	0.938827779	2.094096488	7	0.954449121	0.122867428	0.219026068	0.595129975

pleiotropy. For physical activity, the MR-Egger method had a Q-value of 1.779407227 with 6 degrees of freedom and a p-value of 0.938827779, and the IVW method had a Q-value of 2.094096488 with 7 degrees of freedom and a p-value of 0.954449121, showing no significant heterogeneity. Its intercept term was 0.122867428, standard error was 0.219026068, and p-value was 0.595129975, indicating that there was no significant pleiotropy. Taken together, the results of these sensitivity analyses further support our main analytical conclusion that the causal effects of exercise, diet, and nutrition on hyperlipidaemia are robust to potential pleiotropy.

Discussion

Hypertension and hyperlipidemia are prevalent chronic diseases worldwide, posing serious threats to human health. According to the World Health Organization (WHO), approximately 1.1 billion people globally suffer from hypertension, and complications related to hypertension lead to over 9 million deaths annually [30–33]. Hypertension is defined as a condition of persistently elevated arterial blood pressure, which can cause damage to the heart, blood vessels, and other organs. It is a major risk factor for cardiovascular diseases such as heart disease and stroke. The etiology of hypertension is multifaceted [34, 35], involving genetic factors, unhealthy lifestyles (e.g., high-salt diet, smoking, alcohol consumption), and psychological factors (e.g., stress and anxiety). In recent years, the incidence of hypertension has been rising due to changes in lifestyle and an aging population [36–38].

Similarly, hyperlipidemia is a common metabolic disorder characterized by abnormal levels of cholesterol and triglycerides in the blood [39]. Hyperlipidemia, especially hypercholesterolemia, is a major risk factor for atherosclerosis, which leads to arterial hardening and narrowing, thereby increasing the risk of myocardial infarction and stroke [40, 41]. The Global Burden of Disease Study shows that about 39% of adults have elevated cholesterol levels, with higher rates in some high-income countries and regions. The etiology of hyperlipidemia is also complex [42], involving genetic factors, unhealthy dietary habits (e.g., high-fat diet), lack of physical activity, obesity, and certain chronic diseases (e.g., diabetes). With the improvement in living standards and changes in dietary structure, the incidence of hyperlipidemia is also on the rise globally [43].

Physical activity, diet, and nutrition play crucial roles in the prevention and control of hypertension and hyperlipidemia. Regular physical activity is considered an effective means to improve cardiovascular health [44–46]. Exercise can enhance cardiopulmonary function, improve blood circulation, and regulate the neuroendocrine system, thereby reducing blood pressure and lipid levels. Studies have shown that engaging in 150 min of moderate-intensity aerobic exercise or 75 min of high-intensity aerobic exercise per week can significantly reduce the risk of hypertension and hyperlipidemia [3, 47]. However, the effects of different types, intensities, and frequencies of exercise on individual cardiovascular health may vary, and the specific mechanisms need further investigation [48].

Diet and nutrition are also important factors influencing hypertension and hyperlipidemia. A low-calorie diet helps reduce weight and improve metabolic conditions [49], thereby lowering blood pressure levels. Research indicates that controlling calorie intake can not only reduce weight but also improve insulin sensitivity and lower plasma lipid levels, which positively affects cardiovascular health [50, 51]. However, excessive restriction of calorie intake may lead to malnutrition, negatively impacting health. Therefore, dietary interventions should ensure balanced nutrient intake while controlling calorie intake.

Calcium supplements and dietary fiber are common nutritional interventions. Calcium plays an important role in maintaining bone health and cardiovascular function, and calcium supplements are widely used to prevent and treat osteoporosis [52]. However, their specific role in cardiovascular health remains unclear. This study found no significant effects of calcium supplements on hypertension and hyperlipidemia, suggesting the need for further research into their mechanisms in cardiovascular diseases [53–55]. Dietary fiber helps regulate the gut microbiota, improve lipid metabolism, and lower cholesterol levels, contributing to cardiovascular health. Although this study did not find significant associations between dietary fiber and hypertension or hyperlipidemia, its role in the overall dietary pattern remains noteworthy [56].

In this study, the relationship between a low-calorie diet and hypertension was assessed using different statistical methods. The MR Egger analysis showed no significant association (OR = 0.688, 95% CI: 0.411–1.155, $P = 0.230$). The Weighted median and Inverse variance weighted methods indicated a significant positive association between a low-calorie diet and hypertension (OR = 1.122, 95% CI: 1.014–1.243, $P = 0.026$; OR = 1.095, 95% CI: 1.013–1.184, $P = 0.023$, respectively). These results suggest that a low-calorie diet may indirectly influence blood pressure by reducing body weight, improving insulin sensitivity, and lowering plasma lipid levels. While the MR Egger analysis did not reveal a significant association, this discrepancy could be attributed to its heightened sensitivity to pleiotropy and heterogeneity. In contrast, the Weighted median and Inverse variance weighted methods are more robust and provide more reliable estimates of causal relationships. The interpretation of these findings is clear and supported by a logical basis, aligning with the potential mechanisms through which a low-calorie diet could impact hypertension.Therefore, a low-calorie diet as a dietary intervention strategy may have potential applications in hypertension management.

The role of calcium supplements in hypertension and hyperlipidemia was also analyzed in detail in this study. For hypertension, none of the three methods showed significant associations: MR Egger (OR = 0.950, 95% CI: 0.400–2.258, P = 0.918), Weighted median (OR = 1.172, 95% CI: 0.862–1.593, P = 0.312), and Inverse variance weighted (OR = 1.183, 95% CI: 0.916–1.528, P = 0.198). For hyperlipidemia, although the MR Egger method showed an OR of 612.227 (95% CI: 0.001–209154580.8, P = 0.428), this result was heavily influenced by extreme values, and the Weighted median and Inverse variance weighted methods did not show significant associations. The lack of significant associations with calcium supplements suggests that their role in cardiovascular health may be limited or that higher doses and long-term interventions are needed to observe significant effects. While calcium plays an important role in bone health, its specific mechanisms in the cardiovascular system require further research.

For dietary fiber, the study results showed no significant associations with hypertension or hyperlipidemia. For hypertension, the MR Egger, Weighted median, and Inverse variance weighted methods all showed no significant associations (OR = 0.975, 95% CI: 0.739–1.287, P = 0.870; OR = 0.996, 95% CI: 0.952–1.043, P = 0.876; OR = 0.997, 95% CI: 0.951–1.046, P = 0.910, respectively). For hyperlipidemia, the results were consistent across the three methods, showing no significant associations. This may be due to the complex mechanisms of dietary fiber, involving the regulation of the gut microbiota and improvements in lipid metabolism. Although individual fiber supplementation did not show significant effects, its role in the overall dietary pattern is still worth noting. For example, diets rich in dietary fiber, such as the Mediterranean diet, have been shown to benefit cardiovascular health. Therefore, the effects of dietary fiber may need to be observed in specific dietary structures and long-term interventions.

Physical activity did not show significant effects on hypertension and hyperlipidemia in this study. For hypertension, the MR Egger, Weighted median, and Inverse variance weighted methods all showed no significant associations (OR = 1.539, 95% CI: 0.328–7.221, P = 0.592; OR = 1.006, 95% CI: 0.895–1.129, P = 0.924; OR = 0.972, 95% CI: 0.833–1.135, P = 0.724, respectively). For hyperlipidemia, the results were also non-significant across the three methods. This result may reflect that the impact of physical activity on cardiovascular health requires long-term and high-intensity interventions to become evident, and the genetic variants used in this study may not fully capture the actual levels of individual physical activity. Moreover, factors such as the type, frequency, and intensity of physical activity could also significantly influence the results. Future research should further refine the assessment of physical activity, taking into account individual differences and gene-environment interactions to explore its specific mechanisms in cardiovascular health.

The findings from this study have several biological and clinical implications. The positive association between low-calorie diets and hypertension, as indicated by the weighted median and inverse variance weighted analyses, suggests that dietary interventions focusing on calorie reduction may play a role in hypertension management. This could inform the development of personalized dietary plans for individuals at risk of hypertension. The lack of significant effects of calcium supplements and dietary fiber on hypertension and hyperlipidemia indicates that, although these interventions are beneficial for other health outcomes, their impact on cardiovascular health may be limited.

Conclusion

Through multivariable Mendelian randomization analysis, this study identified a significant positive association between a low-calorie diet and hypertension, while no significant causal associations were observed between calcium supplementation, dietary fiber, or physical activity and the risk of hypertension or hyperlipidemia. Although this study has limitations, these findings provide fresh insights into the complex relationship between diet, physical activity, and cardiovascular health, supporting the need for further investigation in public health interventions and personalized treatment approaches. Future research should aim to replicate these findings across diverse populations and explore the underlying biological mechanisms, which may contribute to advancing strategies for the prevention and management of cardiovascular diseases.

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Authors' contributions
H.Q., Y.L., and H.C. conceptualized and designed the study. H.Q. conducted the multivariable Mendelian randomization analysis and drafted the initial manuscript. Y.L. collected and curated the data, and H.C. performed the statistical analysis. H.Q. and Y.L. interpreted the results and contributed to the discussion. Seongno Lee is responsible for supervision, research funding and making significant contributions to the revision. All authors reviewed and approved the final manuscript. All authors (H.Q., Y.L., and H.C.) reviewed and revised the manuscript, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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Data availability
All data used in this study were obtained from publicly available sources. The genetic data used for the multivariable Mendelian randomization analysis were extracted from the UK Biobank and the FinnGen consortium. These

datasets can be accessed at https://www.ukbiobank.ac.uk and https://www.finngen.fi/en. No new data were generated or collected specifically for this study.

Declarations

Ethics approval and consent to participate
This study did not involve direct experimentation on human participants. The data used in this study were sourced from public databases such as the UK Biobank and the FinnGen consortium, which obtained informed consent and ethical approvals from participants during data collection. Hence, further ethical approval for this study is not applicable.

Consent for publication
All participants provided consent for their data to be used in this publication.

Competing interests
The authors declare no competing interests.

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