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La ingesta de alimentos influye en la incidencia de las enfermedades cardiovasculares impulsando el remodelado cardíaco: evidencia a partir de una aleatorización mendeliana

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Data availability statement: GWAS summary statistics for food intake and cardiovascular diseases were obtained from IEU (https://gwas.mrcieu.ac.uk/); GWAS summary statistics for cardiac magnetic resonance is available at GWAS Catalog (https://github.com/baiwenjia/ukbb_cardiac).

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ABSTRACT

Background: research on dietary habits and cardiovascular diseases shows inconsistent results. Diets on cardiovascular diseases are primarily mediated by cardiac structure, but specific pathways remain unclear.

Material and methods: we conducted a Mendelian randomization study and identified twelve types of food were related to coronary artery disease, 17 to heart failure, and 16 to dilated cardiomyopathy; 13 were associated with atrial fibrillation. We then identified cardiac structure closely related to the four cardiovascular diseases and conducted mediation analysis.

Results: increased consumption of grains, dried fruits, and cheese may tentatively reduce coronary heart disease risk through distinct biomechanical pathways—including reduced segmental longitudinal strain (grains, 18.7 %), decreased left ventricular stroke volume with narrowed ascending aortic area (dried fruits; mediation through 28.9 % and 18.5 % pathways), and attenuated myocardial wall thickness (cheese, 4.25 %)—while elevated alcohol intake might heighten risk via increased stroke volume (18.6 %), amplified segmental strain (8.6 %), and elevated cardiac workload. Exploratory analyses suggest coffee-associated heart failure risk could involve mediation by segmental/global circumferential strain (mediation through 14.5 % and 27.7 % pathways) and left ventricular volume (through 23.1 %, and 22.5 % pathways), whereas cooked vegetables may partially influence dilated cardiomyopathy risk through increased left ventricular mass (14.9 %) and myocardial wall thickness (20.2 %), potentially exacerbating atrial fibrillation via impaired global longitudinal strain (36.1 %). Observational data tentatively link feta cheese to dilated cardiomyopathy risk through altered left heart volumetric parameters: left atrial minimal volume (30.3 %), ventricular end-diastolic (14.8 %)/systolic volumes (14.8 %).

Conclusion: our study provides new insights that dietary adjustments to improve cardiac remodeling may be a potent strategy for the prevention and management of cardiovascular diseases. However, the interpretation of the mediation results requires caution.

Keywords: Food intake. Cardiovascular diseases. Cardiac structure. Mendelian randomization. Mediation analysis.

RESUMEN

Antecedentes: la investigación sobre los hábitos alimentarios y las enfermedades cardiovasculares muestra resultados inconsistentes. Las dietas en las enfermedades cardiovasculares están mediadas

principalmente por la estructura cardíaca, pero las vías específicas siguen sin estar claras.

Material y métodos: realizamos un estudio de aleatorización mendeliana e identificamos que doce tipos de alimentos estaban relacionados con la enfermedad de las arterias coronarias, 17 con la insuficiencia cardíaca y 16 con la miocardiopatía dilatada; 13 estaban asociadas a la fibrilación auricular. Luego identificamos la estructura cardíaca estrechamente relacionada con las cuatro enfermedades cardiovasculares y realizamos un análisis de mediación.

Resultados: el aumento del consumo de granos, frutos secos y queso puede mitigar el riesgo de enfermedad coronaria al reducir la tensión longitudinal segmentaria, disminuir la eyección ventricular izquierda y estrechar el área de la aorta ascendente, disminuyendo el grosor de la pared miocárdica. Por el contrario, el aumento del consumo de alcohol agrava el riesgo de enfermedad coronaria al aumentar el volumen de eyección ventricular izquierda y la tensión longitudinal segmentaria. En el contexto del aumento del riesgo de insuficiencia cardíaca inducido por el café, la tensión circunferencial segmentaria, la tensión circunferencial global, el volumen telediastólico del ventrículo izquierdo y el volumen telesistólico del ventrículo izquierdo actúan como mediadores. Además, el aumento del consumo de yogur puede agravar la insuficiencia cardíaca al afectar la tensión circunferencial segmentaria. Los mediadores del aumento del riesgo de miocardiopatía dilatada por el aumento del consumo de vegetales cocidos incluyen la masa ventricular izquierda y el grosor de la pared miocárdica segmentaria. El aumento del consumo de vegetales cocidos también puede afectar la tensión longitudinal global, aumentando así el riesgo de fibrilación auricular. El queso feta puede influir en los volúmenes del corazón izquierdo, aumentando así el riesgo de miocardiopatía dilatada.

Conclusión: nuestro estudio proporciona nuevas perspectivas de que los ajustes dietéticos para mejorar la remodelación cardíaca pueden

ser una estrategia potente para la prevención y el manejo de las enfermedades cardiovasculares.

Palabras clave: Ingesta de alimentos. Enfermedades cardiovasculares. Estructura cardiaca. Aleatorización mendeliana. Análisis de mediación.

INTRODUCTION

Cardiovascular diseases (CVDs) encompass a group of disorders affecting the heart and blood vessels. They represent a significant public health concern and are the leading cause of mortality worldwide. The 2023 World Heart Report indicates that 17.9 million people globally succumb to cardiovascular diseases annually, accounting for approximately 32 % of all deaths (1). According to the American Heart Association's 2024 Heart Disease and Stroke Statistics Update, in 2021, 26.1 million Americans were afflicted with some form of cardiovascular diseases, with over 800,000 deaths each year. The annual direct and indirect costs of cardiovascular disease mortality exceed $316.1 billion (2).

To adapt to various environmental stresses, the heart flexibly alters its structure and morphology, a process known as cardiac remodeling, encompassing pathological myocardial hypertrophy, interstitial fibrosis, and inflammation mediated by macrophage and neutrophil infiltration (3,4). Pharmacotherapies, including β-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i), can prevent or reverse remodeling and have been proven to reduce cardiovascular morbidity and mortality (5,6). However, humanity continues to explore dietary approaches that can improve cardiac remodeling and thereby prevent or treat cardiovascular diseases.

In recent decades, dietary research in cardiovascular disease prevention has evolved from focusing on single nutrients and specific foods to examining dietary patterns (7,8). However, the optimal diet for enhancing cardiometabolic health remains uncertain. Therefore, a comprehensive and systematic evaluation of the relationship between food intake and cardiovascular diseases, and the potential mediating role of cardiac remodeling, is crucial for developing interventions to reduce cardiovascular risk.

Mendelian Randomization (MR) is an effective method for determining causality. MR is based on the principle of the independent assortment of genetic alleles, using known genetic variations as natural randomization factors, akin to the random assignment of treatments in randomized controlled trials, creating subgroups with similar characteristics and reducing the risk of confounding factors (9). Since genetic variations are predetermined naturally and unaffected by environmental factors, they enhance the reliability of causal inference. In MR analysis, we use single nucleotide polymorphisms (SNPs) associated with exposure as instrumental variables (IVs) to infer whether the exposure increases the risk of the outcome or has a protective effect (10). This method effectively addresses confounding factors and biases due to measurement errors, allowing us to infer causal relationships between exposure and outcomes (11). Genome-wide association studies (GWAS) have identified 226 types of food, 82 cardiac magnetic resonance-related SNPs, and cardiovascular disease-related SNPs, enabling us to use MR analysis to infer the causal relationship between food intake and cardiovascular diseases and the potential mediating role of cardiac remodeling.

We hypothesize that diet may induce specific structural alterations in the heart, leading to cardiac remodeling and various cardiovascular diseases, including heart failure (HF), atrial fibrillation (AF), dilated cardiomyopathy (DCM), and coronary artery disease (CAD). Utilizing cardiac magnetic resonance (CMR) data from GWAS studies to evaluate cardiac structure and function, combined with GWAS data on different types of food and cardiovascular diseases, we designed a MR study to explore the causal relationship between different types of food and cardiovascular diseases. Additionally, we conducted mediation MR analysis to identify potential CMR mediators that may act as intermediaries in diet-driven cardiovascular disease development.

METHODS

Data source

Extensive genome-wide association study (GWAS) data encompassing 82 distinct traits related to cardiac structure were meticulously gathered from a cohort of 31,875 individuals of European descent (12). These comprehensive measurements, obtained through advanced cardiovascular magnetic resonance imaging (MRI), cover a wide array of anatomical features, including but not limited to the left ventricle, left atrium, right ventricle, right atrium, ascending aorta, and descending aorta. Similarly, summary-level GWAS data on food intake were obtained from the UK Biobank study, involving multiple cohorts totalling over 800,000 subjects. We categorized 226 food types into 11 groups, including: fruits and vegetables, grains and cereals, dairy and alternatives, meat and alternatives, alcoholic beverages, non-alcoholic beverages, sweets and desserts, snacks, baked goods and pastries, prepared and processed foods, miscellaneous. The GWAS data related to cardiovascular diseases are derived from cohort studies involving over 200,000 individuals of European descent, including heart failure (ebi-a-GCST009541, 47,309 cases and 930,014 controls), coronary artery disease (ebi-a-GCST005195, 12,233 cases and 424,528 controls), atrial fibrillation (ebi-a-GCST006061, (9,109 cases and 324,121 controls), and dilated cardiomyopathy (ebi-a-GCST90018834, 35,381 cases and 353,937 controls), are accessible online via the IEU. (https://gwas.mrcieu.ac.uk/).

Instrumental variable selection

Strict quality control was applied in selecting instrumental variables (IVs) to meet the three core assumptions of MR analysis. Firstly, to ensure a close association between IVs and exposure factors, we selected SNPs related to food intake and cardiac structure with a genome-wide significance threshold ($p < 5*10^{-6}$) (13). Secondly, we clumped SNPs for linkage disequilibrium (LD) ($r^2 < 0.001$ within a 10,000 kb window) to ensure their independence (14). Thirdly, IVs must influence the outcome only through the exposure, not directly (15). Finally, we calculated the *F*-statistics for all selected SNPs to prevent bias from weak instruments, using the following formula:

$$R^2 = \frac{2 * \beta^2 * EAF * (1 - EAF)}{¿¿}$$

$$F = \frac{\frac{N-k-1}{k} * R^2}{1 - R^2}$$

R^2 is the exposure variation, and the explanation of R^2 is the SNP; k is the number of SNPs. And, N is the sample size.

Specific classifications of cardiac magnetic resonance and food intake are detailed in supplementary Tables I and II. The precise details of the instrumental variable SNPs are found in supplementary Table III. All F-statistics exceed 10, indicating that our study is unlikely to be affected by weak instrumental variables. An overview of this study is shown in figure 1.

Univariate MR analysis

To predict the impact of food intake on CVDs. We employed three complementary methods: inverse-variance weighting (IVW), MR-Egger, and the weighted median approach for MR analysis. The IVW method, known for its superior statistical power, provides accurate results when all selected single nucleotide polymorphisms (SNPs) are valid instrumental variables (IVs), thus serving as the primary statistical method for testing causality (16). The MR-Egger method yields consistent causal estimates under the Instrument strength independent of direct effect (InSIDE) assumption, even if the genetic IV is invalid (17). The weighted median approach assumes that more than half of the instrumental variables is valid and is also used for robustness checks (18). A causal relationship between exposure and outcome is considered when the IVW analysis results in $p < 0.05$, and the directions of the weighted median and MR-Egger results align with the IVW odds ratio (OR) direction.

Sensitivity analysis

Sensitivity analysis primarily assesses heterogeneity and potential horizontal pleiotropy that may severely violate MR assumptions. The IVW method, alongside MR-Egger, employs Cochran's Q statistic for heterogeneity testing. When heterogeneity is suspected, the IVW random-effects model is applied (19). In MR-Egger, the MR intercept tests for horizontal pleiotropy; if the SNP effect is reduced to zero and the MR-Egger intercept is statistically significant, it indicates other unknown factors influencing the outcome, thus violating MR assumptions (20). We performed leave-one-out analysis, sequentially excluding each valid SNP to prevent the results from being influenced by a single SNP. All statistical analyses were conducted using the MR-PRESSO, TwoSampleMR, and MendelianRandomization packages on the R version 4.2.3 software platform.

Mediated MR analysis

We employed a two-step MR approach to investigate potential cardiac structural phenotypes mediating the causal relationship between food intake and CVDs. We utilized the product of coefficients method, which involves calculating two MR assumptions: the causal effect of exposure on the mediator and the causal effect of the mediator on the outcome. Multiplying these estimates yields the indirect effect estimate (21). Initially, the causal relationship between food intake and CVDs was assessed (β all). Subsequently, CMR characteristics causally linked to these food types were identified (β1). Among these CMR phenotypes, those with causal relationships to CVDs were further investigated (β2), considering them as potential mediators. When the mediation effect (β1 × β2) of food on cardiovascular diseases, as mediated by cardiac nuclear magnetic resonance, aligns with the direction of the direct effect (β all), the proportion of the mediation effect will be calculated. The proportion mediated by each medium is calculated as the product of β1 and β2, divided by the β all (22).

RESULTS

We identified 12 dietary types causally linked to coronary heart disease, with alcoholic beverages being particularly significant; 17 dietary types associated with heart failure, primarily including alcoholic beverages, dairy products, and fruits and vegetables; 16 dietary types significantly related to dilated cardiomyopathy, with a higher proportion of meat and fruits and vegetables; and 13 types of food affecting the incidence of atrial fibrillation, with various alcoholic beverages associated with increased risk of atrial fibrillation (Fig. 2). All MR analyses showed no horizontal pleiotropy. Sensitivity analysis results indicated that no single nucleotide polymorphism could alter the overall MRanalysis, demonstrating the robustness of our findings (Supplementary Table IV).

We identified cardiac MRI markers associated with four cardiovascular diseases (Fig. 3) Markers closely related to heart failure include ejection fraction, circumferential strain, myocardial wall thickness, and ventricular volumes. Key markers influencing coronary heart disease encompass multidirectional cardiac strain, arterial area, and wall thickness. Indicators affecting atrial fibrillation include myocardial wall thickness, circumferential strain, and longitudinal strain. Circumferential strain, left atrial and ventricular volume, mass, and myocardial wall thickness are closely linked to dilated cardiomyopathy (Supplement Table V).

In mediation analysis, we identified CMR indicators mediating the causal relationships between food intake and cardiovascular diseases (Table I; Supplement Tables VI and VII). Increased intake of cereal, dried fruit, and cheese reduced the risk of coronary artery disease by lowering longitudinal strain segment 2 (mediation proportion, 18.7 %); reducing left ventricular stroke volume (mediation proportion, 28.9 %), decreasing ascending aorta area (mediation proportion, 18.5 %); and reducing myocardial wall thickness (mediation proportion, 4.25 %). Increased alcohol consumption raised coronary artery disease risk by increasing left ventricular stroke volume (mediation proportion, 18.6 %), increasing longitudinal strain segment 2 (mediation proportion, 8.6 %), and increasing cardiac work. In the process of coffee-induced heart failure risk, circumferential strain segment 12 (mediation proportion, 14.5 %), overall circumferential strain (mediation proportion, 27.7 %), left ventricular end-diastolic volume (mediation proportion, 23.1 %), and left ventricular end-systolic volume (mediation proportion, 22.5 %) played mediating roles. Increased intake of cooked vegetables raised the risk of dilated cardiomyopathy through mediators such as left ventricular mass (mediation proportion, 14.9 %) and myocardial wall thickness segment 6 (mediation proportion, 20.2 %). Cooked vegetable intake also impaired overall longitudinal strain (36.1 %), increasing the risk of atrial fibrillation. Feta cheese affected left heart volumes, including left atrial minimum volume (mediation proportion, 30.3 %), left ventricular end-diastolic volume (mediation proportion, 14.8 %), and left ventricular end-systolic volume (mediation proportion, 19.1 %), increasing the risk of dilated cardiomyopathy.

DISCUSSION

For the various food types identified as related to cardiovascular diseases, we found that diets beneficial to cardiovascular risk largely align with the currently popular Mediterranean diet, DASH diet (Dietary Approaches to Stop Hypertension), and plant-based diets.

The Mediterranean diet emphasizes high intake of fruits, vegetables, whole grains, nuts, and olive oil, with moderate consumption of fish and poultry; the DASH diet emphasizes fruits, vegetables, whole grains, and low-fat dairy products while limiting sodium, red meat, and sweets; plant-based diets include high intake of vegetables, fruits, nuts, seeds, and legumes. The food types emphasized in these diets mostly showed protective effects against the four cardiovascular diseases in our Mendelian randomization analysis. In contrast, the Western diet, which favors high intake of processed foods, red meat, sweets, high-fat dairy products, and refined grains, generally exhibited harmful effects on the four cardiovascular diseases.

Our research demonstrated a significant causal relationship between alcoholic beverages and coronary artery disease (CAD) and heart failure (HF). Most drinking behaviors and types, including alcohol intake frequency (HF, OR = 1.20, 95 % CI 1.13-1.28, p = 3.99 E-08), (CAD, OR = 1.19, 95 % CI 1.10-1.28, p = 9.83 E-06). Alcohol intake versus 10 years previously (HF, OR = 1.80, 95 % CI 1.41-2.29, p = 2.68 E-06), (CAD, OR = 1.68, 95 % CI 1.30-2.15, p = 5.50 E-05), average weekly fortified wine intake (HF, OR = 1.92, 95 % CI 1.01-3.64, p = 0.045), average monthly fortified wine intake (HF, OR = 1.14, 95 % CI 1.03-1.30, p = 0.031), average monthly red wine intake (HF, OR = 1.18, 95 % CI 1.09-1.41, p = 0.042), average weekly red wine intake (CAD, OR = 1.60, 95 % CI 1.31-1.96, p = 4.45257 E-06) and average weekly beer plus cider intake (CAD, OR = 1.28, 95 % CI 1.06-1.55, p = 0.010) increased the risk of CAD or HF. However, we also observed that average weekly champagne plus white wine intake (HF, OR = 0.77, 95 % CI 0.62-0.95, p = 0.017), (CAD, OR = 0.76, 95 % CI 0.61-0.94, p = 0.013) reduced the risk of CAD and HF. Numerous observational studies indicated that light to moderate alcohol consumption might have a protective effect on the heart or might not increase the risk of CAD and HF, excessive alcohol consumption may exacerbate cardiovascular risk (23,24). Our research similarly showed that with increased drinking frequency, the risk of CAD and HF rose.

Particularly, increased alcohol consumption compared to 10 years ago exacerbated the risk of four cardiovascular diseases. (HF, OR = 1.80, 95 % CI 1.41-2.29, p = 2.68 E-06), (CAD, OR = 1.68, 95 % CI 1.30-2.15, p = 5.50 E-05), (AF, OR = 1.30, 95 % CI 1.02-1.64, p = 0.032), (DCM, OR = 0.65, 95 % CI 1.10-6.38, p = 0.030). Previous studies suggested that wine consumption, especially moderate wine consumption, offered protective benefits for CVDs (25). Our research indicated that red wine, fortified wine, and beer consumption still posed a risk for CAD or HF, but the combination of champagne and white wine exerted cardioprotective effects, reducing the risk of CAD and HF. Champagne and white wine contained unique polyphenolic compounds, with white wine having tyrosol, caffeic acid, and shikimic acid, while champagne contained more phenolic acids and matrix metalloproteinases, all of which contributed to antioxidant effects and vascular health maintenance (26,27).

Currently, an increasing number of perspectives suggest that any amount of alcohol consumption, regardless of type, elevates the risk of atrial fibrillation (28,29). Our research similarly found that the frequency of alcohol intake (AF, OR = 1.51, 95 % CI 1.22-1.86, p = 0.00014) and the consumption of various types of alcoholic beverages, including beer and cider wine (AF, OR = 1.46, 95 % CI 1.14-1.86, p = 0.002), red wine (AF, OR = 1.20, 95 % CI 1.05-1.36, p = 0.0058), and other alcoholic drinks (AF, OR = 1.93, 95 % CI 1.09-3.42, p = 0.024), all contribute to an increased risk of atrial fibrillation. For patients with atrial fibrillation, there is no safe level of alcohol consumption, nor any type of alcoholic beverage that can mitigate this risk. Therefore, patients with atrial fibrillation should abstain from all alcoholic beverages. However, we have not found sufficient evidence that alcohol consumption alters cardiac MRI, thereby affecting cardiovascular diseases. Only the frequency of alcohol consumption influences the development of coronary heart disease through segmental longitudinal strain and left ventricular stroke volume. The underlying mechanism may involve the direct

toxic effects of chronic alcohol consumption on cardiomyocytes, leading to cardiac remodeling. This remodeling includes hypertrophy of the remaining cardiomyocytes and interstitial fibrosis, resulting in increased myocardial stiffness and reduced efficiency. This process impairs the longitudinal strain capacity of the myocardium, increases cardiac load, and causes continuous cardiac dilation, ultimately exacerbating coronary artery disease (30,31).

Additionally, we have discovered that dairy products, particularly cheese, can reduce the risk of three types of cardiovascular diseases (HF, OR = 0.74, 95 % CI 0.66-0.83, p = 2.96 E-07), (CAD, OR = 0.66, 95 % CI 0.59-0.75, p = 2.22 E-11), (AF, OR = 0.87, 95 % CI 0.78-0.97, p = 0.013). A meta-analysis of long-term observational studies indicated that higher cheese intake is associated with a reduced risk of cardiovascular events over more than 10 years (32). These studies excluded individuals with pre-existing cardiovascular diseases. Cheese, a full-fat dairy product primarily composed of saturated fatty acids, is not considered beneficial for cardiovascular health and is believed to impact lipid metabolism. However, meta-analyses indicate that cheese consumption, compared to butter, reduces total cholesterol by 0.28 mmol/L and low-density lipoprotein cholesterol by 0.22 mmol/L, with a neutral effect on triglycerides. Other nutrients in cheese, such as minerals, casein, α-lactalbumin, β-lactoglobulin, bioactive peptides, and probiotics, influence nutrient bioavailability and the release of active compounds (33). Probiotics can alter gut microbiota composition and function, enhance intestinal epithelial integrity, and reduce low-grade inflammation caused by metabolic endotoxemia, thereby improving energy homeostasis and intermediary metabolism. Cheese’s higher calcium content, compared to other dairy products, partially inhibits the absorption of saturated fatty acids and regulates excitation-contraction coupling in cells, thereby influencing cardiac contractility and ultimately affecting heart structure (34). Besides, these factors produce beneficial effects on cardiovascular health, including improvements in cardiovascular

biomarkers such as body mass index (BMI), waist circumference, and fasting blood glucose levels (35). Our mediation analysis suggested that increased cheese intake may reduce heart failure risk by reducing wall thickness. However, we have also discovered that Greek feta cheese can directly increase cardiac chamber volume, thereby promoting heart failure (HF, OR = 2.33, 95 % CI 1.23-4.40, p = 0.0087) and dilated cardiomyopathy (DCM, OR = 2.92, 95 % CI 2.52-3.61, p = 0.005). Compared to regular cheese, feta cheese contains higher levels of sodium and saturated fatty acids. Further research is needed to explore the specific cardiovascular risks associated with this novel cheese product.

Similar to the pathway by which feta cheese increases the risk of dilated cardiomyopathy, coffee may elevate the risk of heart failure (HF, OR = 1.22, 95 % CI 1.02-1.45, p = 0.026) through alterations in left ventricular diastolic and systolic volumes, as well as impairments in cardiac circumferential strain. Multiple studies indicated that excessive coffee intake may acutely elevate blood pressure, increase arterial stiffness, and induce ventricular remodeling by stimulating the central nervous system and blocking adenosine receptors (36). Coffee also contains bioactive compounds such as polyphenols and diterpenes, which can influence neurohormonal pathways. These compounds activate the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, leading to fluid retention and vasoconstriction, resulting in ventricular volume overload, impairing left ventricular circumferential strain, and accelerating the onset of heart failure (37).

Vegetable consumption is generally deemed beneficial for cardiovascular health, yet the relationship between cooked vegetables and cardiovascular diseases remains contentious. The PURE study indicated that consuming cooked vegetables may increase the prevalence of cardiovascular diseases (38). Conversely, research from the UK Biobank, involving 400,000 adults, showed no association between cooked vegetable intake and cardiovascular

disease risk (39). Our study did not demonstrate a direct causal relationship between cooked vegetables and heart failure or coronary heart disease, but it did find a causal link with dilated cardiomyopathy and atrial fibrillation (DCM, OR = 3.29, 95 % CI 1.56-6.90, p = 0.002), (AF, OR = 1.26, 95 % CI 1.05-1.51, p = 0.014). Cooked vegetable intake may not directly cause major cardiovascular diseases but could induce atrial fibrillation and dilated cardiomyopathy through changes in wall thickness, longitudinal strain and left ventricular mass. ultimately leading to other cardiovascular conditions such as heart failure and coronary heart disease. Cooked vegetables tend to lose nutrients, such as vitamins and antioxidants, during the cooking process. Therefore, it is essential to use low-temperature methods like steaming, boiling, or microwaving when preparing vegetables. Additionally, maintaining a balanced diet by consuming more raw vegetables, whole grains, and dried fruits is advisable. In contrast, dried fruit intake is directly associated with coronary heart disease and heart failure (HF, OR = 0.69, 95 % CI 0.59-0.82, p = 0.000027), (CAD, OR = 0.73, 95 % CI 0.60-0.88, p = 0.001). Cereal intake is also protective against coronary heart disease (CAD, OR = 0.84, 95 % CI 0.73-0.98, p = 0.028). Polyphenols and other antioxidants in dried fruits and cereal help neutralize free radicals, reducing oxidative stress and inflammation. Their high fiber content aids in lowering cholesterol levels and improving glycemic control (40). Additionally, essential nutrients like potassium and magnesium support heart health by regulating blood pressure and heart rhythm. Based on our mediation analysis results, the primary mechanism by which dried fruit and cereal intake reduces the risk of coronary heart disease is through the reduction of hypertension and atherosclerosis-induced ascending aortic area, as well as decreasing cardiac output, thereby reducing cardiac workload in order to reduce cardiac remodeling and maintain longitudinal myocardial strain capacity.

The strengths of our study lie in the use of Mendelian randomization (MR) analysis, employing genetic variants as instrumental variables to

explore the causal relationships between 226 food types and cardiovascular diseases, as well as the potential mediating role of cardiac structure. To validate our findings, we rigorously selected instrumental variables and utilized various MR analysis methods. Additionally, cardiac magnetic resonance imaging accurately assessed cardiac structure and function phenotypes, enabling this study to elucidate the pathways through which dietary types influence cardiovascular diseases. Previous observational studies rarely established the relationship between cardiac structure and these factors. However, our study has limitations. Firstly, our MR analysis emphasizes linear relationships, thus we cannot exclude the possibility of other non-linear relationships. Secondly, the causal relationships between dietary types and cardiovascular diseases often exhibit racial heterogeneity. This study included only GWAS data from individuals of European ancestry, which, while reducing bias due to population heterogeneity, limits the generalizability of the results to all populations.

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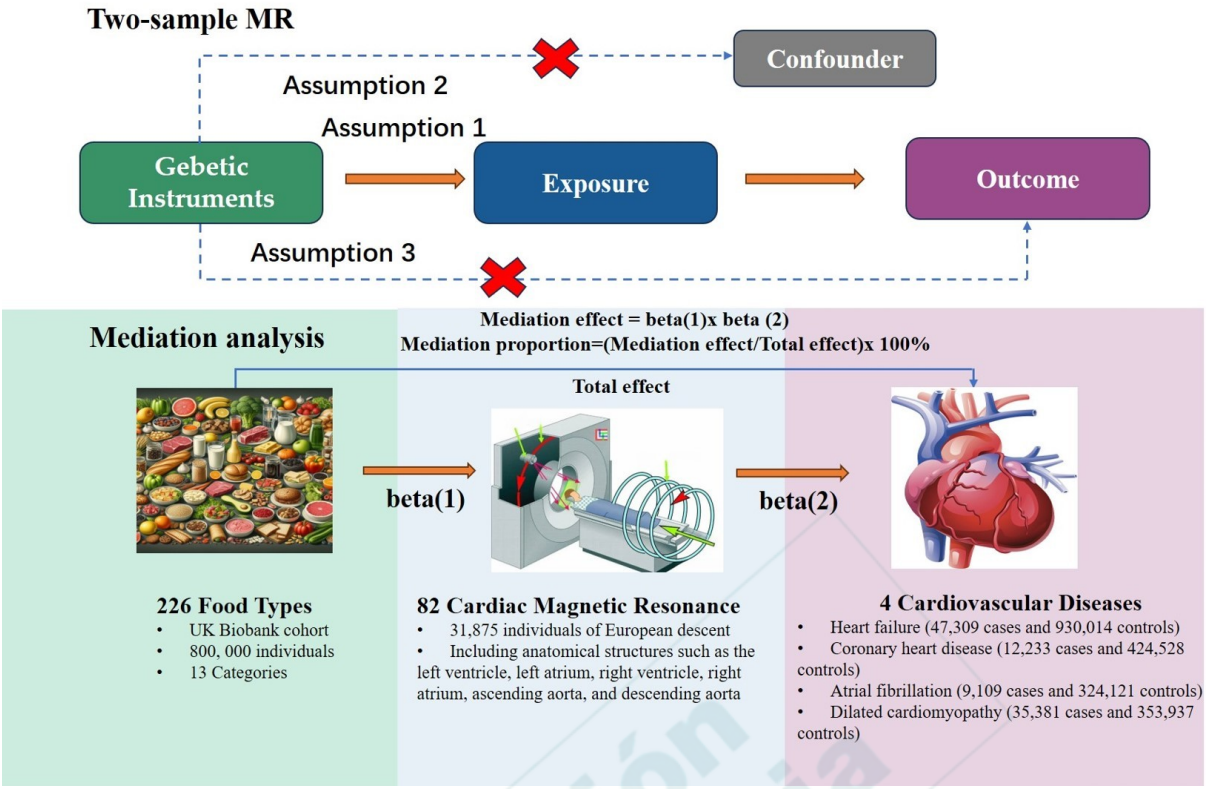

Figure 1. An overview of this MR analysis.

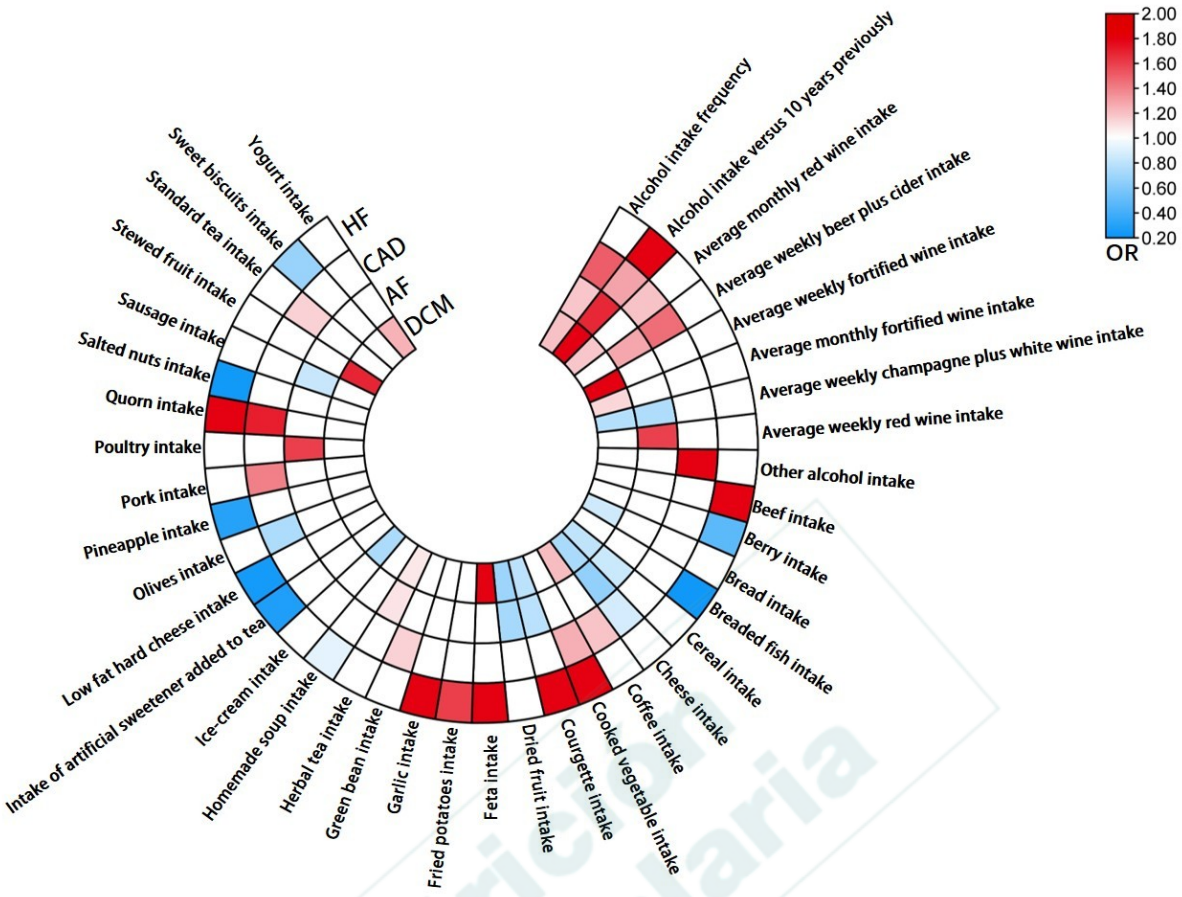

Figure 2. A two-sample Mendelian randomization analysis discerns food intake causally linked to CVDs: heart failure (HF), atrial fibrillation (AF), dilated cardiomyopathy (DCM), and coronary artery disease (CAD).

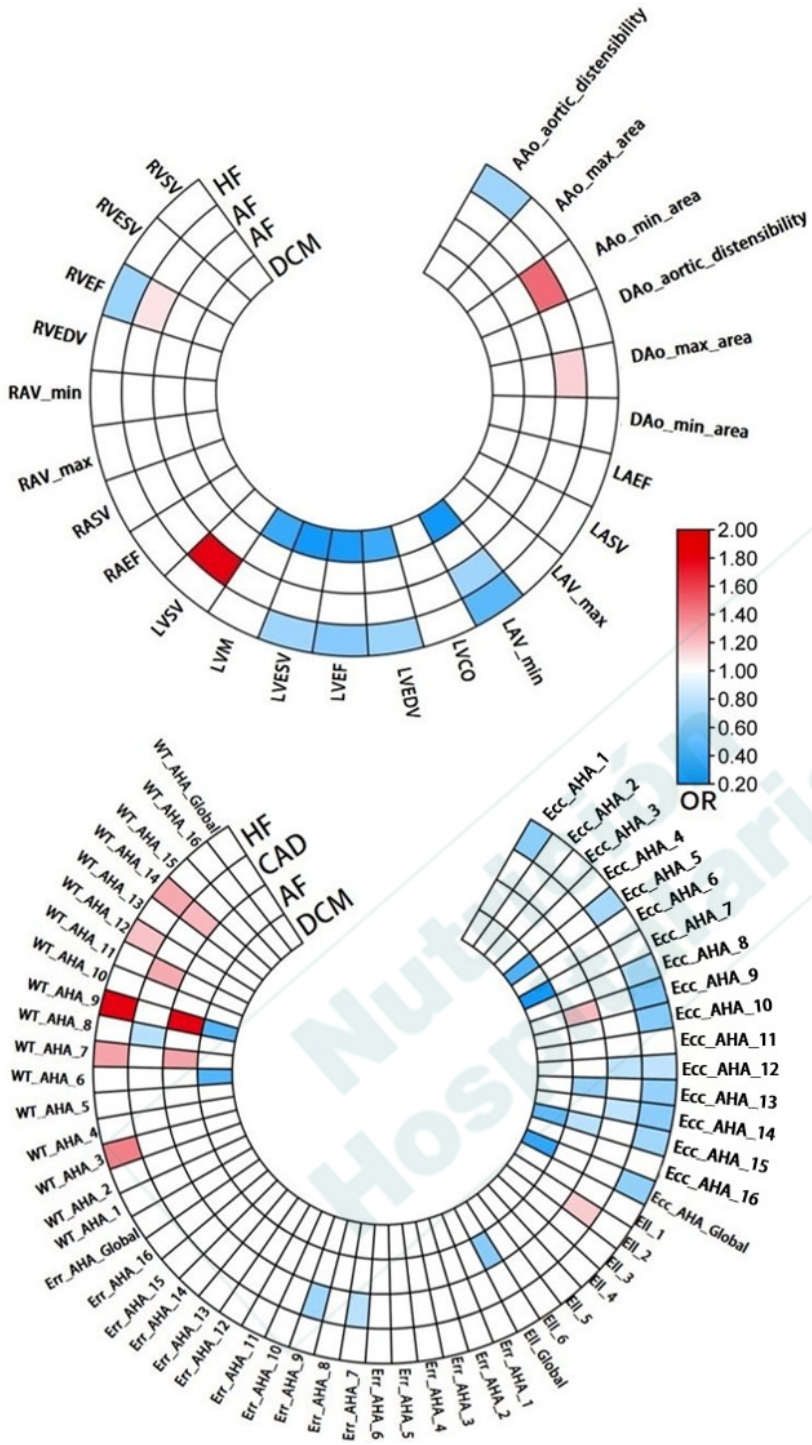

Figure 3. A two-sample Mendelian randomization analysis discerns food intake causally linked to CVDs: heart failure (HF), atrial fibrillation (AF), dilated cardiomyopathy (DCM), and coronary artery disease (CAD) (Aao: ascending aorta; Ao: aorta; Dao: descending aorta; DBP: diastolic blood pressure; Ecc AHA: peak circumferential strain according to the American Heart Association; Ell: longitudinal strain; Err AHA: radial strain according to the American Heart

Association; LAEF: left atrium ejection fraction; LASV: left atrium stroke volume; LAV: left atrium volume; LVCO: left ventricular cardiac output; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; LVM: left ventricular mass; LVSV: left ventricular stroke volume; max: maximum; min: minimum; PP: pulse pressure; RAEF: right atrium ejection fraction; RASV: right atrium stroke volume; RAV: right atrium volume; RVEF: right ventricular ejection fraction; RVEDV: right ventricular end-diastolic volume; RVESV: right ventricular end-systolic volume; RVSV: right ventricular stroke volume; SBP: systolic blood pressure; and WT AHA: myocardial wall thickness at end diastole according to the American Heart Association).

Table I. Cardiac structure mediates the causal relationship between food intake and CVDs: heart failure (HF), atrial fibrillation (AF), dilated cardiomyopathy (DCM), and coronary artery disease (CAD)

Exposure	Beta 1	Mediator	Beta 2	Outcome	Total effect	Mediation effect	Mediation Proportion
Coffee intake	-0.155	phenocode-Ecc_AHA_12	-0.184	HF	0.197	0.029	14.5 %
Coffee intake	-0.143	phenocode-Ecc_global	-0.382	HF	0.197	0.054	27.7 %
Coffee intake	-0.216	phenocode-LVEDV	-0.209	HF	0.197	0.045	23.1 %
Coffee intake	-0.149	phenocode-LVESV	-0.297	HF	0.197	0.044	22.5 %
Cereal intake	-0.181	phenocode-Ell_2	0.174	CAD	-0.169	-0.032	18.7 %
Alcohol intake frequency	0.084	phenocode-Ell_2	0.174	CAD	0.171	0.015	8.6 %
Alcohol intake frequency	0.056	phenocode-LVSV	0.566	CAD	0.171	0.032	18.6 %
Dried fruit intake	-0.157	phenocode-AAo_min_area	0.377	CAD	-0.319	-0.059	18.5 %
Dried fruit intake	-0.163	phenocode-LVSV	0.566	CAD	-0.319	-0.092	28.9 %
Cooked vegetable intake	-0.193	phenocode-Ell_global	-0.428	AF	0.228	0.082	36.1 %
Feta intake	-0.782	phenocode-LAV_min	-1.171	DCM	3.017	0.915	30.3 %
Feta intake	-0.546	phenocode-LVEDV	-0.816	DCM	3.017	0.446	14.8 %

Feta intake	-0.506	phenocode-LVESV	-1.141	DCM	3.017	0.577	19.1 %
Cooked vegetable intake	-0.211	phenocode-LVM	-0.839	DCM	1.189	0.177	14.9 %
Cooked vegetable intake	-0.323	phenocode-WT_AHA_6	-0.743	DCM	1.189	0.240	20.2 %

Aao: ascending aorta; Ao: aorta; Ecc AHA: peak circumferential strain according to the American Heart Association; Ell: longitudinal strain; Err AHA: radial strain according to the American Heart Association; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVM: left ventricular mass; LVSV: left ventricular stroke volume; max: maximum; WT AHA: myocardial wall thickness at end diastole according to the American Heart Association.